Cover Page for Protocol

Sponsor name:	Dicerna Pharmaceuticals, Inc.
NCT number	NCT05021640
Sponsor trial ID:	DCR-AUD-101
Official title of study:	A Phase 1, Double-blind, Placebo-controlled, Single-ascending-dose, Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics Study of DCR-AUD in Healthy Volunteers
Document date*:	14-Mar-2022

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Protocol Title:	**A Phase 1, Double-blind, Placebo-controlled, Single-ascending-dose, Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics Study of DCR-AUD in Healthy Volunteers**
Protocol Number:	DCR-AUD-101
Compound:	DCR-AUD
Study Phase:	1
Short Title:	Phase 1 SAD Study of DCR-AUD in Healthy Volunteers
IND Number:	152401
Sponsor Name:	Dicerna Pharmaceuticals, Inc. 75 Hayden Avenue Lexington, MA 02421 US (617) 621-8097

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	Amendment 2 (version 3.0)	19-Jul-2021
	Amendment 3 (version 4.0)	26-Jul-2021
	Amendment 4 (version 5.0)	28-Jul-2021
	Amendment 5 (version 6.0)	14-Mar-2022

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Sponsor Signature Page

Title: A Phase 1, Double-blind, Placebo-controlled, Single-ascending-dose, Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics Study of DCR-AUD in Healthy Volunteers

Protocol Number: DCR-AUD-101

Version: 6.0

Date: 14-Mar-2022

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PROTOCOL AMENDMENT SUMMARY OF CHANGES

DOCUMENT HISTORY	
Document	**Date**
Amendment 5 (version 6.0)	14-Mar-2022
Amendment 4 (version 5.0)	28-Jul-2021
Amendment 3 (version 4.0)	26-Jul-2021
Amendment 2 (version 3.0)	19-Jul-2021
Amendment 1 (version 2.0)	09-Jul-2021
Original Protocol	24-Jun-2021

Amendment 5:

Overall Rationale for the Amendment:

The 28-Jul-2021 version of the protocol was amended to remove the conduct of the interim analysis scheduled at the conclusion of Cohort 2, as emerging PD data did not dictate it was warranted. Other points of clarification for the timing and scheduling of study visits were also added. A summary of all changes is detailed in the following table.

Protocol Amendment 5 Summary of Changes

Description of Change	Brief Rationale	Affected Sections
Deleted requirement for interim analysis (IA) and clarified that one or more IA may be conducted if warranted, dictated by the nature of available clinical and/or biomarker/PD data.	Interim analysis may be done contingent on a possible safety or PD signal in the emerging blinded data.	9.5 Interim Analyses
Modified text to allow visits to be rescheduled due to COVID-19 or other exceptional circumstances at the discretion of the Investigator, as appropriate.	For clarity	1.1.3 Overall Design 4.1 Overall Design
Modified text to state that if an EIA is missed, the missed EIA may be conducted at the next scheduled visit or at an unscheduled visit at the discretion of the Investigator.	To allow for Investigator discretion in scheduling missed EIAs	1.1.3 Overall Design 4.1 Overall Design 8.7.1 Ethanol Interaction Assessments
Clarified that a venous catheter would be used, and placement could be done at any time prior to sample collection as long as it was at least 20 minutes before ECG, SEAS, vital signs, and facial temperature were recorded.	For clarity	1.3 Table 3, footnote “d”

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Description of Change	Brief Rationale	Affected Sections
Changed diastolic blood pressure out-of-range limit from 55 to 50 mmHg.	To expand the normal diastolic blood pressure range in healthy volunteers as low as 50 mmHg	5.1 Inclusion Criterion #7
Updated the IP storage instructions from "2°C to 8°C" to "at or below 30°C; do not freeze" and specified DCR-AUD should be warmed for approximately 1 hour before administration if stored at 2°C to 8°C.	For clarity, based on updated guidance from Technical Operations	6.2.2 Storage 6.2.3 Preparation and Administration
Clarified SRC review would include all ***available*** safety data collected before expanding or escalating to the next dose.	To clarify	1.1.3 Overall Design 2.3.1 Risks Related to siRNA Molecules 4.1 Overall Design 9.6 Safety Review Committee, Table 7
Updated the pregnancy testing sensitivity range from "at least 10 mIU/mL" to "25 mIU/mL"	To accommodate local testing standards	10.4.3 Pregnancy Testing
Administrative updates	To reflect new version	Throughout the protocol

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1. PROTOCOL SUMMARY

1.1. Synopsis

Protocol Title: A Phase 1, Double-blind, Placebo-controlled, Single-ascending-dose, Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics Study of DCR-AUD in Healthy Volunteers

Short Title: Phase 1 SAD Study of DCR-AUD in Healthy Volunteers

1.1.1. Rationale

DCR-AUD is being developed for the treatment of alcohol use disorder (AUD) in adults using an RNA interference (RNAi) technology platform. DCR-A1203, the drug substance of DCR-AUD, is a synthetic double-stranded (hybridized duplex) RNA oligonucleotide conjugated to *N*-acetyl-D-galactosamine (GalNAc) ligands that enable subcutaneous delivery of stable, safe, highly specific, and long-acting reduction of mRNA in the liver via hepatic GalNAc carbohydrate receptors. The target of DCR-AUD is aldehyde dehydrogenase 2 (ALDH2), one of the primary enzymes required for alcohol metabolism. Alcohol metabolism occurs predominantly in the liver via a 2-step process in which alcohol is first converted to acetaldehyde via alcohol dehydrogenase and then to acetic acid by ALDH2. ALDH2 enzyme inhibition can result in unpleasant symptoms after alcohol consumption such as flushing, headache, tachycardia, nausea, and vomiting, as a result of unmetabolized acetaldehyde accumulation. Unpleasant reactions to alcohol consumption in humans with naturally occurring *ALDH2* mutations are thought to be protective against AUD and account for its low prevalence in individuals who are heterozygous or homozygous for *ALDH2* allele mutations. The magnitude and duration of acetaldehyde accumulation is proportional to both the degree of ALDH2 enzyme inhibition (e.g., partial vs total) and the amount of alcohol consumed.

DCR-AUD is designed to selectively reduce *ALDH2* mRNA and ALDH2 activity in the liver, and thereby decrease the conversion of acetaldehyde to acetic acid after ethanol ingestion. In cynomolgus monkeys, a single SC dose of 3 mg/kg DCR-AUD resulted in reduction of *ALDH2* mRNA expression in liver up to 112 days postdose, with maximum reduction observed at 4 weeks postdose. The DCR-AUD-101 study is the first human study of DCR-AUD.

The overall goals of this study are:

1. To demonstrate that DCR-AUD single doses are safe and well-tolerated
2. To characterize the PK of single doses of DCR-AUD
3. To characterize the PD of single doses of DCR-AUD and obtain safety data after alcohol exposure in adult healthy volunteers (HVs) as assessed by serial standardized Ethanol Interaction Assessments (EIAs)
    a. EIAs will be used to confirm target engagement. The degree of ALDH2 reduction is measurable only after ethanol administration, via levels of plasma acetaldehyde and acetate, and measurement of heart rate and facial skin temperature.
    b. The safety of ethanol ingestion in the presence of DCR-AUD will be assessed during EIAs, each of which will be followed by overnight admission and monitoring in a

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Phase 1 clinical unit. The Investigator will not discharge any participant experiencing ongoing effects of ethanol administration until it is deemed medically safe to do so.

c. Serial EIAs will be used to determine the duration of action of DCR-AUD, so that an appropriate dose and dosing interval and safety monitoring plan for participants can be developed for later clinical trials.

1.1.2. Objectives and Endpoints:

Objectives	Endpoints
Primary	
To evaluate the safety and tolerability of single doses of DCR-AUD administered to adult HVs	• Incidence and severity of AEs, SAEs, and DLTs • Changes from baseline in vital signs, 12-lead ECG, clinical laboratory tests, and physical examination findings
Secondary	
• To characterize the PK of single doses of DCR-AUD in adult HVs • To characterize the PD of single doses of DCR-AUD in adult HVs as assessed by serial standardized EIAs	• Plasma PK parameters of DCR-AUD • Urine PK parameters of DCR-AUD • Change in PD biomarkers during standardized EIAs o Plasma acetaldehyde, acetate, and EtOH o Heart rate and facial skin temperature o SEAS

Abbreviations: AE: adverse event; DLT: dose-limiting toxicity; EIA: ethanol interaction assessment; EtOH: ethanol; HV: healthy volunteer; PD: pharmacodynamics; PK: pharmacokinetics; SAE: serious adverse event; SEAS: Subjective Effects of Alcohol Scale

1.1.3. Overall Design

This is a 24-week, randomized, double-blind, placebo-controlled study to evaluate the safety, tolerability, PK, and PD of single-ascending doses (SAD) of DCR-AUD administered to adult HVs.

Individual participants will be screened for a period of up to 28 days. Participants may undergo rescreening one time at the discretion of the Investigator or Sponsor. The single doses of DCR-AUD will be administered to adult HVs across 3 fixed ascending-dose cohorts (80 mg, 240 mg, 480 mg) and 1 optional cohort (960 mg). Each cohort will comprise a sentinel group of 3 participants (2 active, 1 placebo) who will be followed for the assessment of safety and tolerability and characterization of PK but who will not undergo any EIAs. The sentinel group will remain under observation in clinic until Day 4 (after dosing on Day 1) and will return to clinic on Days 8 and 15 for clinical and laboratory test evaluations. The SRC will review available sentinel group safety data through the Day 15 assessments prior to authorizing cohort expansion within an individual cohort for the remaining 6 participants (4 active, 2 placebo). The 6 participants in the expanded cohort will be followed for the assessment of safety and tolerability, characterization of PK, and assessment of PD (via EIA). In addition to alcohol exposure on Day –1 (prior to administration of study intervention), these participants will undergo serial EIAs on Day 4 before being discharged from clinic on Day 5, and at 6 other times during the 24-week study period. All EIAs will be conducted as in-clinic assessments.

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Participants who have positive ethanol reaction symptoms at the Day 169 EIA (e.g., nausea, vomiting, or substantial flushing) will return every 28 (±7) days for follow-up EIAs until the positive ethanol reaction symptoms abate. These conditional follow-up (CFU) EIAs will not require overnight admission to the clinic, but all other aspects of the EIA will be conducted (see Table 3). Participants will be observed for no less than 6 hours after ethanol administration and will not be discharged until the Investigator deems it medically safe to do so.

If participants are not able to return to the site for assessments or procedures because of COVID-19 or other exceptional circumstances, visits may be rescheduled or conducted by qualified medical professionals as at-home telemedicine and/or home nursing visits at the discretion of the Investigator.

All participants will be given a diary to track AEs and temperance for the study duration. Participants will be trained on the use of the diary prior to discharge from the clinic and will report on the diary at each in-clinic visit.

The SRC will review available safety data from all participants in each cohort through at least the Day 15 assessments prior to authorizing dose escalation to the next cohort.

The Study Schematic is presented in Figure 1. The schedules of activities are presented in Table 1 and Table 3.

Intervention Groups and Duration:

Doses of DCR-AUD to be administered will ascend from 80 mg in Cohort 1, to 240 mg in Cohort 2, to 480 mg in Cohort 3, and to 960 mg in the optional Cohort 4.

Individual participants will be screened for a period of up to 28 days. Randomization and administration with a single dose of study intervention will occur on Day 1. Participants will return to the site for safety, tolerability, PK, and PD monitoring at specified time points as per the Schedule of Activities.

Participants will be followed for 24 weeks (Day 169).

Study Population:

- Overtly healthy men and women aged 21 to 65 years
- Social drinkers of modest amounts (≤ 2 drinks/day and ≤ 3 days/week) who are able to refrain from drinking alcohol during the outpatient portion of the trial
- Willing to participate in repeated low-dose EIAs followed by an overnight clinic stay
- BMI 18.0 to 32.0 kg/m^2 (inclusive)
- No history of suicidal attempt as an adult, or suicide ideation in the past year that resulted in pharmacologic treatment or hospitalization. In addition, any history of severe or recent clinically significant depression, anxiety, bipolar disorder, schizophrenia, or other neuropsychiatric disorder that, in the judgment of the investigator, represents a safety risk to the individual were they to participate in the trial
- No history of substance use disorder (including AUD) or illicit drug use (excluding cannabis) within the preceding 12 months. Nicotine use is permitted

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- No history of delirium tremens or alcohol-related seizures

Treatment Blinding:

This study will have multiple cohorts. Participants, Investigators, site staff (excluding pharmacy staff), the CRO staff, and the Sponsor Medical Monitor will be blinded to the randomization of those cohorts. However, certain members of the Sponsor staff will be unblinded to randomization for the duration of the study. Complete details will be presented in the Study Blinding Plan.

Number of Participants:

Up to 36 participants are planned to be enrolled in this study: 27 HVs in the 3 planned dose cohorts, plus an additional 9 HVs if the optional fourth cohort is enrolled.

Safety Review Committee and Data Safety Monitoring Committee:

An SRC will be convened to review available safety data at a predefined decision point (Visit 2, Day 15) to ensure the safety of the participants in all cohorts. The scope of the review meetings will be defined in the SRC charter. In the event that the SRC decides to suspend or interrupt the study, an independent DSMC may be convened to review the decision by the SRC and recommend whether the study should be stopped, resumed with no changes, or resumed with changes.

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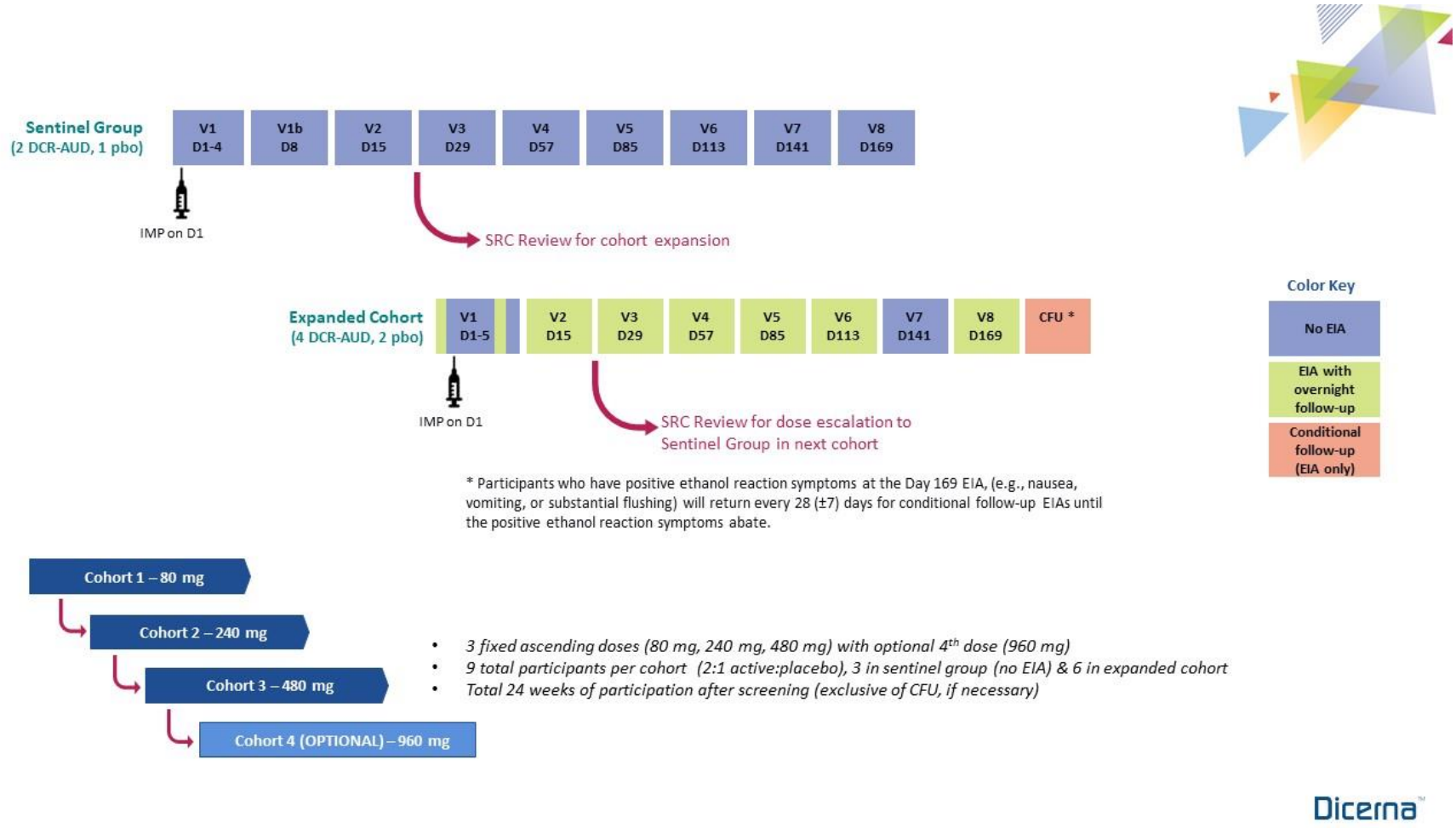
1.2. Overall Study Schema

Figure 1: Study Schematic for DCR-AUD-101



Abbreviations: CFU: conditional follow-up; D: Day; EIA: ethanol interaction assessment; IMP: investigational medicinal product; pbo: placebo; SRC: Safety Review Committee; V: Visit

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1.3. Schedules of Activities

Table 1: Schedule of Activities

	Screening	Visit 1 (In-Clinic)					V1b[a]	Visit 2	Visit 3	Visit 4	Visits 5-6	Visit 7	Visit 8 EOS/ET
Study Day / **Procedure/Assessment**	**-28 to -2**	**-1**	**1**		**2**	**3**	**4**	**8**	**15 ±2 day**	**29 ±2 day**	**57 ±2 day**	**85, 113 ±2 day**	**141 ±2 day**	**169 ±7 day**
			Pre-dose	**Post-dose**										
Informed consent	X													
Clinical site admission/discharge [b]		X					X							
Inclusion/exclusion criteria	X	X	X											
Demographic/baseline characteristics	X													
General medical history	X													
Psychological history	X													
C-SSRS[c]	X	X							X	X		X[d]		X
MINI	X													
Alcohol history/consumption (TLFB)	X	X						X	X	X	X	X	X	X
Diary (AEs, temperance) distribute/collect								X	X	X	X	X	X	X
Drug/alcohol testing (urine, breath) [e]	X	X							X	X	X	X	X	X
Testing for HCV, HIV, and HBV	X													
Randomize to study intervention			X											
Study intervention administration			X											
Medication history/concomitant meds	X	X		X	X	X	X	X	X	X	X	X	X	X
12-lead ECG [f]	X	X	X	X	X	X		X	X	X	X	X	X	X
Vital signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical examination [g]	X	X	X		X	X	X	X	X	X	X	X	X	X

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	Screening	Visit 1 (In-Clinic)					V1b[a]	Visit 2	Visit 3	Visit 4	Visits 5-6	Visit 7	Visit 8 EOS/ET
Study Day / **Procedure/Assessment**	**-28 to -2**	**-1**	**1**		**2**	**3**	**4**	**8**	**15 ±2 day**	**29 ±2 day**	**57 ±2 day**	**85, 113 ±2 day**	**141 ±2 day**	**169 ±7 day**
			Pre-dose	**Post-dose**										
Pregnancy test (WOCBP only) [h]	X		X							X	X	X	X	X
FSH (if applicable)	X													
Clinical safety laboratory tests [i]	X	X			X		X	X	X	X	X	X	X	X
Complement panel [j]			X	X	X									
Blood sample for ADA		X								X				X
SARS-CoV-2 rapid test (at site)[k]		X								X	X	X		X
Blood sample for genotyping [l]		X												
Plasma collection for PK analysis [m]			X	X	X	X	X		X					
Urine collection for PK analysis [n]				X	X	X	X							
Ethanol interaction assessment [o]		X					X		X	X	X	X		X[p]
Record AEs and SAEs [q]	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Abbreviations: ADA: antidrug antibody; AE: adverse event; CFU: conditional follow-up; C-SSRS: Columbia-Suicide Severity Rating Scale; ECG: electrocardiogram; EIA: ethanol interaction assessment; FSH: follicle stimulating hormone; HBV: hepatitis B virus; HCV: hepatitis C virus; HIV: human immunodeficiency virus; ICF: informed consent form; MINI: Mini-International Neuropsychiatric Interview; PK: pharmacokinetic; SAE: serious adverse event; SARS-CoV-2: severe acute respiratory syndrome coronavirus 2; TLFB: Timeline Follow Back; WOCBP: women of childbearing potential

[a] Visit 1b is only required for the 3 sentinel group participants in each cohort.

[b] Participants in the expanded cohort must have fasted for at least 6 hours before admission on Day −1 and will receive a standardized meal prior to the EIA. Participants undergoing EIA will be discharged from the clinic on Day 5. Sentinel group participants will be discharged from the clinic on Day 4, following the 72-hour PK blood draw and completion of pooled urine collection.

[c] At Screening, the 'C-SSRS Baseline' form will be administered, at all other visits indicated, the 'C-SSRS Since Last Visit' form will be administered.

[d] C-SSRS to be administered only on Day 85.

[e] Urine for drugs of abuse and breathalyzer for alcohol. Cannabis will not be recorded as a drug of abuse for this study. Participants will be excluded from EIA evaluation that day if they test positive for breath alcohol on day of study visit prior to EIA.

[f] Standard ECGs will be performed 30 minutes predose, and at 60 minutes and 150 minutes postdose. A ±15-minute window around each time point is allowed if multiple assessments are due. If multiple assessments are due, the order of priority should be ECG, vitals, PK, and then other assessments.

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[g] Complete physical examinations will be conducted at every visit. Height will be measured and recorded at Day 1 and weight will be measured and recorded at every visit.
[h] If a urine pregnancy test is positive, confirm with serum test for pregnancy (see Section 10.4). Local laboratory may be used. Pregnancy testing to be performed every 28 days throughout the study.
[i] Hematology, clinical chemistry, coagulation, and urinalysis samples will be collected at every visit indicated. Only on Days −1, 4, 29, 85, and 169 will additional hematology analytes (mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, and absolute and % of lymphocytes, monocytes, eosinophils, neutrophils, and basophils) be collected. See Table 8 for a complete list of parameters to be assessed.
[j] During in-clinic stay at Day 1 and Day 2, blood samples will be collected for complement predose, and at 2, 8, and 24 hours postdose.
[k] Participants in expanded cohorts will need to undergo SARS-CoV-2 rapid test in compliance with clinic requirements before admittance to the unit for EIA testing. Refer to Study Manual for further details on the timing of this testing.
[l] A separate informed consent form is needed for collection of blood sample for optional genotyping.
[m] At Visit 1, plasma samples for PK analysis will be collected before study intervention administration and at 15 and 30 minutes and 1, 2, 4, 6, 8, 24, 48, and 72 hours after the injection. At Visit 2, only one sample will be collected for PK. If multiple assessments are due, the order of priority should be ECG, vitals, PK, and then other assessments, with the PK sampling being performed preferably at the nominal time point. Table 2 details the windows allowed surrounding collection of PK samples.
[n] Pooled urine collection to be done for PK analyses of DCR-AUD concentration. Participants should have an empty bladder prior to administration of study intervention, and 24-hr urine collection to begin with first void after study intervention administration. Urine to be collected at intervals of 0-4, > 4-8, > 8-12, > 12-24, > 24-48, and > 48-72 hours. Urine will be collected using a polypropylene container.
[o] Each cohort will have a sentinel group (n=3) that does not undergo any EIA assessment. For all other participants, all visits on which an EIA is conducted will require an overnight stay in the clinic. Participants will be admitted after an overnight fast and be provided a standardized meal. EIA estimated time is ~2.5 hours and is conducted at all visits except Visit 7 (Day 141). Note that the Day −1 assessment occurs prior to administration of study intervention and is intended to serve as a baseline for biomarker assessments and to confirm eligibility. See Table 3 for details of EIA.
[p] Participants who have positive ethanol reaction symptoms at the Day 169 EIA (e.g., nausea, vomiting, or substantial flushing) will return every 28 (±7) days for follow-up EIAs until the positive ethanol reaction symptoms abate. These CFU EIAs will not require overnight admission to the clinic, but all other aspects of the EIA will be conducted. Participants will be observed for no less than 6 hours after ethanol administration and will not be discharged until the Investigator deems it medically safe to do so.
[q] 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 2: Allowed Windows for Collection of Plasma Pharmacokinetic Samples and for Complement Panel

Nominal Postdose Sample Time	Window
15 minutes	± 5 minutes
30 minutes	± 10 minutes
1, 2, 4, 6, and 8 hours	± 15 minutes
≥ 24 hours	± 30 minutes

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Table 3: Schedule of Activities: Ethanol Interaction Assessments

Time in minutes / Procedures	Pre-EIA	Rest	Test Period							
		− 20	**0**[a]	**15** ±5	**30** ±10	**45** ±10	**60** ±15	**90** ±15	**120** ±15	**150** ±15
Admit/return to clinic (fasted state)[b]	X									
Standardized meal[c]	X									
Venous catheter placement[d]		X								
Alcohol consumption[e]			← X →							
Blood biomarkers[f g]			X	X	X	X	X	X	X	X
EIA 12-lead ECG[g]			X				X			X
SEAS[g,h]			X		X		X	X	X	X
Facial skin temperature[g i]			X	X	X	X	X	X	X	X
EIA vital sign[g j]			X	X	X	X	X	X	X	X
Heart rate via telemetry			X	X	X	X	X	X	X	X
EIA AEs[k]			X	X	X	X	X	X	X	X

Abbreviations: AE: adverse event; CFU: conditional follow up; ECG: electrocardiogram; EIA: ethanol interaction assessment; EtOH: ethanol; SEAS: subjective effects of alcohol scale;

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

[b] All visits on which an EIA is conducted will require an overnight stay in the clinic except for any CFU visits for participants who have positive ethanol reaction symptoms at Day 169; these do not require an overnight stay.

[c] Participants are required to fast for at least 6 hours prior to consuming the standardized meal.

[d] Participants will have a venous access catheter placed for sample collection. Participant will be given a ≥20-minute rest period following placement of the catheter prior to recording predose ECG, SEAS, vital signs, and facial temperature.

[e] After completion of the standardized meal, alcohol will be consumed in 4 aliquots over a 30-minute period. The ethanol will be mixed in a liquid that has no other alcohol, no caffeine, and is low in sugar. Because BAC is higher in women than men when given the same g/kg EtOH dose (~ 15% higher mean BAC), the EtOH dose will be 0.4 g/kg for male participants and 0.34 g/kg for female participants. The total dose of EtOH will not exceed 28 g in men or 24 g in women.

[f] Blood samples will be collected via a venous access device for biomarker analysis, which include acetaldehyde, acetate, and ethanol. Blood sample collection and processing will be detailed in the Laboratory Manual.

[g] The order of assessments should be blood draw, 12-lead ECG, SEAS, vital signs, and facial temperature.

[h] Participants will rate the extent to which they are feeling each of the 14 SEAS effects in the present moment.

[i] Facial skin temperature will be measured using a surface scanning thermometer and will be collected prior to blood draws.

[j] Vital signs will be recorded prior to blood draws and include blood pressure and pulse/heart rate.

[k] Adverse events associated with administration of ethanol will be recorded continuously throughout the test period, beginning with the first sip of alcohol.

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2. INTRODUCTION

2.1. Study Rationale

DCR-AUD is being developed for the treatment of AUD in adults using an RNAi technology platform. DCR-A1203, the drug substance of DCR-AUD, is a synthetic double-stranded (hybridized duplex) RNA oligonucleotide conjugated to GalNAc ligands that enable specific hepatic access and uptake after subcutaneous administration. Once inside the hepatocyte, the antisense sequence of DCR-AUD is designed to target and reduce the expression of ALDH2 mRNA in the liver.

The target of DCR-AUD is ALDH2, one of the primary enzymes required for alcohol metabolism. Alcohol metabolism occurs predominantly in the liver via a 2-step process in which alcohol is first converted to acetaldehyde via alcohol dehydrogenase and then to acetic acid by ALDH2. DCR-AUD is designed to selectively reduce *ALDH2* mRNA and ALDH2 activity in the liver, and thereby decrease the conversion of acetaldehyde to acetic acid after ethanol ingestion. ALDH2 enzyme inhibition can result in unpleasant symptoms after alcohol consumption such as flushing, headache, tachycardia, nausea, and vomiting as a result of unmetabolized acetaldehyde accumulation. Unpleasant reactions to alcohol consumption in humans with naturally occurring *ALDH2* mutations are thought to be protective against AUD and account for its low prevalence in individuals who are heterozygous or homozygous for *ALDH2* allele mutations. The magnitude and duration of acetaldehyde accumulation is proportional to both the degree of ALDH2 enzyme inhibition (e.g., partial vs total) and the amount of alcohol consumed.

Study DCR-AUD-101 is the first study of DCR-AUD in humans. The aims of the study are to evaluate the safety and tolerability of single-ascending-doses of DCR-AUD and to characterize its PK profile and PD effects.

2.2. Background

2.2.1. Overview of Alcohol Use Disorder

Alcohol use disorder is a chronic condition characterized by compulsive alcohol use, loss of control over alcohol use, and a negative emotional state when not using alcohol. A range of medical, psychological, social, economic, and personal problems are associated with AUD. Diagnosis is defined as meeting ≥ 2 of 11 criteria in the Diagnostic and Statistical Manual of Mental Disorders-5 (DSM 5) during the same 12-month period. A survey of over 36,000 adults found AUD had a 12-month prevalence of 13.9% adults in the US in 2013 (Grant et al., 2015). AUD often goes untreated, possibly due to the lack of adequate treatment options. It is estimated that < 10% of US adults with AUD seek help or treatment, and that similarly low percentages of those treated receive pharmacotherapy (Grant et al., 2015; National Survey on Drug Use, 2014; Litten et al., 2014; Han et al., 2015; Knudsen et al., 2011).

There are 3 FDA-approved medications for AUD: disulfiram, oral and long-acting injectable naltrexone, and acamprosate. However, many individuals show limited or no response to these drugs, with poor compliance a factor (EMA, 2010; Gastfriend, 2014; Chick et al., 1992;

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Jørgensen et al., 2011; Bryson et al., 2011). Thus, there remains an unmet need for an effective AUD treatment.

2.2.2. Nonclinical Overview of DCR-AUD

The pharmacology of DCR-A1203 was characterized in in vivo studies in mice and monkeys to demonstrate the ability to reduce levels of the hepatic *ALDH2* mRNA. The potential for off-target gene silencing was assessed using in silico evaluation of the human transcriptome. The sequence is conserved in mouse, monkey, and human and therefore, DCR-A1203 is active in both nonclinical species evaluated. In addition, a stand-alone comprehensive safety pharmacology study in cynomolgus monkeys was conducted.

Overall, the data support the hypothesis that DCR-A1203 has potential to yield meaningful and robust clinical responses across the AUD patient populations based upon the following:

- A single SC dose of up to 100 mg/kg in mice resulted in a dose-dependent decrease in *Aldh2* mRNA expression in liver, persistent for 14 days postdose, followed by dose-dependent recovery.
- Following a single 3 mg/kg SC dose of DCR-A1203, liver *ALDH2* mRNA expression levels were reduced by > 75% in cynomolgus monkeys, with the nadir at 28 days postdose, and > 50% reduction in *ALDH2* mRNA expression up to 112 days postdose.
- Repeat SC administration of DCR-A1203 up to 300 mg/kg resulted in significant reduction of hepatic *Aldh2* mRNA in mice (> 97%) and hepatic *ALDH2* in monkeys (> 85.9%).
- Based on in silico analysis, potential off-target complementarities with 3 or fewer mismatches and a full seed-region match, were completely absent from the human transcripts analyzed, demonstrating that DCR-A1203 has a high degree of specificity for the *ALDH2* mRNA.

The safety of DCR-A1203 has been characterized in a program of nonclinical studies. Subcutaneous repeat-dose toxicity studies have been conducted at doses up to 300 mg/kg for up to 5 weeks in mice and monkeys. DCR-A1203 has been evaluated for potential genotoxicity in a bacterial reverse mutation assay and an in vitro micronucleus study.

- DCR-A1203 administration had no adverse effects on cardiovascular, respiratory, or central nervous system function in conscious, radiotelemetry-implanted cynomolgus monkeys following a single SC injection of up to 300 mg/kg.
- The administration of DCR-A1203 to mice and monkeys in the 5-week repeat-dose studies resulted in no DCR-A1203-related, adverse findings. The NOAEL in the mouse and monkey repeat-dose toxicity studies was considered by the study director to be 300 mg/kg, the highest dose level administered. Based on input from the FDA regarding clinical pathology and histopathology in a single 300 mg/kg animal in the monkey study, a more conservative approach is being taken, and the mid-dose of 100 mg/kg is being treated as the NOAEL for the purpose of determining a safety margin for the monkey study.

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- DCR-A1203 was not genotoxic in the bacterial reverse mutation and in vitro micronucleus assays.

Overall, the nonclinical safety program of DCR-A1203 did not identify any major safety issues. A detailed description of the chemistry and pharmacology of DCR-AUD is provided in the Investigator's Brochure.

2.3. Benefit/Risk Assessment

The summary of potential risks provided below is based on an in-depth review of literature relating to the proposed approach and insights from the nonclinical pharmacology and toxicology studies.

2.3.1. Risks Related to siRNA Molecules

The potential risks associated with DCR-AUD are limited to the risks associated with the siRNA oligonucleotide portion of the drug product.

To date, DCR-A1203 has been associated with no adverse effects in nonclinical studies. Clinical experience in more than 200 patients and HVs with the Dicerna GalXC™ platform suggests a favorable safety profile with little-to-no evidence of systemic immune stimulation or toxicities. Mild, self-limiting injection site reactions have been reported (Dicerna data on file).

As part of the study's planned mitigation strategy, each cohort will comprise a sentinel group of 3 participants (2 active, 1 placebo) who will be followed for the assessment of safety and tolerability and characterization of PK. Sentinel participants will not undergo EIA tests. The sentinel group will remain under observation in clinic until Day 4 (after dosing on Day 1) and will return to clinic on Day 8 and Day 15 for clinical and laboratory test evaluations. The SRC will review available sentinel group safety data, including the safety laboratory results, through the Day 15 assessments and PK through 72-hours postdose prior to authorizing cohort expansion for the remaining 6 participants, who will undergo EIA tests.

All study participants will be monitored for signs or symptoms of systemic toxicity, decline in liver or kidney function, abnormalities on hematologic parameters (including platelets and coagulation parameters), and abnormalities in vital signs, ECGs, complement activation, or other relevant safety parameters.

2.3.2. Risks Related to DCR-AUD Off-target Effects

The antisense sequence of DCR-AUD is designed to target and reduce the expression of ALDH2 mRNA in the liver. Potential off-target complementarities at the level of a single mismatch were completely absent from the human transcripts analyzed in in silico studies. These findings demonstrate that DCR-AUD has a high degree of specificity for the ALDH2 mRNA. The sequence is conserved in mouse, monkey, and human, and therefore, DCR-AUD is active in all nonclinical species evaluated.

2.3.3. Risks Related to DCR-AUD Mechanism of Action

DCR-AUD is designed to induce intolerance to high-intake alcohol consumption (e.g., ≥ 4 drinks/occasion in men; ≥ 3 drinks/occasion in women) by selective reduction of *ALDH2* mRNA and ALDH2 activity in the liver, and thereby decrease the conversion of

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acetaldehyde to acetic acid after ethanol ingestion. Acetaldehyde accumulation, in sufficient amounts, is associated with unpleasant effects potentially including headache, facial flushing, tachycardia, nausea, and vomiting. More severe reactions to acetaldehyde accumulation can include copious vomiting, sweating, chest pain, palpitation, dyspnea, hypotension, syncope, marked uneasiness, weakness, vertigo, blurred vision, and confusion. The intensity of the reaction varies with each individual but is generally proportional to the amounts of alcohol ingested and the degree of ALDH2 inhibition. The duration of the reaction varies from 30 to 60 minutes and up to several hours in the more severe cases if there is prolonged alcohol exposure in the blood. Symptoms are typically self-limited and managed with watchful observation and supportive care. More severe acetaldehyde reactions have been documented with disulfiram treatment and in individuals who are homozygous for *ALDH2*-gene–inactivating mutations compared with *ALDH2* mutation heterozygotes, proportional to the magnitude of systemic ALDH2 inactivation.

Study participants will be clearly informed of these potential risks. Symptoms that develop with concomitant alcohol consumption are expected to be self-limited and manageable with supportive care and can be avoided by limiting or eliminating alcohol consumption.

In the absence of direct measurement of ALDH2 activity in the liver (e.g., via liver biopsy), EIA assessments are necessary to evaluate and confirm DCR-AUD PD activity. The EIA interventions in this protocol are designed to minimize the amount of alcohol to be administered (approximately 0.4 g/kg, equivalent to 1-2 drinks over a 30-minute period in a 70 kg person), and the signs and symptoms of alcohol intolerance.

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2.3.4. Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/ Rationale for Risk	Mitigation Strategy
FIH study	Standard FIH methodology for testing and analysis	Study will be conducted under close observation in a clinical Phase 1 study unit.
Study Intervention: DCR-AUD		
Dose selection (unknown human safety and tolerability)	The dose range proposed for this study is justified based on the safety profile of such doses in nonclinical toxicity studies	Sequential dose escalation; use of sentinel dose group in each cohort; SRC to review safety and PK and approve dose selection and dose escalation.
Potential risk of DLT or other safety signals	This is a FIH study and the clinical safety profile has not yet been established	SRC may convene a DSMC to adjudicate DLT or safety signals
Potential immune stimulation via the complement cascade	Previously seen in highly phosphorothioated oligonucleotides	Monitoring of complement factors within 24 hours of dosing
Study Procedures		
EIA: alcohol administration is expected to cause unpleasant effects in participants receiving active DCR-AUD	Required to assess and confirm DCR-AUD PD activity, including magnitude and duration of concomitant alcohol interaction	Alcohol to be administered gradually in EIA and performed in a Phase 1 unit clinical setting, with post-administration in-clinic overnight observation. Enroll participants who are tolerant to amount of ethanol to be administered in the EIAs (approximately 0.4 g/kg, equivalent to 1-2 drinks over a 30-minute period in a 70 kg person)
Other		
Prolonged PD activity of DCR-AUD may cause alcohol intolerance for up to 3 months or more after last dose in study participants. Adverse effects are not expected but potentially possible with concomitant small or incidental amounts of alcohol during DCR-AUD treatment.	Adverse effect(s) resulting from high levels of alcohol intake during DCR-AUD treatment is an intentional design element of the DCR-AUD target product profile and predicted based on the core RNAi/GalXC drug platform. The clinical significance is expected to be limited to high or very high alcohol consumption, but adverse effects may occur at lower amounts, including incidental exposures.	Ensure risks related to DCR-AUD potential PD effects and duration are clearly communicated in the informed consent. Adverse effects related to alcohol consumption are self-limited, reversible, and avoidable. Added CFU(s) for any participant who has positive ethanol reaction symptoms (e.g., nausea, vomiting, or substantial flushing) at the Day 169 EIA, until the symptoms abate.

2.3.5. Benefit Assessment

There is no expected benefit for HV participants in the study. Data generated in this study will contribute to the development of a potential new therapy for AUD, an area of significant unmet medical need, and FDA-approved treatment options.

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RNAi-mediated reduction of *ALDH2* via DCR-AUD is designed to offer significant safety advantages relative to agents such as disulfiram, which inhibits multiple aldehyde dehydrogenases as well as other enzymes (Koppaka et al., 2012). siRNA-mediated reduction will only target *ALDH2* in the liver, leaving other aldehyde dehydrogenases able to function. Further, DCR-AUD reduction of ALDH2 will be liver-specific, leaving non-liver ALDH2 unaffected. Thus, the target phenotype of DCR-AUD treatment is expected to be more analogous to that in individuals who are heterozygous for *ALDH2* mutations and demonstrate an intermediate alcohol intolerance phenotype (i.e., fewer, milder symptoms at low levels of alcohol intake).

2.3.6. Overall Benefit:Risk Conclusion

With the measures planned to minimize participant risk in this study, the potential risks identified in association with DCR-AUD are justified by the anticipated benefits that may be afforded to patients with AUD.

3. OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary	
To evaluate the safety and tolerability of single doses of DCR-AUD administered to adult HVs	• Incidence and severity of AEs, SAEs, and DLTs • Changes from baseline in vital signs, 12-lead ECG, clinical laboratory tests, and physical examination findings
Secondary	
• To characterize the PK of single doses of DCR-AUD in adult HVs • To characterize the PD of single doses of DCR-AUD in adult HVs as assessed by serial standardized EIAs	• Plasma PK parameters of DCR-AUD • Urine PK parameters of DCR-AUD • Change in PD biomarkers during standardized EIAs o Plasma acetaldehyde, acetate, and EtOH o Heart rate and facial skin temperature o SEAS

Abbreviations: AE: adverse event; DLT: dose-limiting toxicity; EIA: ethanol interaction assessment; EtOH: ethanol; HV: healthy volunteer; PD: pharmacodynamics; PK: pharmacokinetic; SAE: serious adverse event; SEAS: Subjective Effects of Alcohol Scale

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4. STUDY DESIGN

4.1. Overall Design

This study is a 24-week, randomized, double-blind, placebo-controlled, single-ascending-dose study to evaluate the safety, tolerability, PK, and PD of DCR-AUD in adult HVs. The overall goals of this study are:

- To demonstrate that DCR-AUD single doses are safe and well-tolerated
- To characterize the PK of single doses of DCR-AUD
- To characterize the PD of single doses of DCR-AUD and obtain safety data after alcohol exposure in adult healthy volunteers (HVs) as assessed by serial standardized Ethanol Interaction Assessments (EIAs)

Individual participants will be screened for a period of up to 28 days. Participants may undergo rescreening one time at the discretion of the Investigator or Sponsor. Single doses of DCR-AUD will be administered to adult HVs across 3 fixed ascending-dose cohorts (80 mg, 240 mg, 480 mg) and 1 optional cohort (960 mg), each to include up to 9 participants/dose cohort (6 active and 3 placebo). Each participant will receive a single dose of DCR-AUD (or matching placebo) on Day 1. Participants will be observed to allow collection of data up to 24 weeks after administration of study intervention (Day 169).

Each cohort will comprise a sentinel group of 3 participants (2 active, 1 placebo) who will be followed for the assessment of safety and tolerability and characterization of PK but who will not undergo any EIAs. The sentinel group will remain under observation in clinic until Day 4 (after dosing on Day 1) and will return to clinic on Days 8 and 15 for clinical and laboratory test evaluations. The SRC will review available sentinel group safety data through the Day 15 assessments prior to authorizing cohort expansion within an individual cohort for the remaining 6 participants (4 active, 2 placebo).

The 6 study participants in the expanded cohort will undergo EIAs to evaluate the PD effects of *ALDH2* reduction by DCR-AUD, which include plasma acetaldehyde, acetate, and ethanol; heart rate; facial skin temperature, and subjective feelings of alcohol intoxication or intolerance using the Subjective Effects of Alcohol Scale (SEAS; Table 3). All visits on which an EIA is conducted will require participants to check into the clinic after a 6-hour fast. Participants will be fed a standardized meal in the clinic prior to the EIA and will be admitted for an overnight stay in the Phase 1 telemetry unit. Participants will return to the site for safety, tolerability, PK, and PD monitoring (via serial EIAs) throughout the 24-week double-blind study period, as specified in Table 1. Participants who have positive ethanol reaction symptoms at the Day 169 EIA (e.g., nausea, vomiting, or substantial flushing) will return every 28 (±7) days for follow-up EIAs until the positive ethanol reaction symptoms abate. These CFU EIAs will not require overnight admission to the clinic, but all other aspects of the EIA will be conducted (see Table 3). Participants will be observed for no less than 6 hours after ethanol administration and will not be discharged until the Investigator deems it medically safe to do so.

Cohort expansion will require SRC review of available Day 15 safety data for all participants in the sentinel group before the remainder of the cohort can be enrolled. Dose escalation will require SRC review of available safety data, including the safety laboratory values, for all

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participants through at least Day 15 before the sentinel group of the next cohort can be enrolled (Section 9.6).

Individual participants will be screened for a period of up to 28 days. Screening assessments will include a psychological history and a history of alcohol consumption using the TLFB method to identify participants who are HVs and meet the minimum inclusion/exclusion alcohol consumption requirements. TLFB is a validated method to retrospectively assess drinking behavior history. Randomization and administration of study intervention will occur on Day 1.

If participants are not able to return to the site for assessments or procedures because of COVID-19 or other exceptional circumstances, visits may be rescheduled or conducted by qualified medical professionals as at-home telemedicine and/or home nursing visits at the discretion of the Investigator.

All participants will be given a diary to track AEs and temperance for the study duration. Participants will be trained on the use of the diary prior to discharge from the clinic and will report on the diary at each visit.

4.2. Scientific Rationale for Study Design

SAD testing in a single sequential Phase 1 study design has been successfully used to determine dose tolerability and PK/PD measurements. The Sponsor's proposed Phase 1 study takes this approach. Further, the use of sentinel participants is intended to ensure safe, well-tolerated doses of DCR-AUD are used.

Study participants will undergo EIAs to evaluate the PD effects of *ALDH2* reduction by DCR-AUD and obtain safety data regarding alcohol exposure in adult HVs during concomitant alcohol consumption. Participants will be administered alcohol on Day –1 (prior to administration of study intervention) to establish a baseline for biomarker assessments and evaluate eligibility. Following administration of study intervention, participants will be administered serial EIAs, as specified in Table 1.

- EIAs will be used to confirm target engagement. The degree of ALDH2 reduction is measurable only after ethanol administration, via levels of plasma acetaldehyde and acetate, and measurement of heart rate and facial skin temperature.
- The safety of ethanol ingestion in the presence of DCR-AUD will be assessed during EIAs, each of which will be followed by overnight admission and monitoring in a Phase 1 telemetry unit. The Investigator will not discharge any participant experiencing ongoing effects of ethanol administration until it is deemed medically safe to do so.
- Serial EIAs will be used to determine the duration of action of DCR-AUD, so that an appropriate dose and dosing interval and safety monitoring plan for participants can be developed for later clinical trials.

4.3. Justification for Dose

The initial dose levels to be administered were determined following evaluation of nonclinical PK/PD and safety data (FDA, 2005) and will ascend from 80 mg in Cohort 1, to 240 mg in Cohort 2, to 480 mg in Cohort 3, and 960 mg in the optional Cohort 4.

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Safety margins for DCR-A1203 were determined using the HEDs of the dose levels for the 5-week toxicity studies. The NOAEL in the mouse and monkey repeat-dose toxicity studies was considered by the study director to be 300 mg/kg, the highest dose level administered. Based on input from the FDA regarding clinical pathology and histopathology in a single 300 mg/kg animal in the monkey study, a more conservative approach is being taken, and the mid-dose of 100 mg/kg is being treated as the NOAEL for the purpose of determining a safety margin for the monkey study. The monkey is the more relevant species due to a greater homology with the human transcriptome, allowing for assessment of on- and off-target effects (Cooper et al., 2003). For the planned starting flat dose of 80 mg, the exposure multiple relative to the monkey HED for 100 mg/kg would be 28-fold. For the planned high dose of 960 mg, the exposure multiple relative to the monkey HED for 100 mg/kg would be 2-fold (Table 4).

Table 4: Nonclinical Safety Margins for 5-Week Repeat-dose Toxicity Studies

Species	Dose (mg/kg)	HED [a] (mg/kg)	Exposure Multiple Relative to 80-mg Clinical Dose [b]	Exposure Multiple Relative to 960-mg Clinical Dose [b]
Mouse	30	2.4	2	0.2
Monkey		9.7	8	0.7
Mouse	100 [c]	8.1	7	0.6
Monkey		32.3	28	2
Mouse	300 [c]	24.4	21	2
Monkey		96.8	85	7

Abbreviations: HED = human equivalent dose

[a] The HED is based on the Guidance for Industry: Estimating the Maximum Safe Starting Dose in Initial Clinical Trials for Therapeutics in Adult Healthy Volunteers (FDA, 2005).

[b] A 70-kg human is used for determination of mg/kg for clinical dose and margin determination

[c] The NOAEL in the mouse and monkey repeat-dose toxicity studies was considered by the study director to be 300 mg/kg, the highest dose level administered. Based on input from the FDA regarding clinical pathology and histopathology in a single 300 mg/kg animal in the monkey study, a more conservative approach is being taken, and the mid-dose of 100 mg/kg is being treated as the NOAEL for the purpose of determining a safety margin for the monkey study

4.4. End of Study Definition

A participant is considered to have completed the study if he/she has completed all phases of the study, including the last scheduled procedure shown in the SoA (Section 1.3).

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

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5. STUDY POPULATION

Up to 36 HV participants are planned to be enrolled in this study: 27 in the planned first 3 dose cohorts plus an additional 9 HVs if an optional fourth cohort is enrolled.

Protocol waivers or exemptions are not allowed. Participants may undergo rescreening one time at the discretion of the Investigator or Sponsor. Only pregnancy test, hematology and chemistry, and coagulation tests may be repeated.

5.1. Inclusion Criteria

Participants are eligible to be included in the study only if all the following criteria apply.

Age

1. 21 to 65 years of age, inclusive, at the time of signing the informed consent.

Type of Participant and Disease Characteristics

2. Overtly healthy, as determined by medical evaluation including medical history, physical examination, laboratory tests, and cardiac monitoring.
3. Social drinkers of modest amounts (≤ 2 drinks/day and ≤ 3 days/week) who are able to refrain from drinking alcohol during the outpatient portion of the trial.
4. Negative screen for drugs of abuse (to include at minimum: amphetamines, barbiturates, cocaine, opioids, and benzodiazepines) at Screening and Day 1. Cannabis will not be recorded as a drug of abuse for this study.
5. Willing to participate in repeated low-dose EIAs followed by an overnight clinic stay (see Table 1).
6. Has a negative test for SARS-CoV-2 infection on Day −1 and prior to admission to the clinical unit. (Refer to Study Manual for details on the timing of SARS-CoV-2 testing.)
7. Systolic BP in the range of 90 to 140 mmHg and diastolic BP in the range of 50 to 95 mmHg.

Sex and Childbearing Potential

8. Male or female
   - Male participants with partners of childbearing potential must agree to use contraception from Screening through at least 24 weeks after the last dose of study intervention and refrain from donating sperm during this period (see Section 10.4).
   - Female participants may not be pregnant or breastfeeding, and at least one of the following conditions must apply:
     - Is not a woman of childbearing potential (WOCBP) **or**
     - If a WOCBP, must agree to follow the contraceptive guidance (see Section 10.4), beginning at consent and the first Screening visit and for at least 24 weeks after the last dose of study intervention.

Weight

9. BMI within the range 18.0 to 32.0 kg/m^2 (inclusive).

Informed Consent

10. Capable of giving signed informed consent, which includes compliance with the requirements and restrictions listed in the ICF and in this protocol.

5.2. Exclusion Criteria

Participants are excluded from if any of the following criteria apply:

Medical Conditions

1. History of any medical condition that may interfere with the absorption, distribution, or elimination of study intervention, or with the clinical and laboratory assessments in this study, including (but not limited to): chronic or recurrent renal disease, functional bowel disorders (e.g., frequent diarrhea or constipation), clinically significant cardiovascular or pulmonary disease or has cardiovascular or pulmonary disease requiring pharmacologic medication, GI tract disease, pancreatitis, seizure disorder, mucocutaneous, or musculoskeletal disorder. NOTE: Persons with clinically stable asthma who have not been hospitalized in the prior year and are treated only with orally inhaled medications are not excluded.
2. History of suicidal attempt as an adult or suicide ideation in the past year that resulted in pharmacologic treatment or hospitalization. Specifically:
   - Answer of "yes" on items 4 or 5 of the Suicidal Ideation section of the C-SSRS at screening if ideation occurred in the previous 6 months.
   - Answer of "yes" on any item of the Suicidal Behavior section of the C-SSRS, except for the Non-Suicidal Self-injurious Behavior if this behavior occurred in the previous 2 years.
3. Any history of severe or recent clinically significant depression, anxiety, bipolar disorder, schizophrenia, or other neuropsychiatric disorder that, in the judgment of the Investigator, represents a safety risk to the individual were they to participate in the trial, as informed by the participant's medical history and/or responses to the MINI Screen Questionnaire.
4. History of delirium tremens or alcohol-related seizures.
5. History of significant adverse reaction(s) to alcohol.
6. Any condition that, in the opinion of the Investigator, would make the participant unsuitable for participation or could interfere with participation in or completion of the study including:
   a. Poorly controlled or unstable hypertension
   b. Clinically significant abnormalities in vital signs: pulse rate (< 40 or > 90 bpm), respiratory rate, or temperature

c. Clinically significant abnormalities in 12-lead ECG at Screening or predose on Day 1, including QTcF > 470 msec in females and > 450 msec in males
d. Diabetes mellitus treated with insulin or hypoglycemic agents (including metformin) or $HbA1_C$ > 7%
e. Asthma requiring hospital admission within the preceding 12 months
f. Currently poorly controlled endocrine conditions, except for hypothyroidism that is stable (no treatment change in prior 6 months)
g. Significant infection or known systemic inflammatory process ongoing at Screening
h. History of chronic or recurrent UTI, or UTI within 1 month prior to Screening

7. History of malignancy within the preceding 3 years requiring treatment, with the exception of excised low grade basal cell skin neoplasms.

8. History of substance use disorder (SUD), including alcohol (AUD) or illicit drug use (excluding cannabis) within the preceding 12 months. Nicotine use is permitted.

9. History of any concomitant medical condition for which alcohol consumption is prohibited or advised against by the participant's physician or health care provider.

10. Clinically significant illness within the 7 days prior to the administration of study intervention

Prior/Concomitant Therapy

11. History of multiple drug allergies or a history of allergic reaction to an oligonucleotide-based therapy

12. Use of prescription medications (except for hormonal replacement/contraceptive medication for women and inhaled medication for treatment of clinically stable asthma) within 14 days or 5 half-lives (whichever is longer) prior to administration of study intervention. Participants being treated for hypothyroid disease must be on stable treatment (no treatment changes in the preceding 6 months).

13. Receipt of any vaccine (including COVID-19) within 14 days prior to administration of study intervention.

14. Regular use of OTC medications, including NSAID (Periodic or occasional NSAID use to control temporary pain is not exclusionary.)

Prior/Concurrent Clinical Study Experience

15. Has received an investigational agent within 30 days or 5 half-lives (whichever is longer) prior to dosing or is in follow-up of another clinical study prior to initial dosing with the study intervention.

Diagnostic Assessments

16. Seropositive for antibodies to HIV, HBV, or HCV at Screening (historical testing may be used if performed within the 3 months prior to screening). NOTE: In participants with previous treatment for hepatitis C with direct-acting HCV medication and seropositivity

for HCV, or in participants with prior infection and spontaneous resolution, HCV RNA must be undetectable (at least 2 negative HCV RNA tests at least 12 weeks apart), and the HCV infection must have been resolved or cured > 3 years prior to initial dosing with the investigational medication.

17. Had laboratory-confirmed SARS-CoV-2 infection in the 14 days prior to randomization.
18. Liver function test results (AST, ALT, GGT, total bilirubin) above the normal range.
19. Safety laboratory test result considered clinically unacceptable for study participation by the Investigator.

Other Exclusions

20. History of intolerance to SC injection(s) or significant abdominal scarring that could potentially hinder study intervention administration or evaluation of local injection site tolerability.
21. Scheduled for an elective surgical procedure during the conduct of this study.
22. Donation of > 500 mL of blood within the 2 months prior to administration of study intervention or donation of plasma within 7 days prior to Screening.

5.3. Lifestyle Considerations

Caffeine, Alcohol, and Cannabis

- During each dosing session, participants will abstain from ingesting caffeine- or xanthine-containing products (e.g., coffee, tea, cola drinks, and chocolate) for 12 hours before the start of dosing until after collection of the final PK and/or PD sample.
- Study participants are to refrain from drinking alcohol and using cannabis from the screening visit until the final study visit and must have a negative breath alcohol test on the day of the study visit prior to the EIA.

Activity

- Participants must not have undertaken, or plan to undertake, a significant change in exercise levels from 48 hours prior to entrance into the clinical research center until the end of study.
- Participants should abstain from strenuous exercise for 48 hours before each blood collection for clinical laboratory tests. Participants may participate in light recreational activities (e.g., walking at a pace < 3 miles per hour, shopping, watering plants) in that 48-hour time period.

Meals and Dietary Restrictions

- Participants will be required to be fasted for at least 6 hours and then fed a standardized meal in the clinic prior to administration of EtOH on the days of EIAs.

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5.4. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently randomly assigned to study intervention. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAEs.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened. Participants may undergo rescreening one time at the discretion of the Investigator or Sponsor. Only pregnancy test, hematology and chemistry, and coagulation studies may be repeated. Rescreened participants should be assigned the same participant number as for the initial screening.

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6. STUDY INTERVENTION

Study intervention is defined as any investigational intervention(s), including placebo, intended to be administered to a study participant according to the study protocol.

6.1. Study Intervention(s) Administered

DCR-AUD or placebo will be administered subcutaneously as fixed doses.

6.1.1. Dose Levels and Dose Escalation

Doses of DCR-AUD to be administered will ascend from 80 mg in Cohort 1, to 240 mg in Cohort 2, to 480 mg in Cohort 3, and 960 mg in the optional Cohort 4.

Dose escalation refers to escalation to the next consecutive dose level in line with prespecified dose escalation rules. For the purpose of this protocol, escalation rules are based on the emergent safety and PK profiles.

Clinical doses are expressed in terms of the weight of the DCR-AUD free acid, rather than on that of the sodium salt (Table 5).

Table 5: Study Intervention Administered

Arm Name	Active	Placebo
Intervention Name	DCR-AUD	Physiologic saline (0.9% aqueous sodium chloride) for injection
Intervention Type	Drug	Drug
Dose Formulation	solution for injection	n/a
Unit Dose Strength	160 mg/mL	n/a
Dose Level(s) and Frequency	80 mg, 240 mg, 480 mg, or 960 mg single dose	volume to match active single dose
Route of Administration	SC injection (thigh or abdomen)	SC injection (thigh or abdomen)
Use	Experimental	Placebo comparator
IMP or NIMP	IMP	n/a
Sourcing	Provided centrally by the Sponsor or designee	Provided locally by the study site (Pharmacy staff is not blinded)
Packaging and Labeling	DCR-AUD will be provided in vials. Each vial will be labeled as required per country.	n/a

Abbreviations: IMP: investigational medicinal product; n/a: not applicable; NIMP: non-investigational medicinal product; SC: subcutaneous

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6.2. Preparation/Handling/Storage/Accountability

6.2.1. Handling and Accountability

The Investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study intervention received and that any discrepancies are reported and resolved before use of the study intervention.

Only participants enrolled in the study may receive study intervention and only authorized site staff may supply or administer study intervention.

The Investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (i.e., receipt, reconciliation, and final disposition records).

Further guidance and information for the final disposition of unused study intervention are provided in the Pharmacy Manual.

6.2.2. Storage

DCR-AUD is to be stored at or below 30°C (inclusive); do not freeze.

All study intervention must be stored in a secure, environmentally controlled and monitored (manual or automated) area in accordance with the labeled storage conditions, with access limited to the Investigator and authorized site staff.

The placebo comparator should be stored in accordance with the product labeling.

6.2.3. Preparation and Administration

Study intervention will be prepared by the unblinded pharmacist or designee. A second medically qualified person must check the dose preparation prior to administration to be sure the correct dose has been prepared.

If stored at 2°C to 8°C, DCR-AUD should be allowed to warm to room temperature for approximately 1 hour before administration.

DCR-AUD is administered as a SC injection into the thigh or abdomen. The maximum volume of a single SC injection should not exceed 1.5 mL; if the dose requires an injection volume > 1.5 mL, the total dose will be administered as 2 or more SC injections of equal volume at separate injection sites in the abdomen. All used DCR-AUD vials will be retained and quarantined in the pharmacy. Once drug accountability is recorded to be accurate, the vials will be destroyed on site per clinic SOP.

Placebo will be administered as an SC injection of physiologic saline (0.9% aqueous sodium chloride) in the thigh or abdomen at a volume equal to that of DCR-AUD.

Complete details will be provided in the Pharmacy Manual.

6.3. Measures to Minimize Bias: Randomization and Blinding

This is a randomized, placebo-controlled, double-blind study, where the Investigators, study site personnel (excluding pharmacy staff), CRO staff, sponsor Medical Monitor, and study participants will be blinded for the duration of the study. The Sponsor will remain unblinded for

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the duration of the study. This enables the Sponsor to immediately and comprehensively evaluate the safety of the study participants.

Within each SAD cohort, the sentinel participants will be randomly assigned to DCR-AUD or placebo in a 2:1 ratio. The overall DCR-AUD to placebo ratio within each cohort is also 2:1. All participants will be centrally assigned to randomized study intervention using an Interactive Voice/Web Response System (IVRS/IWRS). Before the study is initiated, the telephone number and call-in directions for the IVRS and/or the log in information and directions for the IWRS will be provided to each site.

Investigators, site staff (excluding pharmacy staff), CRO staff, sponsor Medical Monitor, and participants will remain blinded to each participant's assigned study intervention throughout the course of the study. To maintain this blind, the unblinded site pharmacy staff will be responsible for the preparation and dispensation of all study intervention.

In the event of a Quality Assurance audit, the auditor(s) will be allowed access to unblinded study intervention records at the site(s) to verify that randomization/dispensing has been done accurately.

The IVRS/IWRS will be programmed with blind-breaking instructions. In case of an emergency, the Investigator has the sole responsibility for determining if unblinding of a participant's treatment assignment is warranted. Participant safety must always be the first consideration in making such a determination. If the Investigator decides that unblinding is warranted, the Investigator should make every effort to contact the Medical Monitor prior to unblinding a participant's treatment assignment, unless this could delay emergency treatment of the participant. If a participant's treatment assignment is unblinded, the Medical Monitor must be notified within 24 hours after breaking the blind. The date and reason that the blind was broken must be recorded in the source documentation and case report form, as applicable.

Potentially unblinded study results will not be shared with blinded study participants or site personnel.

For details regarding unblinding associated with interim analyses, see Section 9.5.

6.4. Study Intervention Compliance

At the site, study intervention will be administered by the Investigator or designee. The date and time of each dose administered in the clinic will be recorded in the source documents and recorded in the eCRF. The dose of study intervention and study participant identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study intervention.

6.5. Dose Modification

Cohorts will be filled sequentially, starting with the first dose cohort. Modified dosing regimens may be explored if required based on emergent safety and tolerability data or the occurrence of confirmed DLTs (as defined in Section 7.3.1), and available PD or PK data, where applicable.

At each decision point listed in Section 9.6, the SRC will make a determination as whether to continue the dosing and enrollment as planned; to interrupt dosing and enrollment in the current cohort or escalation to the next dose cohort; or to stop the study. However, if the SRC decides

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not to escalate the dose and a stopping rule has not been met, the SRC may make a recommendation to (1) test a lower dose than planned, (2) retest a previous dose, or (3) stop dosing. The SRC may also elect to have an independent expert Data Safety Monitoring Committee (DSMC) convene if a study stopping rule is triggered to make a recommendation as to resumption, permanent discontinuation, or modification of the trial that has been suspended or interrupted on the basis of an SRC decision (see Section 10.1.5.2).

6.6. Continued Access to Study Intervention After the End of the Study

Not applicable.

6.7. Concomitant Therapy

All study participants must abstain from taking prescription drugs (except for hormonal replacement/contraceptive medication for women and inhaled medication for treatment of clinically stable asthma) within 14 days or 5 half-lives (whichever is longer) prior to administration of study intervention until EOT. Participants being treated for hypothyroid disease must be on stable treatment (no treatment changes in the preceding 6 months).

Regular use of OTC medications (including NSAIDs) is not allowed. Occasional use of NSAIDs for pain management is acceptable.

Regular use of vitamins is acceptable.

Participants must not receive any vaccine in the 14 days prior to or following administration of study intervention.

NOTE: Any medication (including OTC or prescription medicines, vitamins, and/or herbal supplements) or vaccine that the participant is receiving at the time of enrollment or receives during the study must be recorded along with:

1. Reason for use
2. Dates of administration, including start and end dates
3. Dosage information, including dose and frequency

6.7.1. Rescue Medicine

Rescue medication is permitted at the discretion of the Investigator.

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7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Participant Discontinuation/Withdrawal from the Study

A participant may withdraw from the study at any time at his/her own request or may be withdrawn at any time at the discretion of the Investigator for safety, behavioral, compliance, or administrative reasons.

If a participant has a significant adverse reaction to alcohol at the Day –1 visit (before administration of DCR-AUD), the participant will be discontinued from the study. The participant will be replaced.

If possible, at the time of discontinuing from the study, an early termination (ET) visit should be conducted, as shown in the SoA Table 1.

If the participant withdraws consent for disclosure of future information, the Sponsor may retain and continue to use any data collected before such a withdrawal of consent.

If a participant withdraws from the study, he/she may request destruction of any samples taken and not tested, and the Investigator must document this in the site study records.

The reason for participant discontinuation or withdrawal from the study will be recorded on the eCRF. Participants who sign the ICF and are randomized but *do not* receive the study intervention may be replaced. Participants who sign the ICF and are randomized and *do* receive the study intervention, and subsequently withdraw or are withdrawn or discontinued from the study may be replaced at the discretion of the Sponsor.

7.2. Lost to Follow up

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow up, the Investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.
- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study.

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7.3. Cohort Stopping Rules

If a participant experiences a DLT (Section 7.3.1), an SAE (Section 10.3.2), unless it is clearly the result of a non-study-related event, or a clinically relevant ECG finding as noted in Section 7.3.2, enrollment and dosing of additional participants will be paused while the SRC reviews the event. Based on this review, a decision will be made as to whether study enrollment and dosing may resume.

Escalation to the next cohort will be suspended if 2 or more participants in a cohort experience DLTs, until the SRC convenes to review the events and the totality of the safety data generated. Cohorts dosed at levels lower than the dose level at which the above criteria occurred may continue dosing with the approval of the SRC.

Dose escalation will not be advanced if exposure levels in humans exceed the mean AUC and C_{max} values observed at the mid-dose level (100 mg/kg) in the 5-week monkey toxicokinetic study (Study Number 20-A1203-P-030; $AUC_{0\text{-}48h}$ 383000 hr·ng/mL and C_{max} 23300 ng/mL).

All ongoing participants will continue to be followed for safety assessments as indicated in the schedule of activities.

The Sponsor will promptly notify all sites if cohort stopping rules are triggered.

7.3.1. Dose Limiting Toxicities

A DLT is defined as:

- an AE of ≥ Grade 3 intensity (CTCAE Version 5.0) in one participant, unless it is clearly the result of a non-study-related event **OR**
- any 2 AEs of ≥ Grade 2 intensity in the same body system in one participant.

7.3.2. Electrocardiogram Findings

If a clinically significant finding is identified (including, but not limited to, the QTcF findings below) after enrollment, the Investigator or qualified designee will determine if the participant can continue in the study and if any change in participant management is needed. This review of the ECG printed at the time of collection must be documented. Any new clinically relevant finding should be reported as an AE.

- Absolute QTcF > 500 msec and/or
- QTcF change of > 60 msec from baseline

7.4. Study Stopping Rules

All further dosing in the study will be stopped if any of the following conditions occur AND the SRC recommends stopping the study:

- 2 participants develop a Grade 3 CTCAE event unless it is clearly the result of a non-study-related event.
- 1 participant develops a ≥ Grade 4 CTCAE event unless it is clearly the result of a non-study-related event.

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In the event a study stopping rule is triggered and the SRC calls a halt on dosing or dose escalation, the SRC may request that an external, independent and unblinded DSMC be convened to review the decision and make a recommendation to the SRC as to whether the study should stop or continue with no changes or continue with appropriate modifications to address the safety concern (see Section 10.1.5.2). Should the DSMC recommend stopping the study, all ongoing participants will continue to be followed for safety assessments as indicated in the schedule of activities.

The Sponsor will promptly notify the site if study stopping rules are triggered.

8. STUDY ASSESSMENTS AND PROCEDURES

Study procedures and their timing are summarized in the SoA (Section 1.3). Protocol waivers or exemptions are not allowed. Participants may undergo rescreening one time at the discretion of the Investigator or Sponsor. Only pregnancy test, hematology and chemistry, and coagulation tests may be repeated.

Immediate safety concerns should be discussed with the Sponsor immediately upon occurrence or awareness.

Adherence to the study design requirements, including those specified in Table 1 and Table 3 (Section 1.3), is essential and required for study conduct. Participants will be given a diary to track AEs and temperance for the study duration. Participants will be trained on the use of the diary prior to discharge from the clinic for Visit 1 and will report on the diary at each visit.

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

If multiple assessments are due, the order of priority should be ECG, vitals, PK, and then other assessments.

The maximum amount of blood drawn from each participant at any visit (including efficacy, PK, biomarker, and safety laboratory testing) will not exceed:

- Per Visit:
  - 30 mL for Sentinel group
  - 56 mL for Expanded group
- Per 8-week period:
  - 156 mL for Sentinel group
  - 297 mL for Expanded group

Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

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8.1. Efficacy Assessments

This is a Phase 1 study with the primary objective of evaluating safety. Pharmacokinetic and PD assessments are detailed in Sections 8.5 and 8.7, respectively.

8.2. Safety Assessments

Planned time points for all safety assessments are provided in the SoA (Section 1.3). Safety assessments will be conducted in all participants at every study visit unless otherwise specified. Site personnel will be provided training in the use of all study-specific instruments (see the Study Reference Manual).

8.2.1. Physical Examinations

Complete physical examinations will be conducted at every visit.

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.

8.2.2. 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.

Note: In addition to standard vital sign measurements for safety, vital signs will be recorded as part of the EIA and results will be identified as such (e.g., HR for EIA) in the eCRF.

8.2.3. Electrocardiograms

Standard 12-lead ECGs will be performed in the supine position after the participant has rested comfortably for 10 minutes. ECGs will be obtained using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and corrected QT interval (QTcF, Fridericia correction). Refer to Section 7.3.2 for QTc withdrawal criteria and any additional readings that may be necessary.

The Investigator or designee is responsible for reviewing the ECG(s) to assess whether the results are within normal limits and to determine the clinical significance of the results. These assessments will be recorded on the CRF.

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Note: If multiple assessments are due, the order of priority should be ECG, vitals, PK, and then other assessments, with the PK sampling being performed preferably at the nominal time point. ECGs also will be conducted for EIA assessments. These ECG results will be recorded as part of the EIA and will be identified as such (e.g., ECG for EIA) in the eCRF.

8.2.4. Alcohol Consumption via Timeline Follow Back

Study participants are to refrain from drinking alcohol throughout the outpatient portion of the study (sentinel participants will refrain from alcohol throughout the in-clinic portion as well). At every visit, the TLFB will be used to assess each participant's abstention from alcohol since the previous visit. The TLFB was developed as a procedure to aid recall of past drinking (Sobell & Sobell, 1992). Currently, self-reports are the only viable method for retrospectively measuring drinking with any precision. Alternative methods exist, but they are either impractical (e.g., continuous direct observation), fraught with problems (e.g., alcohol sweat patches) or they only measure very recent drinking (e.g., biochemical indicators or blood alcohol tests). Consequently, there is no practical alternative technology other than self-reports for retrospectively assessing drinking. TLFB stands as the most exhaustively evaluated method that can be used for this purpose.

8.2.5. Columbia-Suicide Severity Rating Scale

The C-SSRS is a suicidal ideation rating scale created by researchers at Columbia University (Posner et al., 2011). 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.

8.2.6. Mini-International Neuropsychiatric Interview

The MINI is a brief structured diagnostic interview to meet the need for a short but accurate structured psychiatric interview for multicenter clinical trials (Sheehan et al., 1998). This validated tool can be administered in a short period of time (approximately 15 minutes) and will be administered at screening to exclude participants with major psychiatric disorders. The MINI will be administered by a Health Care Provider.

8.2.7. Clinical Safety Laboratory Assessments

See Section 10.2 for the list of clinical laboratory tests to be performed and the SoAs (Section 1.3) for the timing and frequency.

The Investigator must review the laboratory report, document this review in the eCRF, and record any clinically relevant changes occurring during the study in the AE section of the eCRF. The laboratory reports must be filed with the source documents.

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All laboratory tests with values considered clinically significantly abnormal during participation in the study should be repeated (central laboratory) until the values return to normal or stabilize at a level no longer considered clinically significant by the Investigator or Medical Monitor.

- If such values do not return to normal/baseline within a period of time judged reasonable by the Investigator, the etiology should be identified and the Sponsor notified.
- All protocol-required laboratory assessments, as defined in Section 10.2, must be conducted in accordance with the Laboratory Manual and the SoA (Section 1.3).
- If laboratory values from non-protocol specified laboratory assessments performed at the institution's local laboratory require a change in participant management or are considered clinically significant by the Investigator (e.g., SAE or AE), then the results must be recorded in the eCRF.

8.3. Adverse Events, Serious Adverse Events, and Other Safety Reporting

The definitions of AEs, SAEs, and adverse events of special interest (AESI) can be found in Sections 10.3.1, 10.3.2, and 10.3.4, respectively.

AEs will be reported by the participant.

The Investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following up AEs that are severe or serious, and considered related to the study intervention or study procedures.

8.3.1. Time Period and Frequency for Collecting Adverse Event Information

All AEs and SAEs will be collected from the time the ICF is signed through the last follow-up visit (including CFU, if applicable) at the time points specified in the SoAs (Section 1.3). Ongoing SAEs will be followed until resolution.

Medical occurrences that begin before the start of study intervention but after obtaining informed consent will be recorded on the Medical History/Current Medical Conditions section of the eCRF, not the AE section.

All SAEs will be recorded and reported to the Sponsor or designee within 24 hours, as indicated in Section 10.3.5. The Investigator will submit any updated SAE data to the Sponsor within 24 hours of it being available.

Investigators are not obligated to actively seek AE or SAE after conclusion of study participation. However, if the Investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study intervention or study participation, the Investigator must promptly notify the Sponsor.

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8.3.2. Method of Detecting AEs and SAEs

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the participant is the preferred method to inquire about AE occurrences.

8.3.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the Investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs and AESIs (as defined in Section 10.3.3), will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.2). Further information on follow-up procedures is provided in Section 10.3.4.

8.3.4. Regulatory Reporting Requirements for SAEs

Prompt notification by the Investigator to the Sponsor of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.

The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRBs/IECs, and Investigators.

Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and Sponsor policy and forwarded to Investigators as necessary.

8.3.5. Pregnancy

Details of all pregnancies in female participants and female partners of male participants will be collected after the start of study intervention and until 24 weeks after the last dose.

If a pregnancy is reported, the Investigator should inform the Sponsor within 24 hours of learning of the pregnancy and should follow the procedures outlined in Section 10.4.4.

While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE. Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs.

The participant or pregnant partner will be followed to determine the outcome of the pregnancy. The Investigator will collect follow-up information on the participant or pregnant partner and the neonate, and the information will be forwarded to the Sponsor.

Any post-study pregnancy-related SAE considered reasonably related to the study intervention by the Investigator will be reported to the Sponsor as described in Section 8.3.4. While the Investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.

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8.4. Treatment of Overdose

For this study, any dose of DCR-AUD greater than the specified dose will be considered an overdose.

Dicerna does not recommend specific treatment for an overdose.

In the event of an overdose, the Investigator should:

- Contact the CRO Medical Monitor immediately.
- Closely monitor the participant for any AE/SAE and laboratory abnormalities until DCR-AUD PD effects can no longer be detected.
- Document the quantity of the excess dose.

8.5. Pharmacokinetics

Blood samples will be collected for measurement of plasma concentrations of AUD and/or its metabolites as specified in the SoAs (see Section 1.3). Urine samples will be collected for measurement of urine concentrations of AUD and/or its metabolites as specified in the SoA (Section 1.3).

Instructions for the collection and handling of biological samples will be provided by the Sponsor in the Laboratory Manual and the Laboratory Specification document. The actual date and time (24-hour clock time) of each sample will be recorded.

Each plasma sample will be divided into 2 aliquots (one for PK and one backup). Samples collected for analyses of plasma concentrations of AUD and/or its metabolites may also be used to evaluate safety or efficacy aspects related to concerns arising during or after the study.

Pharmacokinetic parameters to be determined may include clearance (CL) and apparent volume of distribution (Vd/F) estimates, along with secondary parameters of area under the concentration curve (AUC), maximum observed concentration (C_{max}), minimum observed concentration (C_{min}), time to maximum concentration (T_{max}), and terminal elimination half-life ($t_{1/2}$). Additional parameters may be estimated if deemed appropriate.

Any changes in the timing or addition of time points for any planned study assessments must be documented and approved by the relevant study team member and then archived in the Sponsor and site study files but will not constitute a protocol amendment. The IRB/IEC will be informed of any safety issues that require alteration of the safety monitoring scheme or amendment of the ICF.

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

8.6. Genetics

A sample of whole blood for DNA isolation will be collected from participants who have consented to participate in the optional genetic analysis component of the study. Participation is optional; participants who do not wish to participate in the genetic research may still participate in the study.

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In the event of DNA extraction failure, a replacement genetic blood sample may be requested from the participant. Signed informed consent will be required to obtain a replacement sample, unless it was included in the original consent.

See Section 10.5 for information regarding genetic research. Details on processes for collection and shipment and destruction of these samples can be found in the Laboratory Manual.

8.7. Pharmacodynamics

DCR-AUD is designed to selectively reduce ALDH2 activity 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) and objective physiological biomarkers (heart rate and facial skin temperature). Participants' subjective experience of the effects of alcohol will be assessed using the SEAS. Instructions for the collection and handling of biological samples will be provided by the Sponsor in the Laboratory Manual and the Laboratory Specification document

8.7.1. Ethanol Interaction Assessments

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, heart rate, facial skin temperature, and subjective feelings of alcohol intoxication or intolerance using the SEAS (Morean et al., 2013). Adverse events, vital signs, and ECG will also be monitored and recorded for safety. Assessments will be measured for up to 2.5 hours following ethanol administration. Published literature consistently demonstrate that administration of low/moderate alcohol intake (0.1-0.8 g/kg) in human *ALDH2* mutation homo- or heterozygotes results in clearly differentiated and statistically significant increases in blood acetaldehyde, heart rate, and facial skin temperature compared with *ALDH2* normal alleotypic controls (Bae et al., 2012; Peng et al., 1999; Peng et al., 2007; Nishimura et al., 2002; Enomoto et al., 1991).

EIAs will be conducted in accordance with the SoA in Section 1.3. 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. Participants will be required to be fasted for at least 6 hours prior to administration of a standardized meal and then ethyl alcohol (EtOH) and must have a negative breath alcohol test on the day of the study visit prior to the EIA. Prior to each EIA, venous catheters will be placed at least 20 minutes before the first EIA vital signs are assessed at time 0. During the EIA, participants will receive nothing by mouth (remain NPO) except water ad libitum.

Participants will consume a fixed dose of ethanol mixed in a liquid that has no additional alcohol, no caffeine, and is low in sugar. The ethanol dose will be 0.4 g/kg ethanol for male participants and 0.34 g/kg ethanol for female participants, not to exceed 28 grams EtOH for men or 24 g EtOH for women per EIA. Ethanol will be consumed in 4 aliquots over a 30-minute period. Assessments will be made over an estimated 2.5-hour period, as detailed in Table 3.

Participants will remain in the Phase 1 telemetry unit for an overnight admission. The Investigator will not discharge any participant experiencing ongoing effects of ethanol administration until it is deemed medically safe to do so.

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8.7.1.1. PD Biomarkers for EIA

8.7.1.1.1. EIA Blood Biomarkers

Blood biomarkers to be assessed include measurement of acetaldehyde, acetate, and ethanol. Blood samples (maximum 32 mL/day) will be collected via a venous access device immediately prior to EtOH consumption (time 0) and at 15, 30, 45, 60, 90, 120, and 150 minutes postdose (Table 3). Additional details regarding blood sample collection and processing will be detailed in the Laboratory Manual.

8.7.1.1.2. EIA Physiological Biomarkers

EIA assessments will include measurement of heart rate and facial skin temperature. Facial skin temperature will be measured using a surface scanning thermometer. Heart rate will be monitored by telemetry during the EIAs. Site personnel will be provided training in the use of all study-specific instruments (see the Study Reference Manual).

Heart rate, using telemetry, and facial skin temperature will be collected immediately predose (time 0) and at 15, 30, 45, 60, 90, 120, and 150 minutes postdose.

8.7.1.1.3. EIA Subjective Effects of Alcohol Scale

For each EIA, participants will complete the SEAS predose (during the Rest Period) and at 30, 60, 90, 120, and 150 minutes postdose. The SEAS is a 14-item tool that allows participants to rate the subjective effects of alcohol described in Table 6. Participants will rate the extent to which they are feeling each of the effects in the present time.

Table 6: Subjective Effects of Alcohol Scale (SEAS)

Feeling	Not at All				Moderately						Extremely
Relaxed	0	1	2	3	4	5	6	7	8	9	10
Wobbly	0	1	2	3	4	5	6	7	8	9	10
Lively	0	1	2	3	4	5	6	7	8	9	10
Secure	0	1	2	3	4	5	6	7	8	9	10
Rude	0	1	2	3	4	5	6	7	8	9	10
Woozy	0	1	2	3	4	5	6	7	8	9	10
Fun	0	1	2	3	4	5	6	7	8	9	10
Calm	0	1	2	3	4	5	6	7	8	9	10
Aggressive	0	1	2	3	4	5	6	7	8	9	10
Dizzy	0	1	2	3	4	5	6	7	8	9	10
Demanding	0	1	2	3	4	5	6	7	8	9	10
Mellow	0	1	2	3	4	5	6	7	8	9	10
Funny	0	1	2	3	4	5	6	7	8	9	10
Talkative	0	1	2	3	4	5	6	7	8	9	10

Source: Morean et al. 2013.

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8.7.1.2. Stopping Rules for an EIA

During the conduct of an EIA, administration of alcohol to a participant may be stopped for the following physiologic responses, though follow-up EIA assessments will be conducted:

- Any vomiting or severe nausea (as judged by Investigator)
- Systolic blood pressure increase of > 25 mmHg (and/or to a level > 150 mmHg) or decrease of > 10 mmHg (to systolic < 90 mmHg)
- Diastolic blood pressure decrease to < 50 mmHg or any decline accompanied by symptomatic hypotension (pre-syncope, syncope, lightheadedness)
- HR increase of > 20 beats per minute (or to a level > 100 beats per minute)
- Temperature increase of > 1°Celsius
- Any clinically meaningful change in affect or clinical status, per Investigator or supervising designee's clinical judgment.

8.7.1.3. Follow-up of Participants Who Continue to Have Positive Ethanol Reaction Symptoms at Day 169

Participants who have positive ethanol reaction symptoms at the Day 169 EIA (e.g., nausea, vomiting, or substantial flushing) will return every 28 (±7) days for follow-up EIAs until the positive ethanol reaction symptoms abate. These CFU EIAs will not require overnight admission to the clinic, but all other aspects of the EIA will be conducted (see Table 3). Participants will be observed for no less than 6 hours after ethanol administration and will not be discharged until the Investigator deems it medically safe to do so.

8.8. Immunogenicity Assessments

Antibodies to DCR-AUD will be evaluated in serum samples collected from all participants according to the SoA. Additionally, serum samples should also be collected at the final visit from participants who discontinued study intervention or were withdrawn from the study. These samples will be tested by the Sponsor or Sponsor's designee.

Serum samples will be screened for antibodies binding to DCR-AUD, and the titer of confirmed positive samples will be reported. Other analyses may be performed to verify the stability of antibodies to DCR-AUD and/or further characterize the immunogenicity of DCR-AUD.

The detection and characterization of antibodies to DCR-AUD will be performed using a validated assay method by or under the supervision of the Sponsor. All samples collected for detection of antibodies to DCR-AUD will also be evaluated for DCR-AUD serum concentration to enable interpretation of the antibody data. Antibodies may be further characterized and/or evaluated for their ability to neutralize the activity of the study intervention(s). Samples for the detection and characterization of antibodies to DCR-AUD will be stored until a validated assay method is available.

8.9. Health Economics

Health Economics parameters are not planned in this study.

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9. STATISTICAL CONSIDERATIONS

9.1. Statistical Hypotheses

Statistics will be descriptive. No tests of statistical inference are planned.

9.2. Sample Size Determination

No formal sample size estimations were performed. The following sample sizes were 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.

- 27 HV participants (3 cohorts with 9 participants each, 2 to 1 randomization), plus an additional 9 HV participants (2 to 1 randomization), for a total of 36, if an optional fourth cohort is enrolled.

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

9.3. Populations for Analyses

For purposes of analysis, the following populations are defined:

Population	Description
Enrolled	All participants who sign the ICF.
Randomized	All participants who sign the ICF and who are randomly assigned to study intervention.
Pharmacokinetic	All participants randomly assigned to study intervention and who receive a full dose of DCR-AUD and have sufficient data for at least 1 postdose PK assessment.
Pharmacodynamic	All participants randomly assigned to study intervention and who receive a full dose of study intervention and have sufficient data for at least 1 postdose PD assessment.
Safety	All participants randomly assigned to study intervention and who receive a full dose of study intervention. Participants will be analyzed according to dose received.

9.4. Statistical Analyses

9.4.1. General Considerations

In general, summary statistics (n, mean, SD, median, minimum, and maximum for continuous variables, and number and percentage of participants in each category for categorical variables) will be provided for all variables.

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

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All analyses will be based on observed data without imputation for missing values. Except for outlier analyses, measurements collected from unscheduled visits will not be included in the summary tables or figures, but will be included in the subject listings. Source data for the summary tables and statistical analyses will be presented as subject data listings.

9.4.2. Primary Endpoint(s)

The primary endpoint for all parts of the study is assessment of the incidence and severity of AEs, SAEs, and DLTs.

All safety analyses will be performed on the Safety Population. Adverse events will be defined as treatment-emergent AEs if they have a start date on or after the administration of study intervention during the treatment period. Frequency and percentages will be used to summarize AEs, SAEs, AEs of special interest, and AEs by relationship. Laboratory values will be reported by CTCAE grade and summarized, if applicable.

By-subject listings will be provided for deaths, SAEs, and DLTs.

9.4.3. Secondary Endpoint(s)

Pharmacokinetic analyses will be performed on Pharmacokinetic Population. Actual sampling times will be used for all parameter estimations.

Plasma concentrations and PK parameters will be listed and summarized by group and by time point with descriptive statistics. The arithmetic mean, SD, CV%, geometric mean, geometric CV%, minimum, median, and maximum will be presented.

Descriptive statistics and change from baseline will be provided for PD assessments, including acetaldehyde accumulation (absolute values and AUC) during the EIAs, where applicable.

Additional PK parameters may be estimated if deemed appropriate. Details will be provided in the PK Analysis Plan. Analysis of PK parameters may be reported in a supplement to the CSR.

PK analyses will be conducted with noncompartmental and/or compartmental models to determine PK parameter estimates. Population PK and Population PK-PD analyses may be performed and will be reported in a separate report.

9.4.4. Exploratory Endpoint(s)

Exploratory analyses will be conducted as deemed appropriate and will be detailed in the SAP.

9.4.5. Other Safety Analyses

Descriptive statistics and change from baseline will be provided for clinical laboratory parameters, vital sign parameters, exploratory biomarkers, and 12-lead ECG parameters by dose group and visit.

Laboratory parameter shifts from baseline to abnormal post-baseline values will be presented. Mean laboratory values over time will be plotted by dose group.

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9.5. Interim Analyses

One or more interim analyses (IA) may be conducted by the Sponsor contingent on a possible safety or PD signal in the emerging blinded data. The timing of any IA will be dictated by the nature of available clinical and PD data. The Sponsor may elect not to perform an IA if the emerging data do not warrant its conduct.

As part of any IA, all study site personnel will remain blinded, but certain members of the Sponsor staff will be unblinded to randomization for the duration of the study. Complete information regarding unblinding of the Sponsor will be detailed in the Study Blinding Plan.

The SAP will describe the conduct of an IA in greater detail if warranted.

9.6. Safety Review Committee

An SRC will conduct periodic reviews and will review all cumulative safety, tolerability, and available PD data on participants across all cohorts, approximately every 2 months during treatment and postdose 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.

Table 7 shows the minimal required timing of reviews by the SRC, as well as the decisions that the SRC may undertake with respect to cohort expansion, dose escalation, and the possible occurrence of DLTs and study stopping rules (see Section 7.4).

At its discretion, and based on clinical judgment, the SRC may suspend dosing of the study at any time, even for reasons not explicitly stated elsewhere, and refer to the DSMC for any potential concern regarding participant safety or wellbeing. In addition, the DSMC will be convened on an ad hoc basis if an AE triggers stopping rules. The DSMC will review data and advise on whether the study should be stopped to ensure the safety of study participants. Complete details on the responsibilities of the DSMC are provided in the SRC charter.

As noted in Section 6.1.1, progression from one cohort to the next higher dose is contingent upon SRC review.

Table 7: Minimal Timing of the Safety Review Committee Data Reviews

Review of sentinel dose group for continuation of dosing within a cohort	The SRC must review the available safety data (as specified in the SRC charter) collected on the first 3 participants ("sentinel group") dosed in each cohort (randomized 2:1; DCR-AUD: placebo), through at least the Day 15 assessments before the dosing of the next 6 participants in the cohort can occur.
Dose escalation to the next cohort	The SRC must review the available safety data collected on all 9 participants dosed in a given cohort (through at least the Day 15 assessments including Day 15 EIA data for applicable participants) before dose escalation to the next cohort can occur. In addition, the SRC must review 72-hr PK data on all participants in a given cohort before dose escalation, to ensure that exposure levels do not exceed those observed at the mid-dose in the 5-week monkey toxicokinetic study ($AUC_{0\text{-}48h}$ 383000 hr•ng/mL and C_{max} 23300 ng/mL). The data to be reviewed will be specified in the SRC charter.
Occurrence of a DLT	Upon the occurrence of a DLT (see Section 7.3.1), all dosing and enrollment into the current cohort or escalation to the next cohort will be interrupted until safety data can be reviewed by the SRC. The SRC will review the events associated with the DLT as well as the cumulative safety data collected on all participants previously dosed. The SRC will determine whether dosing, enrollment, and/or dose escalation may resume.
Occurrence of a safety issue that, in the SRC's clinical judgment, could affect participant safety or study conduct	Upon the occurrence of a situation or safety question that could affect participant safety or study conduct, the SRC will meet to discuss the issue. Actions to be taken include, but are not limited to: • Discontinuation of an individual participant • Discontinuation of dosing at a certain dose level • Referral to the DSMC for review and recommendation, should a pattern of AEs of concern be identified, regardless of severity
Occurrence of a potential study stopping rule	Upon the occurrence of a potential study stopping rule (see Section 7.4), all dosing and enrollment will be interrupted until safety data can be reviewed by the SRC. The SRC will review the events associated with the triggering of the stopping rule as well as the cumulative safety data collected on all participants previously dosed. The SRC will determine whether dosing, enrollment, and/or dose escalation may resume. The SRC may elect to refer the issue that triggered the study interruption to the DSMC for an independent review and recommendation regarding study resumption.

Abbreviations: AE: adverse event; AUD: alcohol use disorder; DLT; dose-limiting toxicity; DSMC: Data Safety Monitoring Committee; EIA: ethanol interaction assessment; SRC: Safety Review Committee

For additional details on the composition of the SRC and DSMC, refer to Section 10.1.5.

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10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1. Regulatory, Ethical, and Study Oversight Considerations

10.1.1. Regulatory and Ethical Considerations

This study will be conducted in accordance with the protocol and with the following:

- Consensus ethical principles derived from international guidelines, including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
- Applicable ICH Good Clinical Practice (GCP) Guidelines
- Applicable laws and regulations

The protocol, protocol amendments, ICF, Investigator Brochure, and other relevant documents (e.g., advertisements) must be submitted to an IRB/IEC by the Investigator and reviewed and approved by the IRB/IEC before the study is initiated.

Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.

The Investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
- Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
- Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations

10.1.2. Financial Disclosure

Investigators and sub-Investigators will provide the Sponsor with sufficient, accurate financial information as requested to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

10.1.3. Informed Consent Process

Each interested prospective participant (or legally authorized representative) will receive an informed consent document that contains study information and be given ample time to read the information and consider participation. The Investigator or his/her representative will explain the nature of the study and its risks and potential benefits to the prospective participant or his/her legally authorized representative and answer all questions regarding the study.

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Prospective participants must be informed that the study involves research, their participation is voluntary, and that the choice not to participate or to discontinue the study at any time will involve no penalty or loss of benefits to which the individual is otherwise entitled. Consenting participants, or their legally authorized representatives, will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study center. Adolescents (12 to < 18 years of age, or older than 12 years but younger than the age of majority according to local regulations) must be able to provide written assent for participation. For children younger than 12 years of age, assent will be based on local regulations.

The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study, and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.

Participants must be re-consented to the most current version of the ICF(s) during their participation in the study.

A copy of the ICF(s) must be provided to the participant or the participant's legally authorized representative.

10.1.4. Data Protection

Participants will be assigned a unique identifier by the Sponsor. Any participant records or datasets that are transferred to the Sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.

The participant must be informed that his/her personal study-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participants, who will be required to give consent for their data to be used as described in the informed consent

The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the Sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

10.1.5. Committees Structure

10.1.5.1. Safety Review Committee

The SRC will comprise the PI and/or subinvestigator, the Sponsor Medical Monitor, and the CRO Medical Monitor.

See Section 9.6 for further details regarding the SRC.

10.1.5.2. Data Safety Monitoring Committee

The independent DSMC will comprise appropriately qualified clinicians who are not involved in the study. The DSMC will provide a comprehensive review of study safety and tolerability data. Further operational details will be prespecified in the DSMC charter.

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10.1.6. Dissemination of Clinical Study Data

Data collected during the study will be shared with Investigators whose proposed use of the data has been approved by an independent review committee. In compliance with the National Institutes of Health grant, information in the clinical trial record will be updated at least once a year, and tabular study summary results will be posted to www.ClinicalTrials.gov within 1 year of study completion.

10.1.7. Data Quality Assurance

All participant data relating to the study will be recorded on printed or electronic CRF (eCRF), unless transmitted to the Sponsor or designee electronically (e.g., laboratory data). The Investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.

The Investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.

The Investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.

Monitoring details describing strategy (e.g., risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities, and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the Monitoring Plan.

The Sponsor or designee is responsible for the data management of this study, including quality checking of the data.

The Sponsor assumes accountability for actions delegated to other individuals (e.g., CROs).

Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the Investigator for 5 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

10.1.8. Source Documents

Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the Investigator's site.

Data entered in the eCRF that are transcribed from source documents must be consistent with the source documents, or the discrepancies must be explained. The Investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

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10.1.9. Study and Site Start and Closure

The study start date is the date on which the clinical study will be open for recruitment of participants.

The first act of recruitment is site activation and will be the study start date.

The Sponsor designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the Sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The Investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the Sponsor or Investigator may include but are not limited to:

- Investigator noncompliance with the protocol, GCP, or regulatory requirements
- Unsatisfactory enrollment with respect to quantity or quality
- Incomplete data collection; inaccurate or knowingly false data submission
- The PI is no longer capable of performing the tasks of the PI, and no replacement can be found.
- The SRC determines that termination of the study is in the best interest of the research participants.
- The Sponsor, Investigator or IRB/IEC determines that continuation of the study will not serve any scientific purpose.
- Circumstances beyond the control of the Sponsor or Investigator make it unreasonable to require the study's continuation.
- A request to discontinue the study by a regulatory or health authority.

If the study is prematurely terminated or suspended, the Sponsor shall promptly inform the Investigators, the IECs/IRBs, the regulatory authorities, and any CRO(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The Investigator shall promptly inform the participants and should assure appropriate participant therapy and/or follow-up.

The complete set of stopping rules is detailed in Section 7.

10.1.10. Publication Policy

Publication of a summary of the results of the study is permissible according to the Sponsor and is not inconsistent with the preceding affirmation. Scientific dissemination of the results of this study is encouraged. Any formal publication of data collected as a result of the study will be considered a joint publication by the Investigator and the appropriate personnel of Dicerna Pharmaceuticals, Inc. or their designees. Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

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No submission of a manuscript may be made until the results from the study site have been received and analyzed by Sponsor, or the study has been terminated at all centers. A separate, individual publication of the results of the study will be delayed until initial publication of the results of the multi-center study, or a decision not to publish is made. Please refer to clinical study agreement for further details.

For any publication or presentation, a manuscript of the paper or abstract must be received and approved by the Sponsor prior to outside submission. Whether or not there is a Dicerna Pharmaceuticals, Inc. author of the publications or presentations, a manuscript will be forwarded to Dicerna Pharmaceuticals, Inc. for review and approval at least 30 days prior to submission of a journal publication, or at least 10 days prior to submission of an abstract.

Note: Any language relating to these issues appearing in the clinical study agreement will supersede that which is outlined in this section.

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10.2. Clinical Laboratory Tests

Table 8 summarizes the laboratory tests to be conducted. Full details for the testing are provided in the laboratory manual. Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5.

Additional tests may be performed during the study as determined necessary by the Investigator or required by local regulations.

Investigators must document their review of each laboratory safety report.

Laboratory/analyte results that could unblind the study will not be reported to investigative sites or other blinded personnel until the study has been unblinded.

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Table 8: Protocol-Required Safety Laboratory Assessments

Laboratory Assessments	Parameters	
Hematology	Red blood cell count hemoglobin hematocrit reticulocytes platelet count Only at Days -1, 4, 29, 85, and 169 mean corpuscular volume (MCV) mean corpuscular hemoglobin (MCH) mean corpuscular hemoglobin concentration (MCHC)	White blood cell count Only at Days -1, 4, 29, 85, and 169 lymphocytes, abs and % monocytes, abs and % eosinophils, abs and % neutrophils, abs and % basophils, abs and %
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
Routine Urinalysis	specific gravity, pH, glucose, protein, blood, ketones, bilirubin, urobilinogen, nitrite, leukocyte esterase by dipstick microscopic examination (if blood or protein is abnormal)	
Coagulation Parameters	International normalized ratio (INR), PT, PTT	
Complement panel	Bb, C3a, C5a	
Other Screening Tests	• Alcohol breath test • Rapid SARS-CoV-2 (local laboratory testing) • Follicle-stimulating hormone (as needed in women of non-childbearing potential only) • Highly sensitive (urine; serum for confirmation if needed) human chorionic gonadotropin (hCG) pregnancy test (as needed for WOCBP). Any positive urine pregnancy test will be confirmed with a serum pregnancy test. • Urine drug screen (to include at minimum: amphetamines, barbiturates, cocaine, opiates, and benzodiazepines) • Viral serology (human immunodeficiency virus antibody, hepatitis B surface antigen, and hepatitis C virus antibody)	

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10.3. Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.3.1. Definition of Adverse Event

An AE is any untoward medical occurrence in a patient or clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study intervention.

Events Meeting the AE Definition

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the Investigator.
- Exacerbation of a chronic or intermittent pre-existing condition, including either an increase in frequency and/or intensity of the condition.
- New condition detected or diagnosed after study intervention administration, even though it may have been present before the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.

Events NOT Meeting the AE Definition

- Medical or surgical procedure (e.g., endoscopy, appendectomy): the condition that leads to the procedure is the AE.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

10.3.2. Definition of Serious Adverse Event

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met.

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An SAE is defined as any untoward medical occurrence that, at any dose:

- **Results in death**
- **Is life-threatening**

The term 'life-threatening' in the definition of 'serious' refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe.

- **Requires inpatient hospitalization or prolongation of existing hospitalization**

In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.

Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE. Pre-planned hospitalizations scheduled prior to signing the ICF, for an elective medical/surgical procedure do not meet this criterion.

- **Results in persistent disability/incapacity**

The term disability means a substantial disruption of a person's ability to conduct normal life functions.

This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle), which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

- **Is a congenital anomaly/birth defect**
- **Other situations:**

Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.

Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

10.3.3. Definition of Adverse Events of Special Interest

An AESI is a noteworthy event for the particular product or class of products that a Sponsor may wish to monitor carefully (CIOMS IV, 2005).

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Events Meeting the AESI Definition

Injection Site Reaction

An 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 in Table 9 are met. Signs or symptoms at the injection site that occur ≥ 4 hours post-injection but are not specified in Table 9 should be recorded as AEs.

Table 9: Grading of Injection Site Reactions, CTCAE v 5.0

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

10.3.4. Recording and Follow-Up of AEs and/or SAEs

10.3.4.1. AE and SAE Recording

When an AE/SAE occurs, it is the responsibility of the Investigator to review all documentation (e.g., hospital progress notes, laboratory reports, diagnostics reports) related to the event.

The Investigator will then record all relevant AE/SAE information in the eCRF.

It is not acceptable for the Investigator to send photocopies of the participant's medical records to the Sponsor in lieu of completion of the AE/SAE CRF page.

There may be instances when copies of medical records for certain cases are requested by the Sponsor. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to the Sponsor.

The Investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

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10.3.4.2. Assessment of Intensity

The Investigator will make an assessment of each AE and SAE reported during the study. The grade of each event will be determined using CTCAE v 5.0 criteria.

10.3.4.3. Assessment of Causality

The Investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE.

A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.

The Investigator will use clinical judgment to determine the relationship. Alternative causes, such as concomitant therapy and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated. The Investigator will also consult the Investigator Brochure (IB) and/or Product Information (for marketed products) in his/her assessment.

For each AE/SAE, the Investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.

There may be situations in which an SAE has occurred, and the Investigator has minimal information to include in the initial report. However, it is very important that the Investigator always make an assessment of causality for every event before the initial transmission of the SAE data to SAE Coordinator.

The Investigator may change his/her opinion of causality in light of follow-up information and send a SAE follow-up report with the updated causality assessment.

The causality assessment is one of the criteria used when determining regulatory reporting requirements.

The following definitions will be used in assessing causality:

- **Not Related**: Event for which sufficient evidence exists to conclude that the etiology is unrelated to study intervention.
- **Possibly Related**: There is some temporal relationship between the event and the administration of the study intervention, and the event is unlikely to be explained by the participant's medical condition or other therapies.
- **Probably Related**: The temporal relationship between the event and administration of the study intervention is suggestive and the event is unlikely explained by the participant's medical condition or other therapies.
- **Definitely Related**: The event follows reasonable temporal sequence from administration of the study intervention, follows a known or suspected response pattern to the study intervention, is confirmed by improvement upon stopping the study intervention, and reappears upon repeated exposure, if that occurs.

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10.3.4.4. Follow-up of AEs and SAEs

The Investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the Sponsor to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.

If a participant dies during participation in the study or during a recognized follow-up period, the Investigator will provide the Sponsor with a copy of any post-mortem findings including histopathology.

New or updated information will be recorded in the originally completed CRF.

The Investigator will submit any updated SAE data to the Sponsor within 24 hours of receipt of the information.

10.3.5. Reporting of SAEs

Facsimile or electronic transmission of the SAE Report Form is the preferred method to transmit this information to the SAE coordinator.

In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of the SAE data collection tool sent by overnight mail or courier service.

Initial notification via telephone does not replace the need for the Investigator to complete and sign the SAE Report Form within the designated reporting time frames.

Contacts for SAE reporting can be found on the Medical Monitor and Pharmacovigilance Contact Information page.

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10.4. Contraceptive Guidance and Collection of Pregnancy Information

10.4.1. Definitions

Woman of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming post-menopausal unless permanently sterile (see below).

If fertility is unclear (e.g., amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before administration of study intervention, additional evaluation should be considered.

Women in the following categories are not considered WOCBP

1. Premenarchal
2. Premenopausal with one of the following:
   - Documented hysterectomy
   - Documented bilateral salpingectomy
   - Documented bilateral oophorectomy

   For individuals with permanent infertility due to an alternate medical cause other than the above, (e.g., müllerian agenesis, androgen insensitivity), Investigator discretion should be applied to determining study entry.

   Note: Documentation can come from the site personnel's: review of the participant's medical records, medical examination, or medical history interview.
3. Postmenopausal
   - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
     – A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, confirmation with more than one FSH measurement is required.
   - Participants on HRT and whose menopausal status is in doubt will be required to use one of the non-estrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

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10.4.2. Contraception Guidance

Male participants

Male participants with female partners of childbearing potential are eligible to participate if they agree to ONE of the following from Day 1 through the end of study (EOS) visit:

- Are abstinent from penile-vaginal intercourse as their usual and preferred lifestyle (abstinent on a long-term and persistent basis) and agree to remain abstinent,
- Agree to use a male condom plus partner use of a contraceptive method with a failure rate of < 1% per year as described in Table 10 when having penile-vaginal intercourse with a WOCBP who is not currently pregnant.

Male participants must refrain from donating sperm for the duration of the study and following the last dose of study intervention for at least 24 weeks.

Male participants with a pregnant or breastfeeding partner must agree to remain abstinent from penile-vaginal intercourse or use a male condom during each episode of penile penetration during the protocol-defined time frame.

Female participants

Female participants of childbearing potential are eligible to participate if they agree to use a highly effective method of contraception consistently and correctly as described in Table 10.

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Table 10: Highly Effective Contraceptive Methods

Highly Effective Contraceptive Methods That Are User Dependent [a] ***(Failure rate of <1% per year when used consistently and correctly)***
Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation • Oral • Intravaginal • Transdermal Progestogen-only hormonal contraception associated with inhibition of ovulation • Oral • Injectable
Highly Effective Methods That Are User Independent [a]
• Implantable progestogen-only hormonal contraception associated with inhibition of ovulation • Intrauterine device (IUD) • Intrauterine hormone-releasing system (IUS) • Bilateral tubal occlusion • Vasectomized partner A vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP, and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. • Sexual abstinence Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.

[a] Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for participants participating in clinical studies.

10.4.3. Pregnancy Testing:

WOCBP should only be included after a confirmed menstrual period and a negative highly sensitive urine or serum pregnancy test. If a urine test is positive, it must be confirmed with a serum test.

Additional pregnancy testing should be performed as indicated in SoA (Section 1.3).

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Pregnancy testing will be performed whenever a menstrual cycle is missed or when pregnancy is otherwise suspected

Pregnancy testing with a sensitivity of at least 25 mIU/mL will be performed.

10.4.4. Collection of Pregnancy Information

10.4.4.1. Male Participants with Partners Who Become Pregnant

The Investigator will attempt to collect pregnancy information on any male participant's female partner who becomes pregnant while the male participant is in this study. This applies only to male participants who receive DCR-AUD.

After obtaining the necessary signed informed consent from the pregnant female partner directly, the Investigator will record pregnancy information on the appropriate form and submit it to the Sponsor within 24 hours of learning of the partner's pregnancy. The female partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to the Sponsor. Generally, the follow-up will be no longer than 6 to 10 weeks following the estimated delivery date. Any termination of the pregnancy will be reported regardless of fetal status (presence or absence of anomalies) or indication for the procedure.

10.4.4.2. Participants Who Become Pregnant

The Investigator will collect pregnancy information on any participant who becomes pregnant while participating in this study. The initial Information will be recorded on the appropriate form and submitted to the Sponsor within 24 hours of learning of a participant's pregnancy.

The participant will be followed to determine the outcome of the pregnancy. The Investigator will collect follow-up information on the participant and the neonate, and the information will be forwarded to the Sponsor. Generally, follow-up will not be required for longer than 6 to 10 weeks beyond the estimated delivery date. Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for the procedure.

While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE. A spontaneous abortion (occurring at < 22 weeks gestational age) or still birth (occurring at > 22 weeks gestational age) is always considered to be an SAE and will be reported as such. Any post-study pregnancy-related SAE considered reasonably related to the study intervention by the Investigator will be reported to the Sponsor as described in Section 8.3.4. While the Investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.

Any participant who becomes pregnant while participating in the study will discontinue study intervention.

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10.5. Genetics

Use/Analysis of DNA

- DNA samples will be used for research related to genetic allelotypes (including *ALDH2*) that could potentially influence alcohol metabolism and the impact of DCR-AUD. Genetic research may consist of the analysis of one or more candidate genes or the analysis of genetic markers throughout the genome potentially related to alcohol metabolism.
- DNA samples will be analyzed for *ALDH2* genotyping. Additional exploratory analyses may be conducted if it is hypothesized that this may help further understand the clinical data.
- The samples may be analyzed as part of a multi-study assessment of genetic factors involved in the response to DCR-AUD or study interventions of this class to understand study disease or related conditions.
- The results of genetic analyses may be reported in the CSR or in a separate study summary.
- The Sponsor will store the DNA samples in a secure storage space with adequate measures to protect confidentiality.
- The samples will be retained while research on DCR-AUD continues, but no longer than 5 years or other period as per local requirements.

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10.6. Liver Safety: Suggested Actions and Follow-up Assessments

Phase 1 liver chemistry stopping criteria are designed to ensure participant safety and to evaluate liver event etiology (Table 11).

Table 11: Liver Safety: Suggested Actions and Follow-up Assessments

Liver Chemistry Stopping Criteria	
ALT/AST-absolute	ALT or AST ≥ 3×ULN If ALT or AST ≥ 3×ULN **AND** total bilirubin ≥ 2×ULN (> 35% direct bilirubin) or INR > 1.5, report to Sponsor in expedited manner.[a, b] See additional actions and follow-up assessments below
Required Actions, Monitoring, and Follow-up Assessments	
Actions: • Report the event to the CRO Medical Monitor **within 24 hours** • Complete an SAE data collection tool if the event also met the criteria for an SAE [b] • Perform liver function follow-up assessments as described in the Follow Up Assessments below. • Monitor the participant until liver function test abnormalities resolve, stabilize, or return to baseline	
Monitoring: **If ALT or AST ≥ 3×ULN AND total bilirubin ≥ 2×ULN or INR > 1.5** • Repeat liver function tests (include ALT, AST, alkaline phosphatase, total bilirubin, and INR) and perform liver function follow-up assessments within **24 hours.** • Monitor participant twice weekly until liver function test abnormalities resolve, stabilize, or return to baseline. • A specialist or hepatology consultation is recommended. **If ALT or AST ≥ 3×ULN AND total bilirubin < 2×ULN and INR ≤ 1.5:** • Perform liver function tests (include ALT, AST, alkaline phosphatase, total bilirubin, and INR) and perform liver function follow-up assessments within **24 to 72 hours** • Monitor participants weekly until liver function abnormalities resolve, stabilize, or return to baseline	
Follow-Up Assessments	
• Viral hepatitis serology (includes: Hepatitis A immunoglobulin M [IgM] antibody; HBsAg and HBcAb; hepatitis C RNA; cytomegalovirus IgM antibody; Epstein-Barr viral capsid antigen IgM antibody [or if unavailable, heterophile antibody or monospot testing]; and hepatitis E IgM antibody) • Obtain serum CK, LDH, GGT, GLDH, and serum albumin • Fractionate bilirubin, if total bilirubin ≥ 2×ULN • Obtain complete blood count with differential to assess eosinophilia • Record the appearance or worsening of clinical symptoms of liver injury, or hypersensitivity, on the eCRF	

- Record use of concomitant medications or ingestions (including wild mushrooms, acetaminophen, herbal remedies, recreational drugs, and other over-the-counter medications). Note any concomitant medications that have been recently initiated or for which doses have increased.
- Record alcohol use on the eCRF

If ALT or AST ≥ 3×ULN AND total bilirubin ≥ 2×ULN or INR > 1.5 obtain the following in addition to the assessments listed above**:**

- Anti-nuclear antibody, anti-smooth muscle antibody, Type 1 anti-liver kidney microsomal antibodies, and quantitative total immunoglobulin G (IgG) or gamma globulins
- Liver imaging (ultrasound, magnetic resonance, or computerized tomography) and/or liver biopsy to evaluate liver disease
- Liver biopsy may be considered and discussed with local specialists if available, for instance:
  - When serology raises the possibility of autoimmune hepatitis (AIH)
  - When suspected DILI progresses or fails to resolve on withdrawal of study intervention
  - In participants with acute or chronic atypical presentation.

[a] Serum bilirubin fractionation should be performed if testing is available. If serum bilirubin fractionation is not immediately available, discontinue study intervention if ALT ≥ 3×ULN and total bilirubin ≥ 2×ULN. Additionally, if serum bilirubin fractionation testing is unavailable, record the absence/presence of detectable urinary bilirubin on dipstick which is indicative of direct bilirubin elevations suggesting liver injury.

[b] All events of ALT ≥ 3×ULN and total bilirubin ≥ 2×ULN (> 35% direct bilirubin) or ALT ≥ 3×ULN and INR > 1.5 may indicate severe liver injury (possible 'Hy's Law') and must be reported to sponsor in an expedited manner and as an SAE if SAE criteria met (excluding studies of hepatic impairment or cirrhosis).

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10.7. Abbreviations

Abbreviation	Description
ADA	antidrug antibody(ies)
AE	adverse event
AESI	AE of special interest
ALDH2	aldehyde dehydrogenase 2
ALDH2	gene for aldehyde dehydrogenase 2
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the curve
AUD	alcohol use disorder
BAC	blood alcohol concentration
BMI	body mass index
BP	blood pressure
bpm	beats per minute
BUN	blood urea nitrogen
°C	degrees Celsius
CFR	Code of Federal Regulations
CFU	conditional follow-up
CIOMS	Council for International Organizations of Medical Sciences
CK	creatine kinase (creatine phosphokinase)
CL	clearance
C_{max}	maximum observed concentration
C_{min}	minimum observed concentration
CONSORT	Consolidated Standards of Reporting Trials
CRO	contract research organization
CSR	clinical study report
C-SSRS	Columbia-Suicide Severity Rating Scale
CTCAE	Common Terminology Criteria for Adverse Events
CV%	coefficient of variation (percent)
DCR-A1203	drug substance for this IMP
DLT	dose-limiting toxicity

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Abbreviation	Description
DS	drug substance
DSMC	Data Safety Monitoring Committee
ECG	electrocardiogram
eCRF	electronic case report form
e.g.	for example (*exempli gratia*)
EIA	ethanol interaction assessment
EOS	end of study
EOT	end of treatment
EtOH	ethyl alcohol
FDA	Food and Drug Administration
FIH	first-in-human
FSH	follicle stimulating hormone
GABA	gamma-aminobutyric acid
GalNAc	*N*-acetylgalactosamine
GCP	Good Clinical Practice
GGT	gamma glutamyl transferase
GI	gastrointestinal
GLP	Good Laboratory Practice
HbA1c	hemoglobin A1c
HBsAg	hepatitis B surface antigen
hCG	human chorionic gonadotropin
HCV	hepatitis C virus
HIPPA	Health Insurance Portability and Accountability Act
hr	hour(s)
HIV	human immunodeficiency virus
HRT	hormone replacement therapy
HV	healthy volunteer
IA	interim analysis
IB	Investigator's Brochure
ICF	informed consent form
ICH	The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use

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Abbreviation	Description
i.e.	that is (*id est*)
IEC	Independent Ethics Committee
IMP	Investigational Medicinal Product
INR	international normalized ratio
IRB	Institutional Review Board
ISR	injection site reaction
ITT	Intent to treat
IUD	intrauterine device
IVRS/IWRS	Interactive Voice/Web Response System
IUS	intrauterine hormone-releasing system
kg	kilogram(s)
LDH	lactate dehydrogenase
LFT	liver function test
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
MINI	Mini International Neuropsychiatric Interview
miRNA	micro-RNA
mRNA	messenger ribonucleic acid
mg	milligram(s)
min	minute(s)
mL	milliliter(s)
mRNA	messenger ribonucleic acid
M&S	modeling and simulation
NOAEL	no observed adverse effect level
NPO	nothing by mouth
NSAID	nonsteroidal anti-inflammatory drug
OTC	over the counter
PD	pharmacodynamic(s)
PK	pharmacokinetic
PI	Principal Investigator
QTcF	QT interval (Fridericia correction)

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Abbreviation	Description
RNA	ribonucleic acid
RNAi	RNA interference
SAD	single ascending dose
SAE	serious adverse event
SAP	statistical analysis plan
SC	subcutaneous
SD	standard deviation
SEAS	Subjective Effects of Alcohol Scale
siRNA	small interfering RNA
SoA	schedule of activities
SRC	Safety Review Committee
SUD	Substance abuse disorder
SUSAR	suspected unexpected serious adverse reaction
t1/2	terminal elimination half-life
TBD	to be determined
TLFB	Timeline Follow Back
T_{max}	time to maximum observed concentration
ULN	upper limit of normal
UTI	urinary tract infection
Vd/F	apparent volume of distribution
WFI	water for injection
WOCBP	woman(en) of childbearing potential

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10.8. Investigator Signature Page

A Phase 1, Double-blind, Placebo-controlled, Single-ascending-dose, Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics Study of DCR-AUD in Healthy Volunteers

Protocol Number: DCR-AUD-101

Version: 6.0

Date: 14-Mar-2022

I have read this protocol and agree to conduct this trial in accordance with all stipulations of the protocol and in accordance with Good Clinical Practice (GCP) guidelines, the Declaration of Helsinki, and local regulations (as applicable).

Signature:	**Date:**
Name:	**Title:**
Institution:	**Site Number:**

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10.9. Protocol Amendment History

The Protocol Amendment Summary of Changes Table for the current amendment is located directly before the Table of Contents.

Amendment 5: 14-Mar-2022

Overall Rationale for Amendment 5:

The 28-Jul-2021 version of the protocol was amended to remove the conduct of the interim analysis scheduled at the conclusion of Cohort 2, as emerging PD data did not dictate it was warranted. Other points of clarification for the timing and scheduling of study visits were also added.

Amendment 4: 28-Jul-2021

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

Overall Rationale for the Amendment:

The 26-Jul-2021 version of the protocol was amended to address the concerns and questions raised by the FDA in their review of Amendment 3 of the protocol.

Protocol Amendment 4 Summary of Changes

Description of Change	Brief Rationale	Affected Sections
Added group mean AUC_{0-48} and C_{max} values from the 100 mg/kg dose in the 5-week monkey toxicity study to the dose escalation stopping criteria.	For clarity	2.3.4 Risk Assessment 7.3 Cohort Stopping Rules 9.6 Safety Review Committee
Administrative updates	To reflect new version	Throughout the protocol

Amendment 3: 26-Jul-2021

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

Overall Rationale for the Amendment:

The 19-Jul-2021 version of the protocol was amended to address the concerns and questions raised by the FDA in their review of Amendment 2 of the protocol.

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Protocol Amendment 3, Summary of Changes

Description of Change	Brief Rationale	Affected Sections
Added PK stopping criteria and updated the text around the nonclinical safety program to align with changes related to the justification of dose	To ensure that exposure levels in humans do not exceed mean AUC and C_{max} values observed at the mid-dose in the 5-week monkey toxicology study (Study Number 20-A1203-P-030) and to align with FDA input by taking a more conservative approach to safety margins	2.2.2 Nonclinical Overview of DCR-AUD 2.3.1 Risks Related to siRNA Molecules 4.3 Justification for Dose 6.1.1 Dose Levels and Dose Escalation 6.5 Dose Modification 7.3 Cohort Stopping Rules 9.6 Safety Review Committee 11 References
Added assessment of complement levels (Bb, C3a, C5a) and revised maximum planned blood volume to be drawn	To monitor for potential immunostimulatory effects	1.3 Schedule of Activities 2.3.1 Risks Related to siRNA Molecules 2.3.4 Risk Assessment 8 Study Assessments and Procedures 10.2 Clinical Laboratory Tests (Table 8)
Added CFU for participants with ethanol reaction symptoms at Day 169 to return q28 days for follow up	To ensure participants have no residual IP-related symptoms from EIA	1.1.3 Overall Design 1.2 Study Schema 1.3 Schedule of Activities 2.3.4 Risk Assessment 4.1 Study Design 8.3.1 Time Period and Frequency for Collecting Adverse Event Information 8.7.1.3 Follow-up of Participants Who Continue to Have Positive Ethanol Reaction Symptoms at Day 169
Removed the maximum number of EIAs participants may undergo	To account for possibility of additional EIAs during CFU	1.1.3 Overall Design 2.3.4 Risk Assessment 4.2 Scientific Rationale for Study Design 5.1 Inclusion Criteria
Other editorial changes	Correction of errors and to reflect new version and amendment number, and for consistency, accuracy, and precision	8.2.2 Vital Signs 9.5 Interim Analyses Global updates to headers, version history, signature pages, abbreviations list

Amendment 2: 19-Jul-2021

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

Overall Rationale for the Amendment:

The 09-Jul-2021 version of the protocol was amended to address the concerns and questions raised by the FDA in their review of Amendment 1 of the protocol.

Protocol Amendment 2, Summary of Changes

Description of Change	Brief Rationale	Affected Sections
Updated name of CRO medical monitor	Changed to Dr. [redacted]	Medical Monitor Contact Information
Corrected error in study schema that V3 is on Day 29	To ensure schema aligns with schedule of assessments	1.2 Figure 1
Specified blood pressure criteria for eligibility range of 90-140 mmHg systolic and 55-95 mmHg diastolic	To ensure participants' BPs are neither too high nor too low	5.1 Inclusion criteria 5.2 Exclusion criteria 8.7.1.2 Stopping Rules for an EIA
Specified heart rate increase of > 20 bpm or to a level of > 100 bpm would prompt stoppage of EIA	To ensure participant safety	8.7.1.2 Stopping Rules for an EIA
Clarified that participants with adverse reactions to alcohol or underlying conditions that should preclude alcohol consumption should not be enrolled or allowed to continue	To ensure participant safety	5.2 Exclusion criteria 7.1 Participant Discontinuation/Withdrawal from the Study 8.7.1 Ethanol Interaction Assessment
Added statement about required overnight stay in the Phase 1 unit after EIA and that participants will not be discharged until deemed medically safe	To ensure participant safety	8.7.1 Ethanol Interaction Assessment
Added clarifications about Day -1 alcohol exposure, which is not part of an EIA assessment	To emphasize the predose exposure to alcohol to ensure eligibility and establish baseline for biomarker assessments	1.1.3 Overall Design 1.3 Footnote "n" of Table 1 4.2 Scientific Rationale for Study Design

Amendment 1: 09-Jul-2021

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

Overall Rationale for the Amendment:

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The 24-Jun-2021 version of the protocol was amended to address the concerns and questions raised by the FDA in their review of the PIND.

Protocol Amendment 1, Summary of Changes

Description of Change	Brief Rationale	Affected Sections
Provided additional information about placebo	Specified physiologic saline (0.9% aqueous sodium chloride) would be used for placebo	6.1.1 Dose Levels and Dose Escalation (Table 5) 6.2.3 Preparation and Administration
Added use of the Mini International Neuropsychiatric Interview (MINI) 7.0.2	To further identify and monitor participant psychological status	1.3 Schedule of Activities 5.2 Exclusion Criteria 8.2.6 Mini-International Neuropsychiatric Interview
Specified which liver function test results will be used to determine eligibility	To ensure participant safety	5.2 Exclusion Criteria
Clarified instructions about treatment administration	Specified that for dose levels requiring >1 injection, treatment would be administered by multiple injections in the abdomen	6.2.3 Preparation and Administration
Made all physical examinations full examinations	Eliminated option for brief physical examinations for clarity	1.3 Schedule of Activities 8.2.1 Physical Examinations
Clarified documentation of start date of AEs and SAEs and defined start date of TEAE	All AEs and SAEs will be collected after signature of the ICF. AEs will be defined as treatment-emergent if they occur after administration of study intervention.	7.3 Cohort Stopping Rules 9.4.2 Primary Endpoint(s)
Clarified SAE, DLT, and study stopping criteria	This is a FIH study, so all AEs, SAEs, and DLTs will considered at least possibly related unless clearly a result of a non-study related event.	7.3 Cohort Stopping Rules 7.3.1 Dose Limiting Toxicities 7.4 Study Stopping Rules
Removed mention of progression of underlying disease	This is a FIH study, so removed references to disease progression as this is not applicable.	8.2.7 Clinical Safety Laboratory Assessments 10.3.1 Definition of Adverse Event 10.3.2 Definition of Serious Adverse Event 10.3.4.3 Assessment of Causality 10.5 Genetics
Increased requirement for contraceptive use from 12 to 24 weeks	Increased requirement of contraceptive use to cover the full duration of the study.	5.1 Inclusion Criteria 8.3.5 Pregnancy 10.4.2 Contraception Guidance
Added summary of changes for Amendment 1 (dated 09-Jul-2021)	For clarity	

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