Cover Page for Statistical Analysis Plan

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Dicerna Pharmaceuticals

DCR-AUD-102

A Phase 1b, Double-blind, Placebo-controlled, Repeat dose, Safety, Tolerability, Pharmacokinetic, and Pharmacodynamic Study of DCR-AUD in Healthy Volunteers

Statistical Analysis Plan

Version: 2.0

[redacted]

[redacted]

SPONSOR SIGNATURE PAGE

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Parexel Signature Page

Signatures below confirm that the Statistical Analysis Plan was developed in accordance with [redacted] and that it is approved for release.

This document has been approved and signed electronically on the final page by the following:

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REVISION HISTORY

Version No.	Effective Date	Summary of Change(s)
Final 1.0	28 Jun 2023	New document
Final 2.0	01 Sep 2023	Exploratory analysis updated

LIST OF ABBREVIATIONS

Abbreviation/Acronym	Definition/Expansion
ABE	Average bioequivalence
%AUC_{ex}	Percentage of AUC_{inf} obtained by extrapolation beyond t_{last}
ADA	Antidrug antibody
AE	Adverse event
ALDH2	Aldehyde dehydrogenase 2
ALDH2	Gene for aldehyde dehydrogenase 2
AESI	Adverse events of special interest
ATC	Anatomical Therapeutic Chemical
AUC	Area under the curve
AUC_{0-inf}	AUC from time zero extrapolated to infinity
AUC_{0-last}	AUC from time zero to the last quantifiable concentration
AUC_{0-t}	AUC from time zero to a specific time t
AUC_{τ}	AUC over the dosing interval at steady state
B	Baseline
BDRM	Blinded data review meeting
BL	Biostatistician Lead
BLQ	Below the low r limit of quantification
BMI	Body mass ndex
BP	Blood pressure
bpm	Beats per minute
CI	Confidence interval
CL	Clearance
CL/F	Apparent clearance following extravascular (non-intravenous) administration, e.g., clearance following subcutaneous
C_{last}	Last quantifiable concentration at t_{last}
C_{max}	Maximum observed concentration
C_{min}	Minimum observed concentration at steady state
CPMS	Clinical Pharmacology, Modeling, and Simulation
CRF	Case Report Form
CS	Clinically significant
CSP	Clinical Study Protocol

Abbreviation/Acronym	Definition/Expansion
C_{trough}	Concentration at the end of a dosing interval [taken directly before next administration]
CTCAE	Common Terminology Criteria for Adverse Events
CV	Coefficient of variation
DBP	Diastolic blood pressure
DRM	Data Review Meeting
ECG	Electrocardiogram
ENR	Enrolled Analysis Set
EOS	End of study
ET	Early termination
HBsAg	Hepatitis B surface antigen
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
HR	Heart rate
GMR	Geometric mean ratio
IB	Investigator's Brochure
ICF	Informed cons nt form
IMP	Investigational medicinal product
LI	Linearity ind x
LLOQ	Lower limit of quantification
LOCF	Last observation carried forward
LOQ	Limit of quantification
MedDRA	Medical Dictionary for Regulatory Activities
mRNA	Messenger ribonucleic acid
MRT	Mean residence time
NA	Not available
NCS	Not clinically significant
NK	Not known
NR	Not reportable
NS	No sample
PCS	Potentially clinically significant
PD	Pharmacodynamic(s)
PDAS	Pharmacodynamic analysis set
PEth	Phosphatidylethanol

Abbreviation/Acronym	Definition/Expansion
PK	Pharmacokinetic(s)
PKP	Pharmacokinetic population
QTc	corrected QT interval
QTcB	QT corrected using Bazett's formula
QTcF	QT corrected using Fridericia's formula
R_{ac}	Accumulation ratio
SAE	Serious adverse event
SP	Safety population
SAP	Statistical Analysis Plan
SBP	Systolic blood pressure
SD	Standard deviation
SE	Standard error of the mean
SI	Standard international
SOC	System Organ Class
$t_{½}$	Apparent terminal elimination half-life
TEAE	Treatment-emergent adverse event
t_{last}	Time to last quantifiable concentration
t_{max}	Time corresponding to occurrence of C_{max}
V_z/F	Apparent volume of distribution during terminal phase following extravascular dosing
WHO-DD	World Health Organization - Drug Dictionary
λ_z	Terminal elimination rate constant

1 INTRODUCTION

This Statistical Analysis Plan (SAP) describes all planned analyses for the Clinical Study Report (CSR) of Study DCR AUD 102 A Phase 1b, Double-blind, Placebo-controlled, Repeat-dose, Safety, Tolerability, Pharmacokinetic, and Pharmacodynamic Study of DCR-AUD in Healthy Volunteers. This repeat-dose study is being conducted to characterize the safety and tolerability and PK profiles of DCR-AUD when administered monthly, and to determine if a PD effect (resulting from cumulative ALDH2 mRNA knock down) can be observed during Ethanol Interaction Assessments (EIA) in a population of social drinkers after repeat doses of DCR-AUD.

The content of this SAP is based on following study documents:

- Study DCR AUD 102 protocol Version 2.0 17 Jan 2023.
- Electronic Case Report Form (eCRF) Version 13.1.

This SAP will be finalized prior to database lock. Any changes after the finalization of this SAP will be documented in Statistical Method Modification Form.

2 STUDY OBJECTIVES

The objectives of the study are as follows:

2.1 Primary Objective

To evaluate the safety and tolerability of repeat doses of DCR AUD administered to adult HVs

2.2 Secondary Objective

- To characterize the PD symptom profile of repeat doses of DCR-AUD in adult HVs
- To characterize the plasma PD of repeat doses of DCR-AUD
- To characterize the PK of repeat doses of DCR-AUD in adult HVs

2.3 Exploratory Objective(s)

To explore change in alcohol consumption following treatment with DCR-AUD in adult HVs.

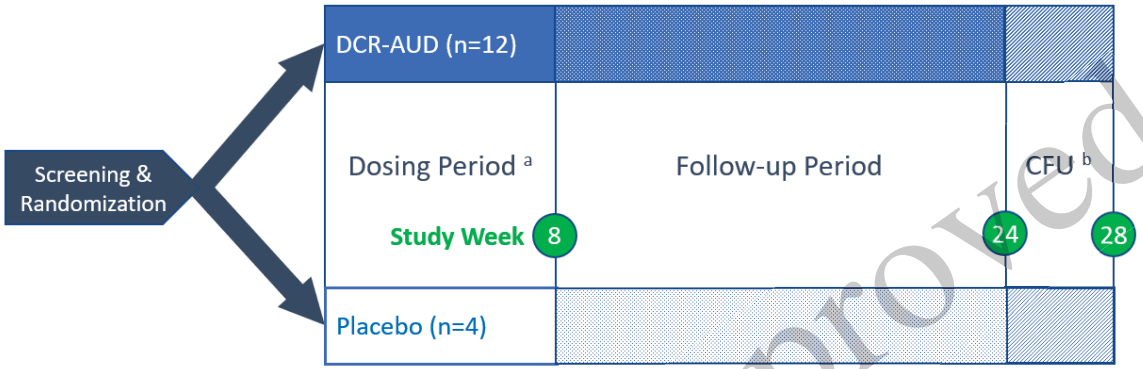
3 INVESTIGATIONAL PLAN

3.1 Overall Study Design and Plan

This is a double-blind, randomized, placebo-controlled study of DCR-AUD to evaluate the safety, tolerability, PK, and PD of repeat doses of DCR-AUD in adult HVs.

Participants will receive 3 injections of study intervention (Day 1, Day 29, and Day 57), and have assessment visits through Week 24. Up to 10 EIAs will be conducted over the 24-week period to characterize the PD of DCR-AUD. For each EIA, participants will consume 4 standard drinks over the course of 80 minutes. Participants will be admitted to the clinic overnight for each EIA. At the discretion of the Investigator, participants who present with increasing positive ethanol reaction symptoms at the Day 169 EIA (flushing, headache, lightheadedness, palpitations, nausea, or vomiting) will be followed for an additional 4 weeks (through Day 197).

Figure 3-1 Study Schematic for DCR AUD-102



a. DCR-AUD (480 mg) or placebo administered on Days 1, 29, and 57
b. 4-Week conditional follow-up (CFU) conducted at the discretion of the Investigator in participants experiencing symptoms at the End-of-Study (Week 24) visit.

3.2 Endpoints and Associated Variables

The endpoints and variables are provided below.

3.2.1 Primary Endpoints

- Incidence and severity of AEs and SAEs
- Changes from baseline in vital signs, 12-lead ECG, clinical laboratory tests, and physical examination findings.

3.2.2 Secondary Endpoints

- Change in the occurrence and/or severity of 6 symptoms related to plasma acetaldehyde accumulation observed during in-clinic EIAs over the course of the study
- Change in plasma PD biomarker assessments during serial EIA
  - acetaldehyde
  - acetate
  - ethanol
- Plasma PK parameters of DCR-AUD

3.2.3 Exploratory Endpoints

- Change in alcohol consumption from baseline using Timeline Follow Back (TLFB)
- Change from baseline in phosphatidylethanol (PEth) levels, reflecting cumulative recent alcohol ingestion.

3.2.4 Safety Variables

- Physical examinations
- Vital signs (Temperature (by skin refraction), pulse rate, respiratory rate, and blood pressure)
- 12-lead electrocardiograms (ECG): Heart rate, PR interval, QRS interval, QT interval and QT interval using Fridericia's correction [QTcF]
- Columbia-Suicide Severity Rating Scale
- Mini-International Neuropsychiatric Interview.
- Clinical laboratory tests (hematology, clinical chemistry, coagulation and routine urinalysis parameters)
- Adverse event (AE) assessments
- Suicidal Ideation and Behavior Risk Monitoring

3.2.5 Pharmacodynamic Variables

DCR-AUD is designed to selectively reduce ALDH2 activity in the liver and the conversion of acetaldehyde to acetic acid after alcohol consumption. The build-up of acetaldehyde causes unpleasant effects after drinking (e.g., flushing, headache, lightheadedness, palpitations, nausea, or

vomiting). As such, the PD activity of DCR-AUD will be assessed during EIAs via these 6 symptoms, and blood biomarkers (ethanol, acetaldehyde, and acetate) PD parameters to be estimated by Clinical Pharmacology, Modeling and Simulation (CPMS) group are provided in Table 3-1.

Table 3-1 Plasma Pharmacodynamic Parameters

Protocol Parameter	WNL Name	Definition
t_{max}	Tmax	Time corresponding to occurrence of C_{max} (For acetaldehyde, acetate, and alcohol)
C_{max}	Cmax	Maximum observed concentration (in the unit of μM and ng/mL) (For acetaldehyde, acetate, and alcohol)
$C_{maxAbove}$	Cmax_Above_B	Maximum observed concentration that is above the baseline (in th unit of μM and ng/mL) (For acetaldehyde)
baseline	Baseline	Response value just prior to treatment administration
AUC_{Above}	AUC_Above_B	Area under the curve that is above the baseline (for acetaldehyde)
AUC_{Below}	AUC_Below_B	Area under the curve that is below the baseline (for acetate)
AUC_{0-4h}	AUCT	Observed partial area under the curve from time 0 to 4 hours (for acetaldehyde, acetate, and alcohol)
Cav	Cav	Average plasma concentration from time zero to 4 hours
PD response change	PD_response_change	Changes in each biomarker level on each EIA day (i.e., D1,14,29,42, 57) compared to the basal level on Day -1
PD response % change	PD_response_%_change	Percent changes in each biomarker level on each EIA day (i.e., D1,14,29,42,57) compared to the basal level on Day -1

3.2.6 Immunogenicity Variables

Immunogenicity testing (anti-drug DCR-AUD antibodies) using designated serum samples from each participant is planned to be conducted.

The ADA samples collected in this study will be stored and analyzed in the future

3.2.7 Pharmacokinetic Variables

Pharmacokinetic concentration data will be obtained at time point(s) described in the protocol version 2.0 as follows:

PK concentrations of DCR-AUD will be determined at the following nominal times: 0 (pre-dose) and at 1, 2, 4, 6, 8, 24, and 72 hours post-dose on days 1, 29, 57 (exception: no 72-hour PK sample is required on Day 57). A single sample will be collected on Days 1, 14, 42, 70, and 168 along with the ADA samples. These single PK concentrations maybe used for deriving the PK parameters, if the concentrations are detectable.
Derivation of PK parameters will be the responsibility of CPMS group, [redacted].

If calculable, the following PK parameters listed in Table 3-2 will be determined for DCR-AUD in plasma following single subcutaneous (SC) dose administration.

Table 3-2 Plasma Pharmacokinetic Parameters After Each Dose Administration of Multiple Dose Study

Parameter	WNL Name	CDISC Name	Definition
C_{max}	Cmax	CMAX	Maximum observed concentration
C_{last}	Clast	CLST	Last measurable concentration
C_{min}	Cmin	CMIN	Minimum observed concentration in a dosing interval after last dose administration
t_{max}	Tmax	TMAX	Time corresponding to occurrence of C_{max}
$t_{½}$	HL_Lambda_z	LAMZHL	Apparent terminal elimination half--life
λ_z	Lambda_z	LAMZ	Terminal elimination rate constant
$AUC_{0\text{-last}}$	AUClast	AUCLST	Observed AUC from time zero to the last quantifiable concentration
$AUC_{0\text{-t}}$	AUCT	AUCINT(0-X)	Observed AUC from time zero to some fixed time t (i.e., AUC_{24} or AUC_{48})
$AUC_{0\text{-inf}}$	AUCINF_obs	AUCIFO	AUC from time zero extrapolated to infinity
$\%AUC_{ex}$	AUC_%Extrap_obs	AUCPEO	Percentage of $AUC_{0\text{-inf}}$ obtained by extrapolation beyond t_{last}

Parameter	WNL Name	CDISC Name	Definition
CL/F	Cl_F_obs	CLFO	Apparent clearance following SC administration
V_z/F	Vz_F_obs	VZFO	Apparent volume of distribution during terminal phase

Source: NCI EVS Terminology Resources website:
http://www.cancer.gov/cancertopics/cancerlibrary/terminologyresources/cdisc.

4 STATISTICAL METHODS

4.1 Data Quality Assurance

All tables, figures, and data listings to be included in the report will be independently checked for consistency, integrity, and in accordance with standard [redacted] procedures.

4.2 General Presentation Considerations

This section is not applicable to PK data.

4.2.1 Treatment

480 mg of DCR-AUD and placebo in each arm.

4.2.2 Study Day

Study days will be numbered relative to the first day of study drug administration.

- If the date of event is before the study drug administration, then:

  Study day = (Date of measurement – Date of study drug administration [i.e. Day 1])

- If the date of event is on or after the study drug administration, then:

  Study day = (Date of measurement – Date of st dy drug administration [i.e. Day 1]) + 1

4.2.3 End of Study

The end of the study is defined as the date of the last visit of the last participant in the study.

4.2.4 Baseline

Baseline is defined as the last non-missing measurement prior to the date and time of the dose of study intervention.

For the exploratory analysis using TLFB, baseline is the mean alcohol level as measured on Day -1.

No imputation will be done for missing baseline value for derivation of change from baseline or summary tables and shift tables.

4.2.5 Controlled, Repeat, Retest, Scheduled and Unscheduled Assessment

Repeat, retest, and unscheduled assessment will not be considered for the calculation of summary statistics and figures, unless assessment qualifies as baseline.

Average of controlled and planned (scheduled) assessment will be considered for the calculation of summary statistics and figures, if more than one controlled/planned assessment will be performed at a specific time point.

4.2.6 Summary and Representation of Data

Continuous data will be summarized in terms of mean, standard deviation (SD), median, minimum, maximum, and number of observations, unless otherwise stated.

Categorical data will be summarized in terms of the number of participants providing data at the relevant time point (n), frequency counts, and percentages.

The minimum and maximum will be reported to the same number of decimal places as the raw data recorded in the database. The mean and median will be reported to one more decimal place than the raw data recorded in the database. The SD will be reported to two more decimal places than the raw data recorded in the database. In general, the maximum number of decimal places reported shall be four for any summary statistics.

Percentages will be presented to one decimal place. Percentages will not be presented for zero counts. Percentages will be calculated using N as the denominator. If sample sizes are small, the data displays will show the percentages, but any textual report will describe frequencies only. Percentage will be presented as whole number if count is 100.

If for any summary table, n is less than three then only n, minimum, and maximum should be presented, and other summary statistics will be left blank.

4.2.7 On-treatment assessment/event

The overall observation period will be divided into three mutually exclusive segments:

1. ***screening period***: from day of participant's informed consent to before date of first administration of study treatment
2. ***dosing period***: from date of first administration of study treatment to *58* days after date of last administration of study treatment (including start and stop date)
3. ***follow-up period***: starting at day *58*+1 after last administration of study treatment.

4.3 Software

All report outputs will be produced using SAS® version 9.4 or later in a secure and validated environment.

The PK analyses will be conducted using Phoenix® WinNonlin (WNL) version 8.3 or later in a secure and validated environment.

All report outputs will be provided to the Sponsor in RTF format.

4.4 Study Participants

4.4.1 Analysis Populations

Enrolled Population (ENR): All participants who sign the ICF.

Randomized Population (RP): All participants who sign the ICF and who are randomized to study intervention.

Safety Population (SP): All participants randomized to study intervention and who receive at least 1 dose of DCR-AUD or placebo. Participants will be analyzed according to the initial dose received.

Pharmacokinetic Population (PKP): All participants randomized to study intervention and who receive at least 1 dose of DCR-AUD and have at least 1 postdose PK assessment.

Pharmacodynamic Population (PP): All participants randomized to study intervention and who

receive at least 1 dose of DCR-AUD or placebo and have at least 1 postdose PD assessment.

A summary table with the number of participants in each of the analysis population will be provided and this table will be displayed by treatment/sequence and overall, for ENR. A listing of participants excluded from analysis populations will also be provided including reason of exclusion for ENR.

4.4.2 Disposition of Participants

A clear accounting of the disposition of all participants who enter the study will be provided from screening (excluding screen failure data) to study completion.

A summary of participant study completion status and reason for study withdrawal will be provided for the ENR. This display will show the number and percentage of participants who withdrew from the study, including primary reasons for study withdrawal.

A by-participant listing of study discontinuation will be presented for the ENR. The listing will include dose date and reasons for study discontinuation.

A randomization listing will be presented and include the following: each participant's randomization number, the treatment to which the participant has been randomized and replacement randomization number (if any) for the RP.

4.4.3 Protocol Deviations

All protocol deviations are predefined in the separat document, Protocol Deviation Assessment Plan.

4.4.3.1 Protocol Deviations with Non-PK Implications

The defined protocol deviations will be collected during the study period by site monitor/clinical team and programming team. All deviations related to study inclusion or exclusion criteria, conduct of the study, participant management or participant assessment, and handling of the participant's rights will be described.

A summary table of important proto ol deviations by study day, and treatment arm will also be provided for RP.

4.4.3.2 Protocol Deviations with PK Implications

Protocol deviations that may potentially impact PK parameter derivations include, but are not limited to:

- SC administration deviations – interruption of administration, etc.
- Missed PK samples that impact estimation of PK parameter(s)
- Concomitant medications not authorized by protocol
- PK samples obtained out of allowance window that may impact the estimation of PK parameter(s)

Protocol deviations (mentioned in Sections 4.4.3.1 and 4.4.3.2) and analysis populations will be reviewed in the blinded Data Review Report (DRR) Meeting to decide inclusion or exclusion of

participant(s) from analyses populations. Decisions regarding the exclusion of participants and/or participant data from analyses will be made prior to database lock and will be documented and approved.

A by-participant- listing of important and not-important protocol deviations will be provided including participant identifier; exclusion from specific analysis sets; and protocol deviation classification, and protocol deviation description and exclusion from specific analysis populations. Protocol Deviations related to COVID-19 will be listed separately.

4.5 Demographics and Baseline Characteristics

Demographic and anthropometric variables (age, sex, ethnicity, race, height, weight, and BMI) will be listed by participant. Demographic characteristics (age, sex, ethnicity, and race) and anthropometric characteristics (height, weight, and BMI) will be summarized by treatment, placebo, and overall, for the SP.

A by-participant listing for substance use will be provided for the SP.

4.6 Medical History

Medical history will be coded using Medical Dictionary for Regulatory Activities (MedDRA®), Version 25.1 and assigned to a System Organ Class (SOC) and Preferred Term (PT).

Medical history data will be summarized by study day, treatment, and overall for the SP and listed by participant including visit, description of the disease/procedure.

4.7 Prior and Concomitant Medication

Prior and Concomitant Medication:

Medications will be considered as prior if the start date of the medication is before the date of first administration of the study drug.

Medications will be considered as concomitant if they are taken at least once in the treatment period starting with the first study administration and ending after the last study drug administration during the study.

Medications starting prior to first administration of study drug and continuing during the study visit will be considered both prior and concomitant medication.

A summary table and by-participant listings of prior and concomitant medications will be provided for the SP.

4.8 Treatment Exposure and Compliance

4.8.1 Treatment Exposure

A by-participant listing of participant exposure to DCR-AUD will be generated. The listing will include dose, date and time, unit, formulation, route, and frequency.

4.8.2 Compliance

Compliance(%) = 100 × Total volume delivered (mL)/Total volume planned (mL)

A by-participant listing of treatment compliance will be provided.

4.9 Analysis Supporting Primary Objective(s)

Not Applicable.

4.10 Analysis Supporting Secondary Objective(s)

Not Applicable.

4.11 Efficacy Evaluation

Not applicable.

4.12 Pharmacokinetic Analysis, Concentration, and Parameter TFLs, and Statistical Analysis of Pharmacokinetic Parameters for Final Analysis

4.12.1 Pharmacokinetic Concentrations

Concentration Listings:

Pharmacokinetic concentration data for DCR-AUD, will be listed by study days, nominal and actual timepoints and participant for the SP. Concentration listings will include nominal PK sampling time, actual sampling times relative to dose administration, deviation from nominal time, and percent deviation from nominal time, and concentrations. Plasma concentrations below the lower limit of quantification (LLOQ) will be presented as below the limit of quantification (BLQ) in the listings and the LLOQ value presented as a footnote. Missing PK samples will be reported as no sample (NS) or not reportable (NR) as appropriate and conside ed excluded from PK analysis.

Concentration Summary Tables:

Source data as reported from the laboratory will be used for calculation of concentration summary statistics. Tabular summaries for concentration-time data will report N (number of participants who received treatment), n (number of participants with non-missing values), and n(BLQ) (the number of participants with BLQ samples).

Concentration for DCR-AUD will be summarized by study days, and nominal timepoint for the PKP. The following descriptive statistics will be presented for plasma concentrations obtained at each nominal time point: N, n, n(BLQ), arithmetic mean, SD, coefficient of variation (CV%), geometric mean, geometric CV% (calculated as: gCV% =SQRT(e^{s^2}-1)*100; where s is the SD of the log-transformed values), median, minimum, and maximum values.

For summary tables, all BLQs will be considered zero, and the number of BLQs and non-BLQs at each scheduled time point will be reported. Summary Statistics will not be calculated if non-BLQ concentrations at a scheduled time point is <3 and will be reported as NC.

The rules followed for calculation and presentation of concentration data with regards to the number of decimal places/significant digits for the listings of participant level concentrations and summary tables of concentration are as follows:

Concentration Listings and Tables	Rounding
Individual concentrations	*n* s.f. as supplied by bioanalytical laboratory
Minimum and Maximum	*n* s.f. at 3
Mean/SD/Median/Geomean	*n* s.f. at 3
CV%/gCV%	*n* s.f. at 3
N/n	Whole number

s.f = significant figures, d.p. = decimal place

Concentration Figures:

For arithmetic mean linear/linear graphs, all BLQ values will be substituted with zero for calculation of arithmetic mean and for log/linear graphs the log transformed arithmetic mean will be displayed (this should not include zero).

For individual linear/linear and log/linear graphs all BLQ values will be substituted as follows:

- BLQs at the beginning of a participant profile (i.e., before the first incidence of a measurable concentration) will be assigned to zero. When using log/linear scale, these timepoints will be considered missing.
- BLQs at the end of a participant profile (i.e., after the last incidence of a measurable concentration) will be set to missing.
- Single BLQs which fall between two measurable concentrations will be set to missing.
- Consecutive BLQs which fall between measurable concentrations will be set to missing. Measurable concentrations after consecutive BLQs will be set to missing.

To visualize participant-level concentrations and the comparison between study days, the descriptive PK graphs listed below will be generated Including LLOQ line in individual and summary plots.

- Figure x.x.x: Individual participant profiles for DCR-AUD Plasma Concentration Time Data by Study Day – (Linear Scale and Semi-Logarithmic Scale) (SP)
- Figure x.x.x : Overlaid individual participant profiles for DCR-AUD Plasma Concentration Time Data by Study Day – (Linear Scale and Semi-Logarithmic Scale) (SP)
- Figure x.x.x : Mean (± SD) DCR-AUD Plasma Concentration Time Data by Study Day – (Linear Scale and Semi-Logarithmic Scale) (PKP)

Figures will be generated in color using unique line style and marker for each plot in the graph. For all PK concentration-time plots, linear scale will be used for x-axis (e.g., do not use an ordinal scale).

4.12.2 Pharmacokinetic Parameters

PK parameters will be provided by CPMS group. PK parameters will be calculated by NCA methods from the concentration-time data using Phoenix® WinNonlin® Version 8.3 or higher following these guidelines:

- Actual time from SC dosing will be used in the calculation of all derived pharmacokinetic parameters.
- There will be no imputation of missing data.
- Handling of BLQ samples for derivation f plasma PK parameters after single dose administration
    - BLQs at the beginning of a participant profile (i.e., before the first incidence of a measurable concentration) will be assigned to zero.
    - BLQs at the end of a participant profile (i.e., after the last incidence of a measurable concentration) will be set to missing.
    - Single BLQs which fall between two measurable concentrations will be set to missing.
    - Consecutive BLQs which fall between measurable concentrations will be set to missing. Measurable concentrations after consecutive BLQs will also be set to missing.
- Handling of BLQ samples for derivation of plasma PK parameters after multiple dose administration
    - BLQs for Day 1 at the beginning of a participant profile (i.e., before the first incidence of a measurable concentration) will be assigned to zero
    - BLQs on subsequent dosing days and not separated by a washout: pre-dose values, BLQs in the absorption phase, and BLQs between evaluable concentrations, will be substituted by LLOQ/2 before the calculation of the PK variables
    - Terminal BLQs (at the end of participant profile) will be set to missing.

Pharmacokinetic parameters will be estimated according to the guidelines presented in Table 4-1.

Table 4-1 Pharmacokinetic Parameter and Estimation

Parameter	Guideline for Derivation
C_{max}, C_{min}, t_{max}, t_{min}, C_{trough}, C_{last},	Obtained directly from the observed concentration-time data
AUC_{last} (or AUC_{0-t})	The AUC from zero time (pre-dose) to the time of last quantifiable concentration will be calculated by a combination of linear and logarithmic trapezoidal methods. Unless specifically requested and justified, the linear up/log down trapezoidal method will be employed. The AUC_{0-t} is the sum of areas up to the time of the last quantifiable sample (no extrapolation will be applied): $AUC_{0-t}=\int_0^t C_{last} * dt$
AUC_{0-x}	The AUC from zero time to the specific time x is the sum of areas up to the specific time x sample (no extrapolation will be applied): $AUC_{0-x}=AUC_{0-x} = \int_0^x Cx * dx$
AUC_{0-tau}	The AUC over the dosing interval will be determined for multiple dose studies using the trapezoidal rule, as stated above. Calculated for days 1, 29 and 57.
AUC_{0-inf}	The area from zero time extrapolated to infinite time will be calculated as follows: $AUC_{0-inf} = AUC_{0-t}+\frac{C_{last}}{\lambda_z}$ where C_{last} is the last observed quantifiable concentration. Calculated for days 1, 29, and 57.
$\%AUC_{ex}$	The percentage of AUC_{0-in} obtained by extrapolation will be calculated as follows: $\%AUC_{ex} = \frac{AUC_{0-inf} - AUC_{0-t}}{AUC_{0-inf}}$ x100 . Unless otherwise determined by PK Scientist's best knowledge and judgment, if the $\%AUC_{ex}$ is greater than 20% the value, $\%AUC_{ex}$, and all dependent parameters (i.e., AUC_{0-inf}, MRT, Vz and CL) will be flagged in listings and excluded from summary tables and statistical analysis of PK parameters. The reason for exclusion will be listed/footnoted in parameter listings.
λz and t½	1. The apparent terminal phase rate-constant (λz) will be estimated by linear regression of concentration versus time data presented in a log-linear scale. 2. Data are primarily monotonically decreasing in magnitude and are representative of the actual decline in the log concentration-time curve. 3. Only those data points that are judged to describe the terminal log-linear decline will be used in the regression. 4. A minimum number of three data points in the terminal phase will be used in calculating λz with the line of regression starting at any post-C_{max} data point (C_{max} should not be part of the regression slope). Unless otherwise determined by PK Scientist's best knowledge and judgment or if instructed by the Sponsor, if the adjusted correlation coefficient (R^2 adjusted) is <0.9, then λz and all the λz dependent

Parameter	Guideline for Derivation
	parameters (i.e. t½, $AUC_{0\text{-inf}}$, CL, MRT, and Vz) will be flagged in listings and excluded accordingly from summary tables and statistical analysis of PK parameters. The reason for exclusion will be listed/footnoted in parameter listings. 5. Unless otherwise determined by PK Scientist's best knowledge and judgment, the interval used to determine λz should be equal or greater than 1.5-fold the estimated t½, and if less than 1.5-fold, λz will be flagged in listings and might be excluded from summary tables and statistical analysis of PK parameters. All the derived parameters (i.e. t½, $AUC_{0\text{-inf}}$, CL, MRT, and Vz) may also be flagged in listings and excluded from statistical analysis of PK parameters. The reason for exclusion will be listed/footnoted in parameter listings. 6. The t½ will be calculated as follows: $t½ = \ln 2/\lambda z = 0.693/\lambda z$ 7. Data points may be dropped from the linear regression if the PK Scientist considers the reported values to be anomalous. Any data points so designated should remain in the listings with a footnote and be identified in the study report with a rationale for exclusion.
CL or CL/F	Apparent clearance (CL/F) following extravascular (e.g. SC) dosing will be calculated as: $CL/F = \frac{Dose}{AUC_{0\text{-}\tau}}/F$ In the case of steady state administration $AUC_{0\text{-}\tau}$ will be the denominator.
V_z/F	Volume of distribution at terminal phase following extravascular (SC) dosing may be calculated from: $V_z/F = \frac{Dos}{\lambda_z \times AUC_{0\text{-}\tau}}/F = (CL/F)/\lambda_z$ Likewise, if derived for steady state administration $AUC_{0\text{-}\tau}$ will be used.
R_{ac}	Accumulation ratio, calculated from comparison of single dose and steady state data: $R_{acAUCx} = \frac{Steady\ state\ AUC_{0\text{-}\tau}}{Single\ dose\ AUC_{0\text{-}\tau}}$ $R_{acCmax} = Steady\ state\ C_{max}/\ Single\ dose\ C_{max}$ Day 1 represents single dose and day 57 represents steady state.

PK Parameters Listings:

PK parameters will be listed by participant for the SP. PK parameters that will be flagged and/or excluded from summary tables and statistical analyses of PK parameters will be flagged and footnoted with the reason for flagging/exclusion.

PK Parameter Summary Tables:

Biostatistics group will consider the derived PK parameters as source data and will use this data without rounding for calculation of PK parameters summary statistics tables.

PK parameters will be summarized by study day with descriptive statistics for the PKP.

Tabular summaries for PK parameters will report N (number of participants who received treatment) and n (number of participants with non-missing values).

Descriptive statistics for calculated PK parameters will include N, n, arithmetic mean, SD, CV%, geometric mean, gCV%, median, minimum, and maximum values. For t_{max}, only N, n, median, minimum, and maximum values will be presented. No descriptive statistics will be determined when fewer than three individual PK parameters are available.

The rules followed for presentation of PK parameters data with regards to the number of decimal places/significant digits for the listings of participant level PK parameters and summary tables of PK parameters are as follows:

PK Parameter Listings and Tables	Rounding
Derived Individual parameters	3 s.f.
Directly Derived Individual parameters (C_{max}, C_{12}, C_{24})	*n* s.f. as supplied by the analytical laboratory but not more than 3 s.f.
Minimum and Maximum	3 s.f.
Mean/SD/Median/Geomean	3 s.f.
CV%/gCV%	3 s.f.
Comparative estimates (e.g. ratios)	3 s.f.
CI and other percentages	2 d.p.
p-values	4 d.p.
N/n	Whole number
Exceptions for PK Tables	
t_{max} individuals and min/max	3 s.f.
t_{max} median only	3 s.f.

s.f = significant figures, d.p. = decimal place

4.12.3 Statistical Analysis of Pharmacokinetic Parameters

We will use a one-way analysis of variance to compare the PK parameters of ALDH2 mutation. If there are 3 or more subjects with ALDH2 mutation, the PK parameters of these subjects as a group will be compared to those without ALDH2 mutation as another group. Otherwise, the PK parameters will be summarized with and without the individual(s) with ALDH2 mutation.
Sample SAS Code:

```
PROC MIXED DATA = DATA1 NOPRINT;
BY PARAMCD;
CLASS MUTATION;
MODEL LN_PK = MUTATION /DDFM = KR;
RUN;
```

WHERE,
PARAMCD :short name of PK parameter

LN_PK; natural log transformed value of PK parameter
MUTATION: Group for the genetic mutation.

4.12.4 Pharmacodynamic Analysis, Concentration, and Parameter TFLs, and Statistical Analysis of Pharmacodynamic Parameters

Pharmacodynamic parameters will be estimated according to the guidelines presented in Table 4-2.

Table 4-2 Pharmacodynamic Parameter and Estimation

Parameter	Guidelines for Derivation
Cmax, tmax,	Obtained directly from the observed concentration-time data
C_{av}	The average concentration from time 0 to time 4 h: AUC_{0-4}/4 h
AUC_{0-4h}-adjusted	The AUC adjusted from zero time to 4 h for Day X: AUC_{0-4h} (Day X) - AUC_{0-4h} (Day -1)
C_{av}-adjusted	The C_{av} adjusted for Day X is time averaged concentration from zero time to 4 h: C_{av} (Day X) - C_{av} (Day -1)
Cmax-adjusted	The Cmax adjusted for Day X is: C_{max} (Day X) - C_{max} (Day -1)
AUC_{0-4h} percent change	Percent change of AUC_{0-4h} on Day X as compared to the basal level (Day -1): ((AUC_{0-4h} (Day X) - AUC_{0-4h} (Day-1)/ day -1)) X 100
C_{av} percent change	Percent change of C_{av} on Day X as compared to the basal level (Day -1): ((C_{av} (Day X) - C_{av} (Day-1)/ day -1)) X 100
Cmax percent change	Percent change of Cmax on Day X as compared to the basal level (Day -1): ((Cmax (Day X) - Cmax (Day-1)/ day -1)) X 100

Individual participant's biomarker (acetaldehyde, acetate, and ethanol) plasma concentration values (baseline unadjusted values only) will be provided by [redacted] Laboratories and [redacted]. Baseline unadjusted and adjusted acetaldehyde, acetate, and ethanol concentration values will be listed by study day, timepoint, ALDH2 mutation, and participant for the PP by [redacted]. Concentration listings will include nominal biomarker sampling time, actual sampling times relative to dose administration, and percentage change from baseline. The corresponding baseline for each timepoint will be taken on Day -1. For the biomarker concentration summary tables, descriptive statistics (N, n, arithmetic

mean, SD, CV%, geometric mean, gCV%, median, IQR (inter quartile range), minimum, and maximum values) will be presented by study day, nominal timepoint, EIA days, and ALDH2 mutation. For time variables only median, T_{min} and T_{max} will be presented. A by participant listing of ALDH2 mutation will be provided.

To visualize the comparison between study days the descriptive biomarker graphs will be generated.

- Figure x.x.x: Individual Participant Profiles for acetaldehyde, acetate, and ethanol, Plasma Concentration Time Data (Unadjusted and Adjusted for Baseline) by study day and EIA day (SP)
- Figure x.x.x: Overlaid Individual Participant Profiles for acetaldehyde, acetate, and ethanol Plasma Concentration Time Data (Unadjusted and Adjusted for Baseline) by study day and EIA day (SP). The profiles for ALDH2 mutation will be plotted with dotted lines.
- Figure x.x.x: Mean (± SD) baseline adjusted acetaldehyde, acetate, and ethanol Plasma Concentration Time Data by study day and EIA day (PP)
- Figure x.x.x: Mean (± SD) baseline adjusted acetaldehyde, acetate, and ethanol Plasma Concentration without ALDH2 Mutant Time Data by study day and EIA day (PP)
- Figure x.x.x: The Mean (± SD) baseline unadjusted acetaldehyde, acetate, and ethanol Plasma Concentration Time profiles by study day and EIA days (PP)
- Figure x.x.x: The Mean (± SD) baseline unadjusted acetaldehyde, acetate, and ethanol Plasma Concentration without ALDH2 Mutant Time profiles by study day and EIA days (PP)
- Figure x.x.x: The mean (± SD) C_{max} (in the units of µM and ng/mL) and $AUC_{0\text{-}4h}$ (in the unit of ng*h/mL) of acetaldehyde, acetate and ethanol following 4 Alcohol Drinks in 60 Minutes and Multiple Dose Administration of DCR AUD in Healthy Adults will be plotted with EIA days by study day (PP)
- Figure x.x.x: The mean (± SD) C_{max} (in the units of µM and ng/mL) and $AUC_{0\text{-}4h}$ (in the unit of ng*h/mL) without ALDH2 Mutant(s) of acetaldehyde, acetate, and ethanol following 4 Alcohol Drinks in 60 Minutes and Multiple Dose Administration of DCR AUD in Healthy Adults will be plotted with EIA days by study day (PP)

For each figure, participants belonging to each category will be shown on the same plot with separate figures for each treatment arm. Participant level figures will use actual time, while mean plots will use planned time, except for pre-dose time point(s), where time 0 will be used rather than actual time.

4.12.5 Pharmacodynamic Parameters

DCR-AUD is designed to selectively reduce ALDH2 levels in the liver and the conversion of acetaldehyde to acetic acid. The build-up of acetaldehyde causes unpleasant effects after drinking (e.g., headache, facial flushing, tachycardia, nausea, vomiting). As such, the PD activity of DCR AUD will be assessed during EIAs using blood biomarkers (alcohol, acetaldehyde, and acetate), assessment of 6 symptoms and their severity induced during EIAs, and objective physiological biomarkers (heart rate and facial skin temperature). Participants' subjective experience of the effects

of alcohol will be assessed. Instructions for the collection and handling of biological samples will be provided by the Sponsor in the Laboratory Manual and the Laboratory Specification document.

PD parameters will be calculated using drug effect model from the biomarker time data using Phoenix® WinNonlin® 8.3 or higher. The biomarker parameters alcohol, acetaldehyde, and acetate unadjusted and adjusted for baseline will be estimated for treatment, nominal point, EIA days, and ALDH2 status. The Phoenix WinNonlin project file including all settings and analysis input file will be transferred to Dicerna when the biomarker PD analyses are completed.

The unadjusted and adjusted biomarker parameters will all be listed, and unadjusted parameters will be summarized by time point and treatment. Descriptive statistics (number, arithmetic mean, SD, CV%, geometric mean, gCV%, minimum, median, and maximum) will be presented by nominal points, treatment, ALDH2 status, and EIA days for absolute, and percentage change from the biomarker baseline, where appropriate. For time variables Tmin and Tmax, only median will be presented.

One way ANOVA model will be used to compare the unadjusted Biomarker parameters for DCR-AUD and Placebo for PP.

To visualize the comparison between treatment and placebo following alcohol consumption the following descriptive PD parameter graphs will be generated:

The mean (± SD) Cmax and AUC0-4h of acetaldehyde, acetate, and ethanol will be plotted with EIA days . Two mean Cmax figures will be prepared: one in µM and another in ng/mL units.

4.12.1.1 Ethanol Interaction Assessments

EIAs will include an active assessment of the six key symptoms (flushing, headache, palpitations, lightheadedness, nausea, and vomiting) that DCR-AUD may induce, in order to determine what dose of DCR-AUD gives the proper constellation of these symptoms.

These symptoms will be collected by active questioning of each participant at different time points during each EIA i.e. before alcohol administration, at 0 minutes, 15minutes, 30 minutes, 45 minutes, 60 minutes, 90minutes, 120 minutes and 150 minutes after study drug administration. Should an EIA be missed, due to COVID-19 or other circumstances, the missed EIA may be conducted at the next scheduled visit or at an unscheduled visit at the discretion of the Investigator.

The following symptom scoring framework would be described as an arbitrary point system, where:

Symptom	No Symptom	Mild symptom	Moderate symptom	Severe symptom
Score	0	1	2	3

Each participant at each timepoint in an EIA after alcohol administration begins will be given a composite score for that timepoint as sum of all six symptom scores.

Baseline for EIA is defined as last non-missing value prior to alcohol administration.

Descriptive statistics of EIA composite score (n, mean, median,Q1 (25 percentile), Q3 (75 percentile), minimum and maximum) for absolute values and changes from baseline will be presented by, treatment, placebo, visit and time point.

Descriptive statistics of Peak EIA composite score (n, mean, median, Q1, Q3, minimum and maximum) for absolute values and changes from baseline will be presented by, treatment, placebo, and visit (Days).

Descriptive statistics of Peak EIA score in a Day (Column U) (n, mean, median, Q1, Q3, minimum and maximum) for absolute values and changes from baseline will be presented by, treatment, placebo, and visit (Days).

Peak EIA composite score is defined as maximum composite score at each visit.

To visualize participant-level composite score and the comparison between treatment the EIA graphs listed below will be generated.

- Figure xx.1: Combined Individual DCR-AUD and placebo EIA composite score-Time Profiles (Linear Scale) by Treatment, (Safety Population)
- Figure xx.1: Combined Individual DCR-AUD and placebo Peak EIA composite score-Visit (Days). Profiles (Linear Scale) by Treatment, (Safety Population)
- Figure xx.1: Combined Individual DCR-AUD and placebo Peak EIA score in a Day (Column U)-Visit (Days). Profiles (Linear Scale) by Treatment, (Safety Population)

Serial EIAs will be performed in designated participants to assess the indirect PD effects of ALDH2 reduction (acetaldehyde increase), including plasma acetaldehyde, acetate, and ethanol levels, induced symptoms, heart rate, facial skin temperature, and subjective feelings of alcohol intoxication or intolerance. Adverse events, vital signs, and ECG will also be monitored and recorded for safety.

To be clear, of interest would be 2 things in addition to plots above:

o At each EIA, change in peak symptom score from baseline after alcohol administration from pre-administration score on that day

o For each EIA change in the peak symptom score on that test day after alcohol administration from the peak score change on day –1 (i.e. On day of EIA challenge before IMP was administered)

(It is expected that most participants would have Day –1 pre-EIA challenge composite score of zero (0), i.e. Reporting none of 6 active surveillance symptoms before IMP and before any alcohol was administered on day –1. However, to the extent that some or few patients might have some symptoms, the most informative change metric that would reflect what the participant experiences is the change in peak composite score at any given EIA after dosing from that pre-IMP and pre-alcohol, i.e. Baseline score at day –1.)

4.12.1.2 PD Biomarkers for EIA

4.12.1.2.1 EIA Blood Biomarkers

Blood biomarkers to be assessed include measurement of acetaldehyde, acetate, and ethanol. A by-participant listing of EIA blood biomarkers will be presented in SP. A summary table of Tmax, Cmax, and AUC0-2.5h of blood biomarkers will be presented by biomarker parameter, visit, time point, EIA days, treatment and placebo in PD population. The same PK parameter analysis method described in Section 4.10 will be applied to the calculations of these biomarker parameters.

The mean (± SD) plasma concentration – time profiles of these biomarkers will be plotted by treatment and EIA days.

The mean (± SD) Cmax and AUC0-4.0h of acetaldehyde, acetate, and ethanol will be plotted with EIA days by treatment.

4.12.1.2.2 EIA Physiological Responses

Quantitative assessment of 6 symptom responses during EIAs:

6 symptom variables include flushing, headache, lightheadedness, palpitations, nausea and vomiting assessed at regular intervals during the EIAs and assessed semi-quantitatively (i.e. mild, moderate, or severe)

Descriptive statistics of 6 symptom EIA assessment (n, mean, median, Q1, Q3, minimum and maximum) for Total Scores, Highest Post Dose Score, Delta 1: Peak post-dose score for a given visit's test minus the score at the pre-alcohol administration time on that day, Delta 2: Peak post alcohol administration score on the day of the test, minus the peak post-alcohol administration score for the same participant on day -1, Delta 3: The highest score attained by that participant in Delta 1 over all 6 tests after DCR-AUD was administered will be presented by treatment, placebo, and visit.

4.12.1.2.3 Relationship of acetaldehyde Cmax and EIA symptom score by EIA days

Mean (±SD) and individual EIA days, Acetaldehyde Cmax (μM) data, and EIA symptom score will be plotted on the x-axis, left y-axis, and right y axis, respectively. The acetaldehyde Cmax (μM) and EIA symptom score profiles should be plotted with different line types and symbols and distinguishable. .

4.13 Safety Evaluation

All safety summaries and analyses will b based upon the SP. All safety and tolerability parameters (AEs, laboratory data [hematology, coagulation, clinical chemistry, routine urinalysis, complement panel, and other screen test parameters], vital signs, physical exam findings, Alcohol Consumption via Timeline Follow Back, Columbia-Suicide Severity Rating Scale, Mini-International Neuropsychiatric Interview, and ECG parameters will be evaluated as following.

4.13.1 Adverse Events

All outputs for AEs/treatment-emergent adverse events (TEAEs) will be based on the SP unless specified separately in TLF shells. Describe the AE dictionary including version that is to be used to classify the AEs.

All AE summaries should provide the number and percentages of participants reporting at least one AE and the total number of events reported.

Summaries of AEs will include the following:

- Incidence of AEs - Overview (by treatment and overall)
- Incidence of TEAEs (by treatment and overall, SOC, and PT)
- Incidence of TEAEs by maximum relationship (by treatment and overall, SOC, and PT)

- Incidence of TEAEs by maximum severity (mild/moderate/severe, by treatment and overall, SOC, and PT)

Summary tables will contain counts of participants, percentages of participants in parentheses, and the number of events where applicable. A participant who has multiple events in the same SOC and PT will be counted only once in the participant counts, but all events will be included.

All Adverse Events (AEs)

All AEs will be listed including pretreatment AEs.

Treatment-emergent Adverse Event

A TEAE will be defined as any AE that emerges during treatment (i.e., AE which started after study drug administration or pre-existed that worsened in severity after study drug administration) and those will be analyzed for the purpose of safety analysis.

TEAEs will be summarized by SOC and PT, including the number and percentage of participants experiencing events, separately.

Severity

TEAEs will be summarized by SOC, PT, and severity, including the number and percentage of participants experiencing events. If a participant reports the same TEAE more than once within that SOC and PT, the TEAE with the highest severity will be used in the corresponding severity summaries.

The summaries including severity will be reported by Common Terminology Criteria for Adverse Events (CTCAE) grade presented as below.

- Grade 1: Mild;
- Grade 2: Moderate;.
- Grade 3: Severe or medically significant but not immediately life-threatening;
- Grade 4: Life-threatening consequences;
- Grade 5: Death related to AE.

participants who experience the same event multiple times will be included in the most severe category. Events with missing intensity will be considered as 'Grade 3' events for summary purposes but recorded as missing in the listings.

.

Relationship (Causality)

TEAEs will be summarized by SOC, PT, and causality, including the number and percentage of participants experiencing events. Relationship to study drug will be tabulated respectively. If a participant reports the same TEAE more than once within that SOC and PT, the TEAE with the worst-case relationship to study drug will be in summaries including relationship to study treatment, the following relationships will be summarized: 'Not related', 'Possibly Related', 'Probably Related' and 'Definitely Related'. Participants who experience the same event multiple times will be included in the most related category. Events with missing relationship will be considered as 'Probably Related' to the last given study drug for summary purposes but recorded as missing in the listings.

Adverse Events of Special Interest (AESI)

An Injection Site Reaction (ISR) is characterized by an intense adverse reaction (usually immunologic) developing at the site of an injection after 4 or more hours post-injection. Subcutaneous administration of the study intervention may cause a specific local reaction originating around the injection site, such as erythema, itching, discomfort, and pain, and could include more severe manifestations such as ulceration or necrosis.

Potential ISRs will be evaluated and recorded as follows:

Individual signs or symptoms at the injection site with an onset of less than 4 hours from the time of study intervention administration will be recorded as individual AEs (bruising, itching, transient erythema, swelling, etc.) and not as ISRs.

Signs or symptoms at the injection site with a time to onset of 4 or more hours post-injection will be recorded as an ISR if any of the CTCAE criteria for ISR detailed below are met. Signs or symptoms at the injection site that occur ⩾ 4 hours post-injection but are not specified in Table 7 should be recorded as AEs.

- Grade 1: Tenderness with or without associated symptoms (e.g., warmth, erythema, itching).
- Grade 2: Pain, lipodystrophy; edema; phlebitis.
- Grade 3: Ulceration or necrosis; severe tissue damage; operative intervention indicated.
- Grade 4: Life-threatening consequences; urgent intervention indicated.
- Grade 5: Death .

AESI will be summarized by SOC and PT, including the number and percentage of participants experiencing events. Listing of AESI will be provided.

4.13.2 Deaths, Serious Adverse Events, and Other Significant Adverse Events

Describe the listings that are to be provided. These may include the following listings:

- A by-participant listing of all deaths that occurred during the study
- A by-participant listing of all SAEs
- A by-participant listing of all AES leading to discontinuation of study treatment
- A by-participant listing of all other significant AEs

Listings should follow the format described for AEs in Section 4.13.1 if appropriate.

4.13.3 Clinical Laboratory Evaluation

Clinical laboratory test results of hematology, biochemistry, urinalysis, urinary drug screening, coagulation and serology will be provided by participant. A list of current reference ranges of laboratory assessments is included in Section 6.3. Since laboratory ranges can be participant to changes over time the reference ranges presented in Section 6.3 might differ from the ones actually used and presented on SDTM. For analysis purposes only the ranges present on the SDTM will be used.

All TLFs will display only the standard international (SI) units after conversion by means of standard conversion factors.

Quantitative clinical laboratory variables, ie, hematology, biochemistry, and urinalysis will be summarized using descriptive statistics (n, mean, SD, minimum, maximum and median) by treatment arm and time-point. Additionally, a within-participant change will be calculated as the post-baseline measurement minus the baseline measurement and summarized in the same way.

Baseline definition will be defined in section 4.2.4.

Any quantitative laboratory parameters that are given as '<xx' or '>xx' in the database will be imputed with the absolute value of the number without the sign (e.g., <2.2 will be imputed as 2.2) for the calculation of the changes from baseline and for the descriptive statistics. In the listings, no imputations will be performed, and all data will be displayed as recorded in the database.

Each laboratory result will be classified as low (L), normal (N), or high (H) at each time point according to the laboratory supplied reference ranges. For hematology and biochemistry, shift tables will be presented showing the number and percentage of participants with shifts from baseline to each postdose time point. Tabulations will be presented by treatment arm.

Measurements obtained at Screening and EOS will not be included in the shift tables.

Measurements obtained prior to dosing in each period will be included in the tabulations for the treatment received in that specific treatment period.

Frequency tabulations of qualitative clinical laboratory variables (urinalysis) will be presented by treatment and time-point.

All laboratory data will be displayed in listings

Laboratory abnormalities that are considered clinically significant (CS) are recorded in the database as AEs. Therefore, no tabulation of laboratory values meeting any CS criteria (except liver chemistry) will be presented as all relevant information will be presented in the AE summaries.

Results of pregnancy tests (females only), serology, drugs of abuse and alcohol tests will be listed only.

4.13.4 Vital Signs,

Temperature (by skin refraction), pulse rate, respiratory rate, and blood pressure will be assessed.

Blood pressure and pulse measurements will be assessed in the seated position with a completely automated device. Heart rate will be measured using telemetry during EIAs. Manual techniques will be used only if an automated device is not available. Blood pressure and pulse measurements should be preceded by at least 5 minutes of rest for the participant in a quiet setting without distractions (e.g., television, cell phones).

Temperature will be obtained in degrees Celsius (°C), pulse rate will be counted for a full minute and recorded in beats per minute, and respirations will be counted for a full minute and recorded in breaths per minute.

Vital signs data will be listed by participant including changes from baseline. Vital signs will be summarized in tabular format to include descriptive statistics (n, mean, SD, median, minimum, maximum) for absolute values and changes from baseline will be presented by treatment, and placebo and time-point.

4.13.5 ECG

Standard safety 12-lead ECGs will be performed as shown in the Schedule of Assessments.

The following ECG parameters will be recorded:

- RR-interval (msec).
- QRS-interval (msec)
- PR-interval (msec)
- QT-interval (msec)
- QTc-interval (msec)
- QT-interval corrected using the Fridericia correction formula (QTcF) (msec)
- Heart rate (HR) (beats per minute [bpm])

The ECG will be evaluated by the Investigator as 'Normal', 'Abnormal, NCS' or 'Abnormal, CS'.

All ECG parameters will be listed by participant including changes from baseline.

Baseline is defined in section 4.2.4.

Descriptive statistics for absolute values and changes from baseline will be presented by treatment.

Measurements obtained at Screening and EOS will not be included in the shift tables.

Measurements obtained prior to dosing in each period will be included in the tabulations for the treatment received in that specific treatment period.

The listing of ECG abnormality will be presented separately.

4.13.6 Physical Examination

Physical examinations will include, at a minimum, assessments of the Cardiovascular, Respiratory, Gastrointestinal, Neurological, and Skin systems. Height will also be measured and recorded at Day 1 and weight will be measured and recorded at every visit.

- Investigators should pay special attention to clinical signs related to previous serious illnesses or AEs.
- All physical examinations should include inspection of the injection site.
- Abnormal physical examination findings will be listed.

4.13.7 Other Analysis

4.13.7.1 Columbia-Suicide Severity Rating Scale

The C-SSRS is a suicidal ideation rating scale created by researchers at Columbia University. It rates an individual's degree of suicidal ideation on a scale, ranging from "wish to be dead" to "active suicidal ideation with specific plan and intent."

The scale identifies behaviors that may be indicative of an individual's intent to commit suicide. The C-SSRS is used extensively across primary care, clinical practice, surveillance, research, and institutional settings and is part of a national and international public health initiative involving the assessment of suicidal ideation and behavior. The C-SSRS requires no mental health training to administer it. The C SSRS will be administered by qualified, trained raters.

The Baseline version will be administered at Screening and at subsequent visits the "C-SSRS Since Last Visit" version will be administered.

C-SSRS and Domain wise scores will be summarized by treatment arm and visit. C-SSRS will be listed by participant.

4.13.7.2 Exploratory Analyses

The descriptive statistics of participant's alcohol consumption measured by TLFB will be present for each arm and study days. Each of the drinks will be multiplied by 14g to achieve the alcohol amount. [3]. Change of baseline from both day -1 and screening visit will be presented for each arm. The mean difference and its 95% CI will be presented for the change from baseline of alcohol consumption for each assessment day. Similar analysis will also be performed for total alcohol consumed from baseline.

For PEth descriptive statistics will be present for assessment days. The mean difference and its 95% CI will be presented for the change from baseline of PEth levels for each assessment day.

By participant listings will be present for the exploratory analyses for SP.

4.13.8 Daylight Saving Time (DST):

Not applicable.

4.13.9 Safety Review Committee

A Safety Review Committee (SRC) will conduct periodic reviews and will review all cumulative safety, tolerability, and available PD data on participants, approximately every month or every 3 weeks during treatment and post dose follow-up. Participant safety will be continuously monitored by the SRC by ongoing review of AEs, laboratory results, and other protocol-specified assessments, to allow safety signal detection throughout the study.

4.14 Cardio Dynamic Analyses

Not applicable.

4.15 Biomarkers

4.16 Adjustments for Covariates

Not applicable

4.17 Handling of Dropouts or Missing Data

Not applicable.

4.18 Subgroup Analysis

Not Applicable

4.19 Planned Interim Analyses

Not Applicable.

4.20 Determination of Sample Size

No formal sample size estimations were performed. The sample size of 16 participants (12 active and 4 placebo) was considered sufficient to provide an initial assessment of the safety profile of DCR-AUD in HVs, and adequate for the purpose of describing PK/PD data in HVs.

The sample size is based on clinical rather than statistical considerations.

4.21 Changes in the Conduct of the Study or Planned Analysis

Not Applicable.

5 REFERENCES

[1] SAS® Version 9.4 of the SAS System for Personal Computers. Copyright © 2002-2003. SAS Institute Inc. SAS and all other SAS Institute Inc. product or service names are registered trademarks or trademarks of SAS Institute Inc., Cary, NC, USA.

[2] Phoenix®WinNonlin® Software Version 8.3. https://www.certara.com

[3] What Is A Standard Drink? | National Institute on Alcohol Abuse and Alcoholism (NIAAA) (nih.gov)

6 APPENDICES

6.1 Schedule of Assessments

[redacted]

Table 6-1 Schedule of Activities – Screening, Dosing, EOS, and CFU Visits (see Table 6-2 for non-dosing visits)

	Screen	Dosing Visits													EOS/ET [a]		CFU [b]
Study Week		—				4				8					24		28
Study Day	−28 to −2	−1	1		2	4	28	29		30	32	56	57		58	168	169	197
Window (days) [c]		–	–		–	–	–	±2		–	–	–	±2		–	–	±7	±7
Procedure/Assessment			Pre	Post				Pre	Post				Pre	Post				
Informed consent	X																	
Inclusion/exclusion criteria	X	X																
Demographic characteristics	X																	
General medical history	X																	
Medication history	X																	
Psychological history	X																	
Urine drug testing [d]	X																	
Screening laboratory testing [e]	X																	
ALDH2 genotyping [f]		X																
MINI Screen	X																	
C-SSRS [g]	X	X					X					X				X		
Alcohol TLFB [h]	X	X					X					X				X		X

[redacted]

	Screen	Dosing Visits													EOS/ET [a]		CFU [b]
Study Week		—				4				8					24		28
Study Day	−28 to −2	−1	1		2	4	28	29		30	32	56	57	58	168	169	197
Window (days) [c]		–	–		–	–	–	±2		–	–	–	±2	–	–	±7	±7
Procedure/Assessment			Pre	Post				Pre	Post				Pre	Post			
Pregnancy test [i]	X	X					X					X			X		X
SARS-CoV-2 test [j]		X					X					X			X		
Drug/alcohol screen [k]		X					X					X			X		
Clinic site admission [l]		X					X					X			X		
Clinic site discharge [m]					X					X				X		X	
EIA [n]		X					X					X			X		
Randomize			X														
Administer study intervention			X					X					X				
12-lead ECG [o]	X		X	X				X	X				X	X		X	
Vital signs	X [p]		X	X [q]				X	X [q]				X	X [q]		X	
Physical examination [r]	X	X					X					X			X		
Blood sample for PEth [s]		X										X			X		

[redacted]

	Screen	Dosing Visits													EOS/ET [a]		CFU [b]
Study Week		—				4				8					24		28
Study Day	−28 to −2	−1	1		2	4	28	29		30	32	56	57	58	168	169	197
Window (days) [c]		–	–		–	–	–	±2		–	–	–	±2	–	–	±7	±7
Procedure/Assessment			Pre	Post				Pre	Post				Pre	Post			
Hematology, chemistry, UA [t]		X					X					X			X		
Coagulation panel [u]		X					X					X			X		
Complement panel [v]			X	X	X								X	X			
Blood sample for ADA [w]			X												X		
Blood sample for PK [x]			X	X	X	X		X	X	X	X		X	X	X		
Alcohol use symptom diary [y]		X			X		X			X		X			X		X
Record AEs & SAEs [z]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Record concomitant meds		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Abbreviations: ADA=antidrug antibody; AE=adverse event; *ALDH2*=aldehyde dehydrogenase 2 gene; CBC=complete blood count; CFU=conditional follow-up visit; C-SSRS=Columbia-Suicide Severity Rating Scale; ECG=electrocardiogram; EIA=ethanol interaction assessment; EOS=end of study; ET=early termination; FSH=follicle-stimulating hormone; HbA1c=hemoglobin A1c; ICF=informed consent form; MINI=Mini-International Neuropsychiatric Interview; PEth=phosphatidylethanol; PK=pharmacokinetic; RBC=red blood cell; SAE=serious adverse event; SARS-CoV-2=severe acute respiratory syndrome coronavirus 2; SIB=suicidal ideation or behavior; TLFB=Timeline Follow Back; UA=urinalysis

[a] At the time of discontinuation for the study, an early termination (ET) visit should be conducted, if possible.

[b] Participants with significant symptoms at the Day 168 EIA will be followed for an additional 4 weeks at the discretion of the Investigator.

[c] Visits without a specified window are to be conducted relative to the associated scheduled visit. For example, Day 28 will always be the day prior to the Day 29 visit, regardless of where Day 29 falls within the ± 2-day visit window

[d] Screening tests positive for cannabis are not exclusionary.

[e] To include hematology (CBC with differential and RBC indices), clinical chemistry, coagulation panel, urinalysis, viral serology, HbA_{1c}, and FSH (as indicated). See protocol for a complete list of parameters.

[f] Baseline genetic testing for *ALDH2* mutations. Participation is optional; participants who do not wish to undergo genotyping may still participate in the study.

[g] The Baseline version will be administered at Screening and at subsequent visits the "C-SSRS Since Last Visi " version will be administered. Participants who exhibit signs of Suicidal Ideation or Behavior (SIB) should undergo a risk assessment. All factors contributing to SIB should be evaluated and consideration should be given to discontinuation of study intervention.

[h] TLFB will be completed for the 2-week period that precedes each study visit, including Screening.

[i] Pregnancy testing required only in female participants. If a urine pregnancy test is positive, confirm with serum pregnancy test. Local laboratory may be used. Female participants must have a negative pregnancy test prior to overnight admission.

[j] Testing to be performed at the site upon admission. Participants with a positive SARS-CoV-2 tes will not be admitted to clinic and will not receive study intervention or undergo EIA. Other assessments not requiring clinic admission (i.e., safety assessments) will be perf rmed. Testing will be performed per site standard processes.

[k] Study participants are to refrain from drinking alcohol and using cannabis for 24 hours prior to each EIA. Participants with a positive urine-drug or breath-alcohol test will not be admitted to clinic and will not undergo EIA. Participants with a positive urine drug test on Day −1 will be excluded from the study.

[l] Participants must be fasting for at least 3 hours prior to admission to the clinic.

[m] Participants may be discharged from clinic following collection of the 24-hour postdose PK sample. Participants will return to clinic for collection of PK samples at 72 hours postdose on Days 4 and 32.

[n] EIA will be conducted on the first day of the visit once ll other ass ssments fo that day have been completed. A total of 10 EIAs will be conducted. The timing of assessments and ethanol administration are detailed in protocol Table 6-3

[o] On dosing days, ECGs will be conducted approximately 30 minutes predose and 15-to-30 minutes postdose. If multiple assessments are due, the order of assessment should be ECG, vitals, PK, and then other assessments; with PK sample collection occurring at the nominal time. At Screening and EOS, one ECG will be performed. Screening ECGs may be repeated one time for determination of eligibility.

[p] Blood pressure, if out of range at Screening, may be repeated one time for determination of eligibility.

[q] Blood pressure and pulse rate to be recorded 15 (±5) minutes postdose.

[r] Height will be measured and recorded at Screening. Weight will be measured and recorded at every visit.

[s] Sample to be collected prior to ethanol administration.

[t] Hematology to include complete blood count with differential and RBC indices. See protocol for a complete list of parameters.

[u] See protocol for a complete list of parameters.

[v] Blood samples for complement testing to be collected predose and 2, 8, and 24 hours postdose on Day 1 and Day 57.

[w] Blood sample for ADA testing to be drawn at same time as predose PK sample on Day 1.

[x] Plasma samples for PK analysis to be collected predose and at 1, 2, 4, 6, 8, 24, and 72 hours postdose (exception: no 72-hour PK sample is required at Day 57). A single sample will be collected on Day 168. If multiple assessments are due, the order of testing should be ECG, vitals, PK, and then other assessments, with the PK sampling performed preferably at the nominal time point. A ±15-minute window will be allowed for collections at 1, 2, 4, 6, and 8 hours postdose. A ±30-minute window will be allowed for collection at 24 hours postdose. A ±60-minute window will be allowed for collection at 72 hours postdose.

[y] Participants to record any symptoms associated with use of alcohol outside of in-clinic EIAs. Diary to be issued at time of discharge from clinic and collected and reviewed upon return to clinic.

[z] AEs and SAEs will be recorded from time ICF is signed. SAEs will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up.

Table 6-2: Schedule of Activities – Non-dosing Visits (see Table 6-1 for Screening, Dosing, and EOS Visits)

Week	2		6		10		12		16		20	
Study Day	14	15	42	43	70	71	84	85	112	113	140	141
Visit Window (days) [a]	–	±2	–	±2	–	±3	–	±5	–	±7	–	±7
Procedure/Assessment												
Drug/alcohol screen [b c]	X		X		X		X		X		X	
Pregnancy test [d]	X		X		X		X		X		X	
SARS-CoV-2 test [e c]	X		X		X		X		X		X	
Clinical site admission [f]	X		X		X		X		X		X	
Physical examination [g]	X		X		X		X		X		X	
C-SSRS [h]							X					
Hematology, chemistry, UA [i j]							X					
Coagulation panel [j]							X					
Blood sample for ADA [k]	X		X		X							
Blood sample for PK [k]	X		X		X							
Blood sample for PEth [k]									X			
EIA [l]	X		X		X		X		X		X	
Alcohol TLFB [m]	X		X		X		X		X		X	
Alcohol use symptom diary [n]	X	X	X	X	X	X	X	X	X	X	X	X
Record AEs and SAEs [o]	X	X	X	X	X	X	X	X	X	X	X	X

[redacted]

Week	2		6		10		12		16		20	
Study Day	14	15	42	43	70	71	84	85	112	113	140	141
Visit Window (days) [a]	–	±2	–	±2	–	±3	–	±5	–	±7	–	±7
Procedure/Assessment												
Record concomitant meds	X	X	X	X	X	X	X	X	X	X	X	X
Clinical site discharge [p]		X		X		X		X		X		X

Abbreviations: ADA=antidrug antibody; AE=adverse event; C-SSRS=Columbia-Suicide Severity Rating Scal ; EIA=ethanol interaction assessment; PEth=phosphatidylethanol; PK=pharmacokinetics; SAE=serious adverse event; SARS-CoV-2=severe acute respiratory syndrome coronavirus 2; SIB=suicidal ideation or behavior; TLFB=Timeline Follow Back; UA=urinalysis

[a] Visits without a specified window are to be conducted relative to the associated schedul d visit. For example, Day 14 will always be the day prior to the Day 15 visit, regardless of where Day 15 falls within the ± 2-day visit window.

[b] Study participants are to refrain from drinking alcohol and using cannabis for 24 hours prior to each EIA. Participants with a positive urine-drug or breath-alcohol test will not be admitted to clinic and will not undergo EIA. Other assessments not requiring clinic admission (i.e., safety assessments) should be performed.

[c] Other assessments not requiring clinic admission (i.e., safety sessments) should be performed.

[d] Pregnancy testing required only in female participants. If a urine pregnancy test is positive, confirm with serum pregnancy test. Local laboratory may be used. Female participants must have a negative pregnancy test prio to overnight admission.

[e] Participants with a positive SARS-CoV-2 test will not be admit ed to clinic and will not undergo EIA. Testing will be performed per site standard processes.

[f] Participants must be fasting for at least 3 hours prior to admission to the clinic.

[g] Weight will be measured and recorded at each visit.

[h] The "C-SSRS Since Last Visit" version will be administered. Participants who exhibit signs of SIB should undergo a risk assessment.

[i] Hematology to include complete blood count.

[j] See Section 10.2 for complete list of testing parameters.

[k] Sample to be collected prior to ethanol administration for EIA.

[l] EIA will be conducted once all other assessments for that day have been completed. The timing of assessments and ethanol administration are detailed in protocol.

[m] TLFB will be completed for the 2-week period that precedes each study visit.

[n] Participants to record any symptoms associated with use of alcohol outside of in-clinic EIAs. Diary to be issued at time of discharge from clinic and collected and reviewed upon return to clinic.
[o] AEs and SAEs will be recorded from time ICF is signed. SAEs will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up.
[p] Participants will be discharged in the morning when the PI deems it medically appropriate to do so.

Table 6-3: Schedule of Activities - 4-Hour Ethanol Interaction Assessments

	Pre-EIA		EIA Test Period										
Time (minutes)	**-50**	**-20**	**0** [a]	**20**	**30**	**40**	**60**	**90**	**120**	**150**	**180**	**210**	**240**
Window (minutes)			-	±5	±5	±5	±10	±10	±10	±10	±10	±10	±10
Procedure:													
Standard meal [b]	X												
Venous catheter placement [c]		X											
12-lead ECG [d]			X				X						X
Vital signs [d e]			X	X		X	X	X	X		X	X	X
Plasma biomarker sample [d f]			X		X		X	X	X		X		X
Questionnaire of 6 EIA symptoms [d g]			X		X		X [d]		X		X		
Ethanol consumption [h]			X	X		X	X						
EIA AEs [i]			X	X		X	X	X	X	X	X	X	X

Abbreviations: AE=adverse event; ECG=electrocardiogram; EIA=ethanol interaction assessment; PK=pharmacokinetics

a "Time 0" is immediately before the first sip of ethanol is consumed. All Time 0 assessments must be performed prior to initiation of alcohol intake.

b Participants will arrive at the site after a minimum 3-hour fast, then will be provided a standardized meal before receiving the first drink. Participants will be given 30 minutes to consume the meal.

c Catheter placement may be performed earlier in the day if preferred, but participants must be given at least a 20-minute rest period following placement of the venous access catheter prior to recording predose vital signs and ECG. For EIAs conducted prior to a dosing day, the venous catheter will be left in place for PK sample collections.

d If multiple assessments are due at the same timepoint, the order of assessments should be ECG, vitals, blood draw, then any other assessments. The 60-minute symptom assessment should be conducted before the start of the 4th drink.

e To include pulse rate and blood pressure.

f Blood samples will be collected via venous access device. To include acetaldehyde, acetate, and ethanol.

g Participants will be questioned by site staff to assess the 6 symptoms (flushing, headache, lightheadedness, palpitations, nausea, and vomiting) associated with increased blood acetaldehyde levels.

h Ethanol will be consumed in 4 aliquots over an 80-minute period (20 minutes for each aliquot). Time windows do not apply to ethanol consumption. The ethanol will be mixed in a liquid that has no other alcohol, no caffeine, and is low in sugar. The dose of ethanol will be 0.8 g/kg (to a maximum of 56 g) for men and 0.68 g/kg (to a maximum of 48 g) for women. See protocol for ethanol administration stopping rules.

i AEs associated with administration of ethanol will include events spontaneously reported by participants beginning with the first sip of ethanol (symptoms elicited under direct questioning [footnote g] are not considered AEs).

6.2 Imputation Rules for Partial Dates

Imputed dates and time will NOT be presented in the listings.

Table 6-4 and Table 6-5 present algorithm for imputing partial dates for TEAE and prior/concomitant medication respectively.

Table 6-4 Algorithm for Treatment-Emergent Adverse Events:

Start/Increase Severity Date	Stop Date	Action
Known	Known	Considered as a treatment-emergent adverse event (TEAE) if start date on or after the date of the first dose of investigational product (IP)
	Partial	Considered as a TEAE if start date on or after the date of the first dose of IP. The last day of the month and the last month (ie, December) will be used if the stop day/month is missing.
	Missing	Considered as a TEAE if start date on or after the date of the first dose of IP
Partial, but known components show that it cannot be on or after first IP taken date	Known	Not a TEAE. The first day of the month and January will be used if the start day/month is missing.
	Partial	Not a TEAE. The first day of the month and January will be used if the start day/month is missing. The last day of the month and the last month (ie December) will be used if the stop day/month is missing.
	Missing	Not a TEAE. The first day of the month and January will be used if the start day/month is missing.
Partial, could be on or after first IP taken date	Know	Considered as TEAE, if stop date is after first IP taken date. The first IP taken date will be used if start date is in the same month/year with first IP taken date, or the first day of the month and January will be used if the start day/month is after first IP taken date Considered as not TEAE, if stop date is prior to first IP taken date. The first day of the month and January will be used if the start day/month is missing.
	Partial	Considered as TEAE. The first IP taken date will be used if start date is in the same month/year with first IP taken date, or the first day of the month and January will be used if the start day/month is after first IP taken date. The last day of the month and the last month (ie, December) will be used if the stop day/month is missing.
	Missing	Considered as TEAE. The first IP taken date will be used if start date is in the same month/year with first IP taken date, or the first day of the month and January will be used if the start day/month is after first IP taken date.
Missing	Known	Considered as TEAE if stop date is on or after the date of the first dose of IP.

Start/Increase Severity Date	Stop Date	Action
	Partial	The last day of the month and the last month (ie, December) will be used if the stop day/month is missing. If the imputed stop date is on or after the first dose of IP considered as a TEAE; if the year is missing, considered as a TEAE
	Missing	Considered as a TEAE

Table 6-5 Algorithm for Prior/Concomitant Medications Categorization:

Start Date	Stop Date	Action
Known	Known	If stop date is prior to the date for the first dose of IP, considered as prior; if stop date is on or after the date for the first dose of IP, considered as concomitant.
	Partial	The last day of the month and the last month (ie, December) will be used if the day/month of stop date is missing. If the impuated stop date is prior to the date for the first dose of IP, considered as prior; if the imputed stop date is on or after the date for the first dose of IP, considered as concomitant.
	Missing	Considered as concomitant.
Partial	Known	If stop date is prior to the date for the first dose of IP, considered as prior; If stop date is on or after the date for the first dose of IP, considered as concomitant. The first day of the month and January will be used if the start day/month is missing.
	Partial	The last day of the month and the last month (ie, December) will be used if the day/month of stop date is missing. If the impuated stop date is prior to the date for the first dose of IP, considered as prior; if the imputed stop date is on or after the date for the first dose of IP, considered as c ncomitant. The first day of the month and January will be used if the start day/month is missing.
	Missing	Considered as concomitant. The first day of the month and January will be used if the start day/month is missing.
Missing	Known	If stop date is prior to the date for the first dose of IP, considered as prior; if stop date is on or after the date for the first dose of IP, considered as concomitant.
	Partial	The last day of the month and the last month (ie, December) will be used if the day/month of stop date is missing. If the impuated stop date is prior to the date for the first dose of IP, considered as prior; if he imputed stop date is on or after the date for the first dose of IP, considered as concomitant.
	Missing	Considered as concomitant.

6.3 Laboratory Test Parameters

Laboratory Assessments	Parameters	
Hematology	Complete Blood Cell Count: red blood cells hemoglobin hematocrit platelets white blood cells	Complete Blood Cell Count with differential and RBC indices: red blood cells hemoglobin hematocrit platelets reticulocytes mean corpuscular volume (MCV) mean corpuscular hemoglobin (MCH) mean corpuscular hemoglobin concentration (MCHC) white blood cells: lymphocytes, abs and % monocytes, abs and % eosinophils, abs and % neutrophils, abs and % basophils, abs and %
Coagulation parameters	International normalized ratio (INR), prothrombin time (PT), partial thromboplastin time (PTT)	
Clinical chemistry	alanine transaminase (ALT) aspartate transaminase (AST) gamma-glutamyl transferase (GGT) alkaline phosphatase (ALP) bilirubin (total and direct) lactate dehydrogenase (LDH) total protein albumin	creatine kinase (CK) sodium chloride potassium creatinine blood urea nitrogen (BUN) fasting blood glucose
Urinalysis	specific gravity, pH, glucose, protein, blood, ketones, bilirubin, urobilinogen, nitrite, leukocyte esterase by dipstick microscopic examination (if blood or protein is abnormal)	
Complement panel	Bb, C3a, C5a	
Immunogenicity	Antidrug antibodies	
Laboratory tests for admission to clinic	SARS-CoV-2 (local laboratory testing) Breath alcohol test (local laboratory testing) Urine drug screen (to include at minimum: amphetamines, barbiturates, cannabis, cocaine, opiates, and benzodiazepines)	
Pregnancy testing	Highly sensitive urine hCG pregnancy test (in female participants). Any positive urine pregnancy test will be confirmed with a serum pregnancy test (local laboratory testing)	
Other tests performed at Screening	Follicle-stimulating hormone (as needed to confirm menopausal status) Viral serology (human immunodeficiency virus antibody, hepatitis B surface antigen, and hepatitis C virus antibody) Hemoglobin A1c Urine drug screen (to include at minimum: amphetamines, barbiturates, cocaine, opiates, and benzodiazepines)	

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