A Phase 1b Multiple Ascending Dose Study to Assess the Safety, Tolerability, and Pharmacokinetics of SZN-043, in Participants with Severe Alcohol-Associated Hepatitis

Short title: A Phase 1b study evaluating safety and pharmacokinetics of SZN-043 in participants with severe alcohol-associated hepatitis

Protocol Number: CL-0043-1002

Authors: Surrozen Operating, Inc.
Development Phase: Phase 1b
Document Version: 1.0
Protocol Version 3.0, dated 13 January 2025

IRAS ID Number: 1009585

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History of Amendments

This amendment supercedes global Protocol Version 2.0, dated 05 July 2024.

The summary of changes included are described in the tables below:

Amendment	Version	Version Date	# Enrolled
2	3.0	13 January 2025	TBD

Reason(s) Amendment:	Primary: • Augment the use of the cohort after the multiple ascending dose cohorts (Primary and Optional Cohorts) have completed from a dose expansion cohort to a dose ranging cohort (Cohort 4) designed to further assess SZN-043 safety and tolerability between the highest tolerated dose tested in prior cohorts and a dose below, minimizing bias by blinding and randomizing assignment to dose. • Update eligibility criteria	Other: • Update for clarity and expanded definition the eligibility criteria for BMI assessments, MELD scores, hemodynamic stability, allergies, CV safety, liver imaging, and antibiotic use. • Allow for removal of pharmacodynamic assessments in future cohorts to reduce burden and risk to participants related additional blood draws. • Expanded use of markers for early signals of potential drug induced liver damage (e.g. elevated GGT, ALP, Hy's law section)
Summary of Major Changes:	1. Revise the Dose Ranging Cohort to a blinded, randomized (1:1) Dose Ranging Cohort (Cohort 4) with 18-24 participants will be opened after Multiple Ascending Dose Cohorts have completed dosing. Selection of the doses and frequency for Cohort 4 will 1) match the highest dose from the previously completed cohorts cleared for safety by the SRC and 2) a lower dose. • Expanded inclusion to allow participants with MELD scores up to 33	
Is this amendment likely to have a substantial impact on safety or rights of the participants, or on the reliability and robustness of the data generated in the clinical study?	Yes, for participants yet to be recruited under this Amendment 2. There will be no impact on participants who have enrolled under Amendment 1 of this protocol. The addition of a blinded and randomized cohort seeks to assess variability in safety between the highest tolerated dose tested in this protocol and a lower dose in a manner that reduces bias in differentiating dose safety profiles.	

Detailed Summary of Changes

Impacted Section #	Description of Change	Brief Rationale for Change
Title Page	Changes to reflect amendment	Administrative update
Investigators Agreement	Update title to align across protocol sections	Administrative update
Synopsis	Changes reflecting updates in Protocol as outlined in the summary of major changes above.	Reconcile detail with protocol amendment changes.
Section 1.3	Update MELD score to include participants with values up to 33	Expanded inclusion for broader patient population
Section 2.1 (Table 4)	Update primary objective to add Cohort 4 assessment of safety and tolerability across two doses of SZN-043	Revised to reflect purpose of Cohort 4, and declare intent to further analyze safety variability between doses.
Section 3.1	Revised to summarize the design changes including the design of dose Cohort 4 (dose ranging cohort) and corresponding update to Figure 3, including details for the number of participants and dosing frequency.	Highlight design change incorporating Cohort 4 .
Section 3.3	Update section with investigator team composition and study completion.	Improve clarity
Section 3.4.1	Provide guidance to investigators should a DILI event be suspected.	Provide guidance on additional laboratory tests for suspected DILI event.
Section 4.1.1	Update inclusion criteria for BMI, AH clinical diagnosis, and MELD scores.	Expand eligibility using MELD score; Improved clarity to facilitate participant screening.
Section 4.1.2	Update Exclusion Criteria 2 to add additional restrictions and clarifications on restrictions for certain prior and concomitant treatments. Expand excluded medications with potential hepatotoxicity to include piperacillin and tazobactam. Update Exclusion Criterion 7 re: Organ failure to Multisystem organ failure. Improved specificity is provided for allergic reactions, clinically significant EKG, significant GI bleeding and lesions observed in liver imaging.	Participant safety factors are further expanded in exclusion criteria for allergic responses, clinically significant EKG and GI bleeding. With respect to the potential of both drugs representing risks to the liver, and drug-drug interactions based on the MoA of SZN-043 (CYP2E1), additional guidance is given on medications to exclude/timing of exclusion for entry into the study to further protect potential participants.
Section 4.2.3	Updated contraception for males from screening up to 30 days.	Descriptions are more comprehensive and globally applicable.
Section 5.3	Added section 5.3.2 detailing Randomization for Cohort 4.	Amended design incorporates 1:1 randomization and blinding to provide greater confidence in trial data.
Section 5.5	Added section 5.5 detailing double-blind design for Cohort 4.	Blinded nature of cohort will reduce bias in assessment of safety between doses.

Impacted Section #	Description of Change	Brief Rationale for Change
Section 7	Added Piperacillin / Tazobactam to table of potential hepatotoxic medications (Table 6).	Improve site guidance on excluded medications.
Section 8	Randomization visit for Cohort 4 added as Section 8.2	Provide guidance on randomization visit and screening procedures for updated design incorporating Cohort 4.
Section 9.1.5.2	Expanded use of prior hepatic imaging to assess lesions indicative of cancer, after review and approval by sponsor medical monitor.	Eliminate need for repetition of assessments during screening period of study where the outcome of a recently conducted assessment would suffice reducing burden on participants, and any risks associated with those procedures.
Section 9.1.6.1	Update timing of ECG relative to dosing.	Improve clarity
Section 9.1.8.11	Greater specificity and details provided for DILI assessment	Improve specificity and clarity
Section 9.5	Allow for removal of Pharmacodynamic Biomarkers assessments if data analyzed during the study fails to demonstrate utility.	Provide potential to remove PD assessments.
Section 9.5.3	Update HepQuant DuO test to provide exemption for contraindications.	Clarify requirements, and guidance for contraindications.
Section 10.2	Expanded guidance to Investigator and Medical monitor to consider other indicators of drug induced liver damage (DILI)	Expand DILI assessment scope and improve clarity
Schedule of Events, Table 1a	Updated Serum alcohol test (PEth, D0) and added randomization at screening; footnotes to table were updated for ECG, HepQuant test and pharmacodynamic measurement.	Update to align with changes with amendment
Appendix Table 2	Table updated for addition of Cohort 4 and pharmacodynamic measurements.	Update to align with changes with amendment
Appendix 2	Note added prior to introduction to use IFU in laboratory manual as primary information source.	Provide clarity on location of most complete instructions for the HepQuant lab test.

PROTOCOL AUTHORISATION

Title: A Phase 1b Multiple Ascending Dose Study to Assess the Safety, Tolerability, and Pharmacokinetics of SZN-043 in Participants with Severe Alcohol-Associated Hepatitis

As an authorised representative of Surrozen Operating, Inc. ("Sponsor"), I confirm that the study protocol has undergone critical review. The information it contains is consistent with current knowledge of the risks and benefits of the investigational product (IP), as well as with the moral, ethical, and scientific principles governing clinical research as set out in the current Declaration of Helsinki (Ethical Principles for Medical Research Involving Human Participants) and the International Council for Harmonisation (ICH) guidelines on Good Clinical Practice (GCP).

Signed by Craig Parker
Craig Parker
I approve this document
21 January 2025 | 16:47 PST
[redacted]4B9CDB5463F322AAAC

Name: Craig Parker

Position: Chief Executive Officer / Interim Head of Development

Company: Surrozen Operating Inc.

Table 1: Contact Information

Role in Study	Name	Address and Telephone Number
Sponsor	Josh Koons Study Manager	Surrozen Operating, Inc. 171 Oyster Point Blvd, Suite 400 South San Francisco, CA 94080 Tel: 1-650-475-2818
Sponsor (Legal Representative, UK)	Harold Pothoven (NL) Craig Parker (US Contact)	Surrozen Netherlands, B.V. Strawinskylaan 569, 1077XX Amsterdam, The Netherlands (NL) Tel: +31 (0)20 737 2215 Tel: + +1 650 443 7353
Local Sponsor (Australia)	See Study Contact List	Novotech (Australia) Pty Limited Level 19, 66 Goulburn Street Sydney NSW 2000, Australia Tel: +61-2-8569-1400
Local Sponsor (New Zealand)	See Study Contact List	Novotech (New Zealand) Limited Level 6, 2-6 Crowhurst Street Newmarket Auckland 1023, New Zealand Tel: +64-9-307-4360
Local Sponsor (South Korea)	See Study Contact List	Novotech Asia Korea Co., Limited 20F, SamWon Tower 124, Teheran-ro, Gangnam-gu Seoul, South Korea, 06164 Tel: 02-2143-6000
Sponsor Medical Monitor	Chris Stevens, MD Chief Medical Officer	Surrozen Operating, Inc. 171 Oyster Point Blvd, Suite 400 South San Francisco, CA 94080 Tel: 1-650-475-2818
Contract Research Organization (Australia, New Zealand, South Korea)	See Study Contact List	Novotech (Australia) Pty Limited Level 19, 66 Goulburn Street Sydney NSW 2000, Australia Tel: +61-2-8569-1400
Contract Research Organization (Canada, United Kingdom)	See Study Contact List	Alimentiv 100 Dundas Street London, Ontario N6A 5B6 Canada Tel: 1-226-270-7868
Medical Monitor 24-hour Emergency Contact	As noted on the Site Contact List	As noted on the Site Contact List

INVESTIGATOR'S AGREEMENT

Title: A Phase 1b Multiple Ascending Dose Study to Assess the Safety, Tolerability, and Pharmacokinetics of SZN-043 in Participants with Severe Alcohol-Associated Hepatitis

All documentation for this study that is supplied to me and that has not been previously published will be kept in the strictest confidence. This documentation includes but is not limited to this study protocol, Investigator's Brochure(s), electronic Case Report Forms (eCRFs), documents describing the Investigational Product, and other scientific data.

The study will not be commenced without the prior written approval of a properly constituted Ethics Committee meeting at least the criteria outlined in ICH. No changes will be made to the study protocol without the prior written approval of the Sponsor, the responsible Ethics Committee, and the applicable regulatory authority (where required), except where necessary to avert an immediate hazard to the participants.

I have read the protocol and agree that the study will be conducted in compliance with the protocol and in accordance with the principles of the current version of the Declaration of Helsinki (Ethical Principles for Medical Research Involving Human Participants), and with the Guideline for GCP E6 (European Medicines Agency (EMA)/CHMP/ICH/135/1995), as adopted by the regulatory authority responsible for the country in which I am managing the study.

I acknowledge that I am responsible for the overall study conduct. I agree to personally conduct or supervise the described clinical study. I agree to ensure that all associates, colleagues, and employees assisting in the conduct of the study at my site are informed about their obligations. Mechanisms are in place to ensure that site staff receive the appropriate information throughout the study.

Investigational Site

Printed name of Investigator

_____

Signature of Investigator

_____

Date

SYNOPSIS

Name of Sponsor/Company:
Surrozen Operating, Inc.

Name of Investigational Product:
SZN-043

Name of Active Ingredient:
SZN-043

Protocol Number:
CL-0043-1002

Title of Study:
A Phase 1b Multiple Ascending Dose Study to Assess the Safety, Tolerability, and Pharmacokinetics of SZN-043 in Participants with Severe Alcohol-Associated Hepatitis

Study Locations:
Multicentre and multicountry: Australia, Canada, New Zealand, South Korea, United Kingdom and USA

Phase of Development:
Phase 1b

Objectives	Endpoints
Primary Objectives: • To evaluate the safety and tolerability of MAD of SZN-043 in participants with severe alcohol-associated hepatitis • In Cohort 4 assess safety and tolerability across two doses of SZN-043	**Primary Endpoints:** • Safety and tolerability of SZN-043 at proposed doses, based on the frequency and severity of TEAEs, TESAEs, treatment-emergent laboratory, ECGs, and physical examination findings.
Secondary Objectives:	**Secondary Endpoints:**
• To assess the change from baseline in alcohol-associated hepatitis disease progression within and across cohorts as measured by Model for End-Stage Liver Disease (MELD), Lille Model for alcohol-associated hepatitis (Lille) score, and mortality.	• Percent of participants alive at Days 28, 60, and 90 • Percent and absolute change in MELD score from baseline to Days 4, 7, 28, 60, and 90 • Lille Score o Percent and absolute change from baseline at Days 4 and 7 o Percent of participants with Lille score <0.45 at Days 4 and 7
• To assess the change from baseline in functional measures of liver function within and across cohorts.	• Percent and absolute change from baseline in ALT, AST, bilirubin, international normalised ratio, and albumin over time
• To characterize the PK of SZN-043.	• Measure PK parameters after multiple doses of SZN-043, as data allow
• To evaluate immunogenicity (measured as ADA) to SZN-043	• Prevalence of ADA for SZN-043 at baseline and incidence of ADA during the study

Exploratory Objective:	Exploratory Endpoints:
• To characterize the effect of SZN-043 on serum PD biomarkers	• PD parameters of SZN-043 administration including, but not limited to the following (as data is available): o Change from baseline in biomarkers of SZN-043 activity including, but not limited to, serum ALP, AFP, and (if tested within a cohort) angiogenin and LECT2. o Change from baseline of the metabolism of ^{13}C-methacetin by cytochrome P4501A2, as measured by the Methacetin Breath Test. o Change from baseline in liver function as measure by the HepQuant DuO test.
• To characterize PK, PD, ADA, and safety relationships as data allow	• Evaluate PK-PD, PK-ADA, PK safety, ADA-safety, and ADA-PD relationships, as data allow.
• Explore the change from baseline in clinical condition assessments.	• Change from baseline to Days 7, 28, and 90 of the following items: o mDF (Maddrey's Discriminant Function) o ABIC (age, serum bilirubin, INR, and serum creatinine) • Change from baseline to Days 7 and 28 of the following items: o Albumin o Child-Turcotte-Pugh (CTP) score o Fibrinogen o Liver regeneration markers: alpha-fetoprotein o Hepatocyte damage markers: glutamate dehydrogenase
• Quality of Life assessments	• Quality of Life measured by CLDQ at Days 28, 60, and 90
• Health Care Utilization assessments	• Health care utilization including but not limited to length of hospital and ICU stays

Abbreviations::ADA=antidrug antibodies; ALP=alkaline phosphatase; ALT=alanine aminotransferase; AST=aspartate aminotransferase; CLDQ=Chronic Liver Disease Questionnaire; ECGs=electrocardiograms; GGT=gamma glutamyltransferase; ICU=intensive care unit; INR= international normalized ratio; IV=intravenous; LECT2=leukocyte cell-derived chemotaxin-2; MAD=multiple ascending dose; PD=pharmacodynamics; PK=pharmacokinetics; TEAE=treatment-emergent adverse events; TESAEs=treatment emergent serious adverse events

Methodology:

This is a multicentre, multiple ascending dose (MAD), escalation study in participants with severe alcohol-associated hepatitis (sAH). Initial cohorts with escalating doses will be open-label. These will be followed by a cohort inclusive of the highest tolerated dose and a dose below to observe variability in safety across two doses in a blinded setting.

Multiple Ascending Dose Cohorts

The study will comprise up to 3 Planned Cohorts of escalating doses of SZN-043 at Days 0 and 4 (Primary), 1 planned Dose Expansion Cohort and 3 Optional Cohorts of variable doses and dose frequencies in participants with sAH. The use of Optional Cohorts will be determined based on emerging data, and as consequently proposed and agreed by the Sponsor and Safety Review Committee (SRC). Optional cohorts may occur after a planned cohort has completed but are not required and may never be implemented if dosing can progress as described in the planned cohorts. Optional cohorts will have a frequency no higher than previously tested, and the specified dose may be the same, lower, or at a level below the next planned cohort. The dose expansion cohort will repeat the dosing and frequency of

a previous cohort. This cohort may occur at any time once the Sponsor and/or SRC have recommended that increasing doses to the next level is not warranted for any reason, and that the dose to be expanded has been determined by the SRC to be safe to use for continued testing in additional participants.

Participants who provide voluntary documented informed consent will undergo screening evaluations to determine eligibility to become study participants. All study visits and assessments will occur as delineated in the Schedule of Assessments (see Appendix 1).

All Cohorts will be defined by dose and frequency. The Primary Cohorts are planned as follows but may be adjusted based on emerging data as proposed by the Sponsor with agreement by the SRC, and with input from the Investigators Team, as applicable.

Cohort	Dose	Number of Participants	Frequency
1	0.5 mg/kg	6/cohort	Day 0 only (sentinels in Cohort 1) Days 0 and 4 (all other participants)
2	1.0 mg/kg		
3	1.5 mg/kg		

To ensure participant safety, the Primary Cohort 1 will include sentinel dosing. For this study, 3 participants will receive a single dose of SZN-043 before the remainder of the cohort. Sentinel participants will be observed for at least 14 days. The SRC will review available safety data and provide a recommendation on whether multiple doses are supported or if additional action is required before dosing the remainder of the cohort.

Optional Cohorts may explore the same or lower doses as completed in a prior Primary Cohort up to a maximum of 1.5 mg/kg in cohorts of up to 6 participants. These cohorts may may also explore additional dosing regimens, including changing timing or reducing the frequency. Optional Cohorts will be recommended by the Sponsor and implemented if agreed by the SRC. The proposal must be supported by (at a minimum) emerging safety data from any study with SZN-043 and/or other data about the product that can be made available to SRC to review to make its assessment.

While a maximum of 6 participants is planned per cohort, the Sponsor may, at its discretion, allow the entry of additional participants in any one cohort if at the time a 6th participant is identified, more than 1 participant is in screening that may meet eligibility criteria.

Cohort progression assessment will proceed 14 days after number of participants (see above) have completed dosing (Section 3.2):

- The Sponsor, in collaboration with the Investigator Team will:
    - propose conditions for an Optional Cohort (in accordance with allowances specified in this protocol) before progressing to the next Planned Cohort, OR
    - propose revised conditions to the next anticipated Planned Cohort (in accordance with allowances specified in this protocol) based on outcomes from an Optional Cohort to the SRC (eg, expand current dose, proceed to higher dose, change frequency, etc.)
- The SRC will meet to review available safety data to confirm whether the safety data support the proposed dose escalation for the next Primary or Optional Cohort. The SRC may also propose alternatives to the Sponsor.
- The Sponsor will review the SRC recommendation and will make the final decision on next steps, with the following guidance:
    - If the SRC agrees with the proposal, then recruitment may open.

- If the SRC is not in agreement with the initial proposal, the Sponsor decision may include accepting any alternative SRC recommendations, proposing other possible revisions within the confines of this protocol that are acceptable to the SRC, or may consider amending the protocol and/or terminating the study, if applicable.

A cohort will be considered complete once all participants have completed procedures described in the Schedule of Assessments, the participant has withdrawn from study (including willingness to allow vital sign check at day 90), had a liver transplant or died.

Dose Ranging Cohort

A Dose Ranging Cohort (Cohort 4) will be opened after Multiple Ascending Dose Cohorts have completed dosing, and (based on upon review of availability data) the Sponsor is able to recommend and the SRC is able to endorse two different doses of SZN-043 with the following guidelines:

- Selection of the doses and frequency for Cohort 4 will 1) match the highest dose from the previously completed cohorts cleared for safety by the SRC and 2) a lower dose.
- The number of participants to be included will result in at least 18 participants exposed to the selected dose and frequency in order to better characterize the study endpoints at that dose. Total participants in this Cohort is planned for at least 18, as recommended by the Sponsor and endorsed by the SRC. An additional 6 participants may be added upon recommendation and endorsement from the SRC.
- Dosing frequency is intended to be completed at Days 0 and 4, however, this may be altered upon recommendation of the Sponsor and endorsement of the SRC.

Cohort	Dose	Number of Participants	Frequency
4	TBD mg/kg	18-24	Days 0 and 4 (or as determined by SRC)

Investigators will be informed by memo of the planned dose and dosing frequency.

Dosing Requirements (all cohorts)

Participants will receive each dose of drug under the following conditions:

- Blood ethanol level is less than 50 mg/dL, or 0.05% concentration
- On subsequent doses, safety events observed in the participant that are assessed in the Investigator's opinion may undermine the participants' welfare with further dosing (regardless of relatedness) are sufficiently resolved or are considered not clinically significant in consideration of the overall clinical status of the participant as assessed by the Investigator.
- Dosing may continue or be delayed beyond the specified endpoint to allow for appropriate resolution of AEs as required if the last dose administered is within 28 days of the first dose.

NOTE: The Investigator must obtain Sponsor agreement to dose if a related adverse event (AE) is ongoing at the prespecified timepoint.

In addition to receiving SZN-043, other supportive care, including steroids, will be provided in accordance with local standard-of-care and medical practices.

Participants in any cohort who receive at least 1 dose of study drug and then request withdrawal from additional treatment and study procedures or are withdrawn by either the Investigator or Sponsor, will be asked to allow continued contact for vital status at Days 28, 60 and 90. Even after withdrawal, participants will be followed to Day 90 or until their death, whichever comes first. If consent is

withdrawn, every effort will be made by the Investigator to check on the participant's vital status on Days 28, 60, and 90.

Safety Review Committee (SRC) and Investigator Team

An independent SRC will provide safety oversight for the study. The SRC will be composed of 2 independent specialists in liver disease, at least one expert in liver injury assessment, and moderated by the Sponsor's pharmacovigilance representative.

The SRC may seek external consultation as required (e.g., the Sponsor or clinical research organization medical monitor [MM], other applicable specialist relevant to the observed safety signal). The SRC remit is to monitor safety in the study and prespecified timepoints, up to and including termination of a cohort or the study after review of observed safety data. The Sponsor will make proposals, developed in collaboration with the Investigator Team, in open session with the SRC in accordance with the study design protocol. The Sponsor will be responsible to make the final decision on whether dosing continues based on the recommendations provided, which may include halting the study sooner than planned even if progression is deemed safe by the SRC. Responsibilities of the SRC are detailed in the SRC charter.

The Investigator Team comprises the actively recruiting Investigators from participating countries and will support the Sponsor in determining appropriate proposals for study progression.

Study Completion

The study will be considered complete once all planned Cohorts have completed and no further Optional Cohorts are proposed, or the Sponsor with input from the SRC determines that further exploration in multiple doses in any combination of dose and frequency is no longer warranted, regardless of the number of cohorts completed.

Stopping Criteria:

Individual Participant Stopping Criteria

All participants will be requested to participate in follow-up safety assessments to the planned end of study regardless of having achieved any stopping rules below.

Further dosing will be halted if participants experience any of the following:

1. An AE that (regardless of relationship to SZN-043, including worsening of disease) in the opinion of the investigator would make continuation of the study drug potentially detrimental to the participant's health and well-being.
2. Either of the following:
   a. AST or ALT >500 U/L and >1.5 x highest predose measure
   b. Increase in MELD score of ≥5 points from the prior dose.
3. The participant becomes or is intending to become pregnant, and/or impregnate a partner.
4. Participant does not comply with protocol and in the opinion of the Investigator or Sponsor potentially compromises safety and/or integrity of data collected.
5. Other indicators not mentioned above of overall participant welfare as judged by the Investigator to make continued treatment unsafe.

In the event that after meeting Stopping Criteria 1 or 2, a participant's condition significantly improves such that the Principal Investigator responsible for the participant considers continued dosing may be appropriate, the Principal Investigator may make such a request and must receive approval from both the Sponsor and SRC before another dose is provided.

Cohort Stopping Criteria

Dosing will be halted and the SRC will meet if any of the following criteria are met:

1. If any 1 participant experiences a TEAE ≥Grade 4* (National Cancer Institute-Common Terminology Criteria for Adverse Events [NCI-CTCAE]) (NCI 2017) within 14 days after receiving the last dose of study drug;
2. If 2 or more participants in the same cohort experience the same TEAE ≥Grade 3* (NCI-CTCAE) within 14 days after receiving the last dose of study drug (NCI 2017) considered at least possibly related to study drug (except for isolated alkaline phosphatase elevations defined as alkaline phosphatase elevations without preceding or concurrent NCI-CTCAE ≥ Grade 3 elevations in ALT, AST, or bilirubin).
3. If 2 or more participants in the same cohort experience at least 1 unanticipated TEAE ≥Grade 3* (NCI-CTCAE) within 14 days after receiving the last dose of study drug (NCI 2017) considered at least possibly related to study drug; OR
4. If 2 or more participants experience an AST or ALT (central laboratory) value >500 U/L and 1.5 x the highest predose measure.

The SRC will make a recommendation for the applicable Cohort, after review of safety and other applicable data, whether to continue the cohort or discontinue any further dosing in the current cohort. The SRC may make further recommendations to the Sponsor on next steps in the study, including, but not limited to, a change in either the dose or dose frequency and beginning a new cohort up to and including discontinuing the study.

The SRC will be responsible for making the final decision on next steps and may make the decision to discontinue the study at any time.

Number of Participants (Planned):

Up to 36 participants are planned across the Primary Cohorts, Dose Expansion Cohort, and Optional Cohort(s) (if any). The Sponsor may, at its discretion, replace participants who do not receive the planned number of doses, or who withdraw consent prior to Day 30. The Sponsor may also allow the inclusion of more than 6 participants per Cohort as specified in the Protocol.

The sample size for this trial is based on safety analyses considerations and not based on any statistical criteria.

Eligibility Criteria

Inclusion Criteria:

To be eligible for this study, a participant has to meet ***all*** of the following inclusion criteria:

1. Be a male or female (sex assigned at birth), 18 years of age or older AND considered to be an adult in accordance with local law;
2. Have a body mass index (BMI) between ≥18.0 and ≤ 36.0 kg/m^2 at Screening which may be calculated using actual or dry weight for eligible participants with ascites or edema at the Investigator's discretion;
3. Be willing to provide informed consent or have a legally authorized representative who can provide informed consent on behalf of the participant (if approved by the applicable ethic committee and allowed by applicable laws):

4. Have a clinical diagnosis of alcohol-associated hepatitis (AH) that is anticipated to require inpatient care for a period to encompass at a minimum the first dose of study drug based on typical serum chemistry (as determined by local laboratory) meeting all of the following parameters:

   a. Onset of jaundice within prior 8 weeks to consent;
   b. History of heavy alcohol abuse: >40 (female) or 60 (male) g alcohol/day for ≥6 months;
   c. Consumed alcohol within 8 weeks before study entry;
   d. AST >50, AST/ALT >1.5, and both values are: <400 IU/L;
   e. Serum total bilirubin >3.0 mg/dL.

   At the investigator's discretion, a liver biopsy may be performed to confirm diagnosis in participants who meet criteria a-c above but where other causes of liver disease are not otherwise possible to rule out (viral, drug, autoimmune, etc.).

5. MELD score of 21 to 30, inclusive, as calculated as early as Day -1. Participants with a MELD score as high as 33 may be entered into study if approved by the Medical Monitor.

6. Acceptable methods of contraception defined in protocol Section 4.2.3 must be used from Screening until study completion. Surgically sterile males or females (Section 4.2.3) or women who are postmenopausal for ≥12 months do not need additional contraception methods. Postmenopausal status will be confirmed by testing follicle-stimulating hormone (FSH) levels ≥40 IU/L at Screening for amenorrhoeic female participants.

7. Must have the ability and willingness to attend the necessary visits to the clinical research unit (CRU).

Exclusion Criteria:
A participant who meets ***any*** of the following exclusion criteria must be excluded from the study:

1. Previous receipt of antibody or biologic therapy whether licensed or investigational (immunoglobulin products, monoclonal antibodies, or antibody fragments) within the past 6 months.

2. Treatment with:

   a. any experimental drug within 30 days, or within 5 half-lives (whichever is longer), before Day 0 visit (Baseline);

   b. (or are likely to require treatment with), dapsone within 7 days of Day 0 and up to 14 or 21 days after last dose (see Section 7 for details); or

   c. (or are likely to require treatment with) any drug whose elimination could be affected by CYP2E1 within 1 day before Day 0 and up to 14 or 21 days after last dose (see Section 7 for details)

3. Other causes of liver disease including:

   a. Evidence of chronic viral hepatitis (hepatitis B or C)
   b. Biliary obstruction or cholestatic liver disease (e.g., primary biliary sclerosis, sclerosing cholangitis)
   c. Drug-induced hepatotoxicity (e.g. acetaminophen)
   d. Hepatocellular carcinoma
   e. Wilson's disease
   f. Budd Chiari Syndrome
   g. Metabolic dysfunction-associated steatotic liver disease

h. Metabolic dysfunction-associated steatohepatitis
i. Auto-immune hepatitis
j. Acute hepatitis A

4. Introduction of a new medication with potential hepatotoxicity within 60 days of screening or any anticipated increase in dose or dose regimen of any potential hepatotoxic medication which include, but are not limited, to the following: allopurinol, gold salts, pyrazinamide, amiodarone, halothane, rifampin, anabolic steroids, hydralazine, simvastatin, atorvastatin, isoniazid, sulfamethoxazole/trimethoprim, azathioprine/6-mercaptopurine, ketoconazole, sulfasalazine, busulfan, methotrexate, sulfonamides, carbamazepine, minocycline, telithromycin, chlorpromazine, nevirapine, thioguanine, disulfiram, nitrofurantoin ticlopidine, erythromycin, phenytoin, valproate, floxuridine, propylthiouracil, flutamide, quinidine, piperacillin, tazobactam.
5. Have a portosystemic shunt or scheduled for transjugular intrahepatic portosystemic shunt placement or highly likely to receive a liver transplant (in the clinical judgment of the Investigator) during the study period.
6. Dependent upon inotropic or vasopressor support due to hemodynamic instability or ventilatory support.
7. Multi-system organ failure.
8. Requires renal replacement therapy or creatinine >2.5 mg/dL (or 221 mmol/L) at time of dosing.
9. Uncontrolled hyperthyroidism, history of Paget's disease, osteomalacia, or fracture within 4 weeks of Screening:
10. Uncontrolled bacterial infections, as determined by the Investigator's judgment after a minimum of 2 days of antibiotic therapy.
11. History of a previous severe allergic reaction (with generalised urticaria, angioedema, or anaphylaxis) to SZN-043 or any of its components. Participants with known similar allergic reactions relative to other treatments should be approved by the Medical Monitor prior to inclusion.
12. QT duration corrected for heart rate by Fridericia's formula (QTcF) >450 msec for males and >470 msec for females based on either single or averaged QTcF values of triplicate ECGs before study drug administration; OR in the judgement of the Investigator and the Medical Monitor, an abnormal, clinically significant EKG is obtained such that there is concern for participant safety and/or study outcomes.
13. A history of malignant neoplasm, except for adequately treated non-metastatic basal or squamous cell cancers of the skin (>1 year ago) or carcinoma in situ of the uterine cervix (>3 years ago) that has been fully treated and shows no evidence of recurrence. Participants under evaluation for possible malignancy are also not eligible.
14. Significant gastrointestinal (GI) bleeding within 1 week of enrollment requiring transfusion of more than 3 units of blood.
15. Grade 3 or higher encephalopathy by West Haven Criteria. (note: Grade 3 may be acceptable if EC approved process for obtaining legally authorized representative consent/assent is in place)

16. The development of Acute Kidney Injury (AKI) within 7 days prior to dosing as determined by the Investigator. In determining the diagnosis of AKI, the Investigator will consider the following: an increase in serum creatinine (sCr) ≥0.3 mg/dL within 48 h or an increase in sCr ≥50% from Baseline. Baseline sCr is the initial value that per the Investigator's clinical judgment adequately establishes participant's kidney function during screening.
17. Presence of portal vein thrombosis.
18. Presence of acute pancreatitis.
19. Cerebral hemorrhage, extensive retinal hemorrhage, acute myocardial infarction (within the last 6 weeks) or severe cardiac arrhythmias (not including atrial fibrillation).
20. Liver imaging at screening within 45 days of dosing showing any lesions consistent with either primary hepatoma or metastatic liver disease (except benign lesions, i.e., hemangiomas are permitted).
21. Known infection with HIV or HIV Ab positive at screening.
22. Organ transplantation (such as liver, kidney, lung, heart, bone marrow, or stem cell etc.), other than cornea transplant.
23. Positive urine screen for amphetamines, cocaine, or opiates (i.e,, heroin, morphine) at Screening. Participants receiving stable methadone or buprenorphine maintenance treatment for at least 6 months before Screening may be included in the study. Participants with positive cannabis drug screen may be included in the study. Participants with a positive urine drug screen due to prescription opioid or amphetamine-based medication are eligible if the prescription and diagnosis are reviewed and approved by the Investigator.
24. Pregnant or lactating at Screening or planning to become pregnant (self or partner) at any time during the study.
25. Planning to donate sperm (male) or ovum (female) within 90 days after the last dose of study drug.
26. Prior or ongoing medical conditions, medical history, concomitant medication, physical findings, laboratory or EKG abnormalities that, in the Investigator's (or delegate's) opinion, could adversely affect the safety of the participant, make it unlikely the participant will comply with the protocol or complete the study per protocol, lead to premature mortality during the study period, or interfere with the interpretation of the data.
27. Current use of anticoagulants that affect prothrombin time or INR.

Investigational Product (IP), Dosage and Mode of Administration:

SZN-043 is supplied in a 10R vial as a colourless to slightly yellow/brown/yellow-brown liquid drug product filled to 10.6 mL with an extractable volume of 10.0 mL containing nominally 350 mg of SZN-043 (at a concentration of 35 mg/mL).

SZN-043 will be administered via intravenous (IV) infusion and dose will be based on participant body weight and planned dose levels. The IP preparation is further described in the Pharmacy Manual.

Participants will be observed for 4 hours during and after SZN-043 infusion.

Duration of Participation and Treatment:

Study participation will be approximately 13 weeks: up to a 1-week screening period, a 1-day (sentinel participant) or approximately 1-week (multiple-dose participants) treatment period, and a 12-week observation period after treatment completion.

The duration of the entire study (first patient screened to last patient last visit) is anticipated to be approximately 18 months but will depend on the enrolment rate.

Reference Therapy, Dosage and Mode of Administration:

N/A. Participants will be treated as per standard of care as determined by their treating physicians.

Criteria for Evaluation:

Safety and tolerability:

The safety and tolerability of SZN-043 will be investigated according to the following specific assessments: Vital signs, physical examinations, clinical laboratory tests (haematology, coagulation, serum chemistry, c-reactive protein [CRP], GLDH, complement, other laboratory tests [lipid profile and thyroid-stimulating hormone testing], 12-lead ECGs and liver biopsies if needed, liver volumetric measurement via computed tomography/magnetic resonance imaging, and review of TEAEs and treatment-emergent serious adverse events .

Efficacy Assessments

MELD score, Lille model for score, and survival

Pharmacokinetics:

PK parameters will be calculated from SZN-043 serum concentrations.

Pharmacodynamics/biomarkers and Immunogenicity:

PD and immunogenicity of SZN-043 will be investigated based on:

- Changes in concentrations of biomarkers in blood samples, including but not limited to: AFP, ALP, angiogenin, LECT2,
- HepQuant DuO Test measuring liver function.
- Metabolism of ^{13}C-methacetin cytochrome P450 1A2 system, as measured by the Methacetin Breath Test.
- Prevalence of ADA for SZN-043 at baseline and incidence of ADA during the study.

Statistical Methods:

Full details of the statistical analyses will be provided in the Statistical Analysis Plan (SAP). Statistical analyses will be descriptive in nature. Summaries will be provided for participant disposition, demographics, baseline characteristics, safety, PK, PD, and ADA parameters and presented by cohort and treatment group.

Data will be summarised by cohort and treatment group. In general, continuous variables will be summarised with descriptive statistics (number of participants with available data, mean, standard deviation, minimum, median, and maximum). For PK and PD parameters, coefficient of variation (CV) and geometric mean will also be presented, as appropriate. Categorical endpoints will be summarised with frequency counts and percentages within each category. All data in the database will be presented in by-participant data listings.

The number and percentage of participants reporting TEAEs and serious adverse events (SAEs) will be summarised by System Organ Class and Preferred Term. Separate summaries will be provided for all

TEAEs, TEAEs by toxicity grade, TEAEs by relationship to study treatment, treatment-emergent SAEs, and treatment-emergent SAEs by relationship to study treatment. By-participant data listings will be provided for deaths, SAEs, participants meeting DILI criteria, and AEs leading to discontinuation of study treatment.

All other safety parameters, including clinical laboratory results, vital sign measurements, and ECG interval results, will be summarised using descriptive statistics for continuous variables, and counts and percentages for categorical variables by treatment group. For continuous variables, observed values and changes from baseline for each protocol-specified visit will be presented.

PK endpoints and results of PD biomarker analysis (both observed values and changes from baseline) will be summarised using descriptive statistics and presented graphically by cohort, treatment group, and protocol-specified visits and time points, as appropriate. The relationship between PK levels and ECG interval results will be analysed. If data permit, the relationship between PK levels and PD or safety endpoints may be explored.

Observed values for ADA levels/status will be summarised with descriptive statistics by cohort and treatment group. If data permit, the relationship between ADA levels and PK, PD, or safety endpoints may be explored.

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

The following abbreviations and specialist terms are used in this protocol.

Table 2: Abbreviations and Specialist Terms

Abbreviations or Specialist Term	Explanation
ABIC	Age, serum bilirubin, international normalised ratio, serum creatinine
ADA	Antidrug antibodies
AE	Adverse event
AFP	Alpha-fetoprotein
AH	Alcohol-associated hepatitis
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ASGPR	Asialoglycoprotein receptor
ASGR1	H1 protein of ASGPR
AST	Aspartate aminotransferase
AUC	Area under the curve
BMI	Body mass index
CDR	Complementarity-determining regions
CLDQ	Chronic Liver Disease Questionnaire
C_{max}	Maximal observed concentration
CRP	C-reactive protein
CRU	Clinical research unit
CTCAE	Common Terminology Criteria for Adverse Events
CTP	Child-Turcotte-Pugh
CV	Coefficient of variation
DILI	Drug-induced liver injury
ECG	electrocardiogram
eCRF	Electronic case report form
EDC	Electronic Data Capture
EOS	End of study
Fc	Crystallizable fragment
FcRn	Neonatal FC receptor
FSH	Follicle stimulating hormone

Abbreviations or Specialist Term	Explanation
FZD	Frizzled
FZD1-10	Frizzled 1-10 E3 ligases specifically targeting Wnt-receptor
GCP	Good Clinical Practices
GGT	Gamma glutamyltransferase
GI	gastrointestinal
GLDH	glutamate dehydrogenase
GLP	Good Laboratory Practices
HBsAg	Hepatitis B surface antigen
ICF	Informed Consent Form
ICH	International Council for Harmonisation
INR	International normalised ratio
IP	Investigational product
IR	Infusion reaction
ITT	Intent to treat
IV	intravenous
LECT2	Leukocyte cell-derived chemotaxin-2
LFTs	Liver function tests
LGR 4-6	To leucine-rich repeat-containing G-protein coupled receptor 4-6
LRP5 and LRP6	Low-density lipoprotein receptor 5 and 6
MAD	Multiple ascending dose
MBT	Methacetin breath test
mDF	Maddrey's Discriminant Function
MELD	Model for end-stage liver disease
MM	Medical Monitor
NCI	National Cancer Institute
PD	Pharmacodynamics
PK	Pharmacokinetics
QTcF	QT duration corrected for heart rate by Fridericia's formula
RNF43	Ring Finger Protein 43
RSPO1-4	R-spondens 1-4
RTSM	Randomisation and Trial Supply Management

Abbreviations or Specialist Term	Explanation
SAD	Single ascending dose
SAE	Serious adverse event
sAH	Severe alcohol-associated hepatitis
SAP	Statistical analysis plan
sCR	Serum creatinine
SOA	Schedule of Assessments
SRC	Safety review committee
TEAEs	Treatment-emergent adverse events
ULN	Upper limit of normal
ZNRF3	Zinc and Ring Finger 3

FACILITIES AND PERSONNEL

For details of study contacts including, but not limited to, project management, site management, data management, pharmacovigilance, laboratories, etc., refer to the study contact list at each site.

1. BACKGROUND AND INTRODUCTION

1.1. Introduction

Alcohol-associated liver disease represents a spectrum of liver injury resulting from alcohol use, ranging from hepatic steatosis to more advanced forms including alcohol-associated hepatitis (AH), alcohol-associated cirrhosis, and severe alcohol-associated hepatitis (sAH) presenting as acute on chronic liver failure (Crabb 2020). AH is characterised by liver inflammation and impaired hepatocyte proliferation caused by chronic, excessive alcohol consumption (Dubuquoy 2015; Lanthier 2015). Signs and symptoms of AH include jaundice, ascites, fatigue, and hepatic encephalopathy; its histological features include neutrophilic lobular inflammation, degenerative changes in hepatocytes (ballooning and Mallory-Denk inclusions), steatosis, and pericellular fibrosis often superimposed on the background of underlying cirrhosis (Baptista 1981).

AH may present acutely after binge drinking or after years of excess alcohol intake. Clinical diagnosis is based upon a history of significant alcohol intake (consumption of >40 (female) or >60 (male) grams of alcohol/day for ≥ 6 months, with <60 days of abstinence before the onset of jaundice), worsening liver function tests, including elevated bilirubin (typically >3.0 mg/dL) and liver enzymes (aspartate aminotransferase [AST] >50, AST/alanine aminotransferase [ALT] >1.5 with both values <400 IU/L), and onset or recent worsening of jaundice (within the prior 8 weeks) (Crabb 2020). Mild to moderate cases are self-limiting, but severe cases have high mortality. The mDF (Maddrey Discriminant Function) and Model for End-stage Liver Disease (MELD) multivariate composite scores, which include bilirubin, blood clotting and other variables, are used to characterise AH patients based on prognosis. Severe AH is defined as an mDF ≥32 and MELD score > 20. It is associated with 15 to 20% mortality at 1 month and 30% mortality at 3 months (Thursz 2015).

1.1.1. Unmet Need in Severe Alcohol-Associated Hepatitis

Current options for specific treatment of sAH are inadequate and there is a clear unmet need for new therapeutic approaches for the treatment of sAH. Anti-inflammatory therapies have been evaluated extensively; currently, corticosteroids are the only class of drug recommended for sAH. However, they are associated with only modest reductions in mortality at 28 days and no benefit at 3 months or beyond (Louvet 2018). Only 25 to 45% of patients are eligible for corticosteroid therapy due to infections, poorly controlled diabetes mellitus, renal failure, and active gastrointestinal bleeding (Singal 2012).

Prednisolone 40 mg per day orally or methylprednisolone 32 mg intravenous(ly) (IV) for a maximum duration of 28 days is recommended as first-line therapy in patients with sAH. However, approximately 40% of patients in most AH trials did not respond to steroids. Since continued steroid use is associated with a high risk of infection, the Lille score* has been used for early identification of treatment futility (Louvet 2018). A Lille score ≥ 0.45 after 1 week of steroid therapy indicates non-response and was highly predictive of death at 6 months. Progressive liver disease with multiple organ failure is the major cause of death among sAH patients who do not respond to corticosteroids. Because of ongoing alcoholism, most patients are ineligible for early liver transplantation.

Other pharmacological options that have been used without survival benefit include pentoxifylline (Thursz 2015); anti-tumor necrosis factor agents like infliximab and etanercept (Naveau 2004; Boetticher 2008), antioxidant cocktails including vitamin E (Singal 2012), insulin and glucagon (Trinchet 1992), testosterone or oxandrolone (Rambaldi 2007), propylthiouracil (Israel 1982), and extra-corporeal albumin dialysis (Bañares 2013). These interventions do not directly address the loss of hepatocytes and the resultant reduction in hepatic function, nor do they address the lack of hepatocyte regeneration characteristic for AH.

*Role of Wnt in Liver Disease

Wnt/β-catenin signalling plays an important role in liver homeostasis, as well as in hepatocyte regeneration and maturation, such as in the response to injury (Russell 2018; Rmilah 2019). Wnt proteins bind to receptors of the Frizzled (FZD) and low-density lipoprotein receptor (LRP) families on the cell surface, initiating a signal that is then relayed through several cytoplasmic proteins to stabilise the transcription factor, β-catenin. Accumulation and nuclear localisation of β-catenin leads to the activation of Wnt target genes, contributing to key biological changes that impact cell proliferation and maintenance of stem cell potency in a variety of tissue-specific contexts.

One important negative feedback mechanism of Wnt signalling is activation and recruitment of Zinc and Ring Finger 3 (ZNRF3) and Ring Finger Protein 43 (RNF43). ZNRF3 and RNF43 are membrane-bound E3 ligases specifically targeting Wnt receptors (FZD1-10 and LRP5 or LRP6) for degradation. R-spondins 1-4 (RSPO1-4) are a family of ligands that amplify Wnt signals through binding to ZNRF3/RNF43 via their Furin 1 domain and to leucine-rich repeat-containing G-protein coupled receptor 4-6 (LGR4-6) via their Furin 2 domain. Binding of an RSPO to ZNRF3/RNF43 and LGR4-6 triggers inactivation and removal of the ZNRF3/RNF43 from the cell surface which stabilises FZD and LRP receptors, resulting in enhanced Wnt signalling.

Wnt/β-catenin signalling is critical to hepatocyte proliferation following various forms of liver injury (Monga 2001; Kaidi 2007; Apte 2009; Lehwald 2011; Huang 2015). Liver regeneration (with variations depending on types of injury) typically goes through the following phases:

1. priming or initiation phase in which key cytokines and growth factors start to be produced and cells, including mature hepatocytes, are prepared to enter cell cycles;
2. proliferation phase in which liver cells proliferate and expand to compensate for loss;
3. termination phase in which regeneration is completed with initial organisation of tissue architecture and prevention of overgrowth (Rmilah 2019).

Usually, the proliferative features of the remaining parenchymal and non-parenchymal liver cells play the major role in liver regeneration upon liver injury. Increased Wnt/β-catenin signalling induces the remnant hepatocytes to enter the cell cycle to restore the original liver mass (Michalopoulos 2007; Mao 2014).

1.1.2. SZN-043 Mechanism of Action and Rationale for Development of SZN-043 in Severe Alcohol-Associated Hepatitis

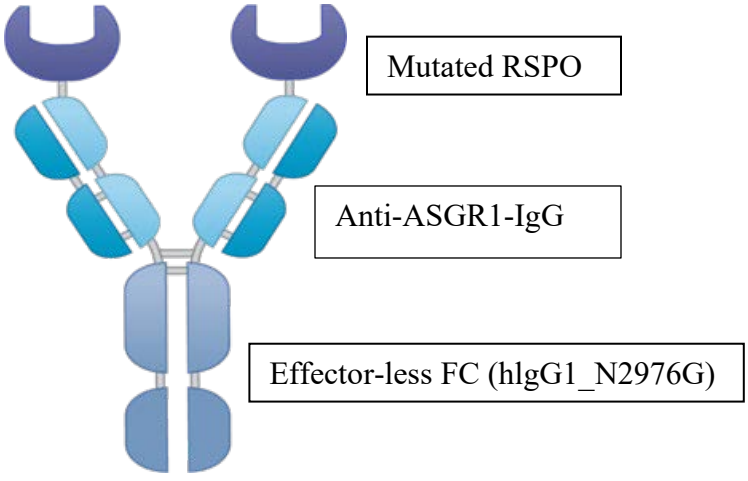
SZN-043 is a RSPO mimetic specifically targeted to hepatocytes through ASGR1 binding. RSPO1-4 amplify Wnt signalling by stabilizing FZD and LRP receptors at the plasma

membrane. RSPOs play an important role in liver regeneration, including RSPO1 in carbon tetrachloride and hepatectomy animal models (Planas-Paz 2016; Lin 2017). However, the effect of RSPOs is not restricted to hepatocytes, and RSPOs induce responses in other tissues including small intestine hyperplasia (Kim 2005). Additionally, enhanced Wnt signalling in hepatic stellate cells may contribute to liver fibrosis (Nishikawa 2018). Thus, to specifically increase hepatocyte proliferation without effects in other cells or tissues, Surrozen developed a hepatocyte-specific RSPO mimetic, SZN-043.

The asialoglycoprotein receptor (ASGPR) is a Type C, carbohydrate-binding lectin whose major role is the binding and clearance of desialylated serum glycoproteins (Geffen and Spiess 1992; Das 2019). In addition, ASGPR has been reported to play an immunomodulatory role, to function in the clearance of other serum proteins (including alkaline phosphatase [ALP]), and to promote binding and uptake of other serum components (e.g., chylomicrons, activated lymphocytes, platelets). ASGPR is abundantly expressed on the sinusoidal and basolateral membranes of mammalian hepatocytes with a density estimated at 100,000-500,000 receptors per cell with little or no reported expression in other cells making it an excellent target for a hepatocyte-specific drug (Das 2019).

SZN-043 is a humanized IgG1 monoclonal antibody with complementarity-determining regions (CDRs) against ASGR1 to which a mutated RSPO2 has been fused via a flexible 3xG4S linker to each N-terminus of the heavy chain (Figure 1). The binding of the CDRs to ASGR1, a receptor expressed nearly exclusively on hepatocytes confers hepatocyte specificity to SZN-043 (Zhang 2020). Mutations in the Furin 2 domain of the RSPO2 fragment abolish the LGR interaction while preserving Furin 1 domain-mediated binding to ZNRF3/RNF43.]

Figure 1: Structure of SZN-043



ASGR1=H1 subunit of asialoglycoprotein receptor; Fc=crystallizable fragment; IgG=immunoglobulin G; N2976G=asparagine position 297 mutated to Glycine; RSPO2=R-spondin 2.

The Fc region of SZN-043 has been engineered to eliminate crystallizable fragment (Fc) effector function by virtue of an N2976G mutation (Jacobsen 2017). These modifications result in a therapeutic candidate with bispecific binding to both ASGR1 and E3 ligases, and the capacity to

bind to the neonatal Fc receptor (FcRn) thus conferring monoclonal antibody-like disposition properties.

SZN-043 acts on hepatocytes by binding to ASGR1 via its CDR and engaging the E3 ligases via mutated RSPO resulting in the removal of these E3 ligases from the hepatocyte surface. As the function of these E3 ligases is to ubiquitinate the FZD receptors, their removal prevents the degradation of the FZD receptors. This stabilizes FZD and LRP receptors on the surface of hepatocytes, making them more responsive to the available Wnt induced by liver injuries and associated inflammation (Ge 2014).

Severe AH is associated with impaired hepatocyte proliferation, and increased Wnt signalling along with increased hepatocyte proliferation has been linked to increased survival (Dubuquoy 2015; Lanthier 2015). This deficit in hepatocyte proliferation provides an opportunity for treatment with a RSPO-mimetic agent like SZN-043 that can enhance Wnt signalling specifically in hepatocytes and induce hepatocyte proliferation resulting in improved liver function and patient outcomes.

Figure 2: SZN-043 Mechanism of Action

ASGPR=asialoglycoprotein receptor; B-cat=β-catenin; LRP=low-density lipoprotein receptor-related protein. RNF43=ring finger protein 43; ZNRF=zinc and ring finger 1 protein.

1.2. Summary of Nonclinical and Clinical Studies

1.2.1. Nonclinical Studies

Please refer to the SZN-043 Investigator's Brochure (Edition 2, November 2023) for a detailed description of the pharmacology studies in mouse disease models of hepatic disease (AH, liver fibrosis, acetaminophen overdose), and pharmacokinetic (PK) and toxicology studies (2-week

and 30-day) in mice and cynomolgus monkeys. The SZN-043 Investigator's Brochure will also serve as the Reference Safety Information for SZN-043.

Based on preclinical data, it is hypothesized that SZN-043 may have meaningful clinical benefit in human disease states associated with hepatocyte injury and inadequate regenerative repair, such as in sAH. Since improved hepatocyte proliferative capacity has been linked to increased survival in AH (Lanthier 2015; Dubuquoy 2015), therapies that can stimulate hepatocyte proliferation may have substantial benefits in this patient population.

Data from nonclinical studies with SZN-043 showed a favourable safety profile with no significant adverse events identified in the 2-week and 30-day toxicology studies in mice and cynomolgus monkeys and an adequate estimated safety margin for dosing up to 3 mg /kg in this study. Findings associated with SZN-043 in the mouse and monkey Good Laboratory Practices (GLP) studies were limited to non-adverse increases in ALP, an expected pharmacology effect that is reversible after dosing cessation, and liver and other organ weight changes, which lacked microscopic correlates and were reversible. The increase in serum ALP levels is related to the binding of SZN-043 to the hepatic cell surface receptor ASGR1 followed by receptor internalization. This prevents the elimination of ALP from the serum as the HI subunit of asialoglycoprotein receptor-1 (ASGR1) is the major subunit of the hepatic asialoglycoprotein receptor (ASGPR) known to recognize and mediate the endocytosis and degradation of a variety of desialylated glycoproteins and ALP (Geffen and Spiess 1992, Das 2019). The increase in serum ALP levels was not accompanied by changes in other hepatic markers (e.g., transaminases, gamma-glutamyl transferase [GGT] and bilirubin), nor was there any evidence of hepatic injury by histopathology.

1.2.2. Clinical Studies

This is the second study in humans with SZN-043. The first study, CL-0043-1001, is a Phase 1a single and multiple ascending dose study examining the safety, tolerability, and PK in healthy volunteers and patients with a history of liver cirrhosis. To date, cohorts in single doses up to 3 mg/kg have been studied in healthy volunteers, cohorts in multiple doses up to 1.5 mg/kg have been studied in healthy volunteers, cohorts in single doses up to 1 mg/kg have been studied in patients with a history of liver cirrhosis. No stopping rules have been met, and the study remains on-going. A summary of the non-clinical studies and observations from the clinical studies are described in the Investigator's Brochure, Edition 2.

1.3. Participant Population

The study will be conducted in male and female participants, 18 years of age or older, with a body mass index (BMI) between ≥18 and ≤36 kg/m^2, a clinical diagnosis of sAH, and a MELD score between 21 and up to 33.

Up to 82% of participants with sAH have underlying cirrhosis or bridging fibrosis (Altamirano 2014), and ASGPR expression in cirrhotic livers has been reported to be reduced compared to healthy participants (Witzigmann 2016; Burgess 1992). Furthermore, ASGPR activity has been shown to be substantially reduced in cirrhotic livers (Kudo 1991; Sawamura 1984), perhaps due to the receptors being mostly expressed on the canalicular surface of hepatocytes (Burgess 1992) whereas in normal livers, ASGPR is mainly located on the

sinusoidal surface. Additionally, mouse studies have shown that alcohol reduces ASGPR expression (Kato 1998; Casey 2004). In liver samples of patients with alcohol-associated cirrhosis, ASGPR expression was similar to healthy controls; however, receptor localisation or activity were not assessed (refer to the SZN-043 Investigator's Brochure). These potential differences in ASGPR expression and activity could result in the PK and pharmacodynamics (PD) of SZN-043 in participants with cirrhosis more closely resembling those of patients with AH than healthy volunteer participants. Based on observations to date of the ongoing clinical study in healthy volunteers and participants with a history of liver cirrhosis, the safety profile appears similar. The PK of SZN-043 appears similar between cohorts with preliminary evidence of faster clearance in participants with cirrhosis at the lowest dose tested (0.5 mg/kg).

1.4. Dosage Rationale

The selection of doses in this study is based on the totality of the available clinical PK data to date, and the prior nonclinical pharmacology, PK, and toxicology data and aligned with the regulatory guidances (e.g., 2005, FDA "Guidance for Industry: Estimating the Maximum Safe Starting Dose in Initial Clinical Trials for Therapeutics in Adult Healthy Volunteers"; 2017 EMA "Guideline on strategies to identify and mitigate risks for first-in-human and early clinical trials with investigational medicinal products").

Study CL-0043-1001 was initiated at a recommended starting dose of 3 mg/kg IV as a single dose to human healthy volunteers. This dose recommendation was based on a favourable safety profile of SZN-043 in GLP-compliant 30-day toxicology studies in mice and cynomolgus monkeys, in which SZN-043 was administered twice weekly for 4 weeks and a no -observed- adverse -effect level of 125 mg/kg/dose was determined in both studies. This starting dose was also expected to be minimally pharmacologically active based on nonclinical data in normal mice and mouse models of liver injury. The recommended starting dose was estimated to provide a predicted human serum area under the curve (AUC) and maximal observed concentration (C_{max}) that was 77- and 41-fold below that observed after a single dose of SZN-043 in cynomolgus monkeys, and 36- and 24-fold below that observed in mice (Section 4.7 of SZN-043 Investigator's Brochure), respectively. The observed mean C_{max} and AUC at 3 mg/kg (Table 3) agreed with the predicted values (61.9 µg/mL, 28.7 µg*day/mL), respectively.

Based on observations in Cohort 1 of that study, additional lower dose level cohorts were added to assess the safety, PK, and/or PD in healthy volunteers of a single dose of SZN-043 (1 mg/kg) and repeated doses of SZN-043 administered on Days 0 and 4 at 0.5, 1.0, and 1.5 mg/kg. The repeated dose regimen selected was consistent with the PK of SZN-043 in humans at these doses and the observed duration of PD activity observed in nonclinical mouse studies. In addition, safety, PK, and PD assessments were performed in participants with a history of liver cirrhosis (single doses of 0.5 and 1 mg/kg). The PK profile of SZN-043 in healthy volunteer and participants with a history of cirrhosis cohorts is summarized in Table 3.

Table 3: Mean (SD) Pharmacokinetics of SZN-043 in Humans

PK parameter	1 mg/kg	3 mg/kg	0.5 mg/kg X2	1.0 mg/kg x 2	1.5 mg/kg x 2	0.5 mg/kg cirrhosis	1 mg/kg cirrhosis
AUC (µg-day/mL)	3.2 (1.9)	34.9 (6.6)	2.09 (1.81)	6.73 (2.31)	17.6 (4.67)	0.475 (0.145)	3.34 (0.893)
CL (mL/day/kg)	454 (324)	89.0 (19.8)	734 (450)	327 (112)	181 (48.1)	1110 (310)	312 (72.3)
Terminal half-life (Days)	0.737 (0.218)	3.40 (1.27)	1.06 (1.09)	1.29 (1.34)	1.37 (0.285)	0.346 (0.160)	0.638 (0.109)
C_{max} (µg/mL)	12.6 (4.12)	61.9 (8.25)	4.68 (1.74)	12.9 (1.63)	26.4 (4.47)	4.61 (0.477)	14.1 (1.90)
V_c (mL/kg)	85.0 (27.2)	48.7 (6.81)	113 (50.3)	85.6 (10.3)	61.8 (11.4)	96.4 (9.12)	69.1 (9.91)

AUC=area under the concentration-time curve from time 0 to infinity; CL=clearance; C_{max}=maximum observed serum concentration; Vc=central compartment volume of distribution

The doses proposed in this Phase 1b study do not exceed those evaluated in either healthy volunteers or participants with cirrhosis in the Phase 1 Study CL-0043-1001.

Based on human PK observed to date, the starting dose in this study (0.5 mg/kg x 2) should provide an SZN-043 exposure, as determined by AUC, that is >20-fold below that observed at the highest tested dose in healthy volunteers (3 mg/kg) and similar to that observed at 0.5 mg/kg as a single dose in subjects with a history of cirrhosis. The expected C_{max} in subjects with sAH at the starting dose is predicted to be approximately 6 x below that observed in healthy volunteers at 3 mg/kg and approximately 2 x below that observed in participants with cirrhosis at 1 mg/kg.

The SZN-043 exposure (AUC and C_{max}) after the highest proposed dose in participants with sAH (1.5 mg/kg x 2) should not exceed that observed at 3 mg/kg as a single dose in healthy volunteers.

1.5. Ethical Principles

This study will be conducted in accordance with the principles of the current Declaration of Helsinki (Ethical Principles for Medical Research Involving Human Subjects) and with the Guideline for GCP E6 (EMA ICHE6 R2) as further adopted by the applicable regulatory authority.

This study will be conducted under a protocol reviewed and approved by an Ethics Committee and investigations will be undertaken by scientifically and medically qualified persons, where the benefits of the study are in proportion to the risks.

2. TRIAL OBJECTIVES AND PURPOSE

2.1. Objectives and Endpoints: Multiple Ascending Dose in Participants with Severe Alcohol Associated Hepatitis

The objectives and endpoints are presented in Table 4.

Table 4: Objectives and Endpoints

Objectives	Endpoints
Primary Objectives: • To evaluate the safety and tolerability of MAD of SZN-043 in participants with severe alcohol-associated hepatitis • In Cohort 4 assess safety and tolerability across two doses of SZN-043	**Primary Endpoints:** • Safety and tolerability of SZN-043 at proposed doses, based on the frequency and severity of TEAEs, TESAEs, treatment emergent laboratory, ECGs, and physical examination findings.
Secondary Objectives: • To assess the change from baseline in alcohol-associated hepatitis disease progression within and across cohorts as measured by Model for End-Stage Liver Disease (MELD), Lille Model for alcohol-associated hepatitis (Lille) score, and mortality. • To assess the change from baseline in functional measures of liver function within and across cohorts. • To characterize the PK of SZN-043. • To evaluate immunogenicity (measured as ADA) to SZN-043.	**Secondary Endpoints:** • Percent of participants alive at Days 28, 60, and 90 • Percent and absolute change in MELD score from baseline to Days 4, 7, 28, 60, and 90 • Lille Score o Percent and absolute change from baseline at Days 4 and 7 o Percent of participants with Lille score <0.45 at Days 4 and 7 • Percent and absolute change from baseline in ALT, AST, bilirubin, international normalised ratio, and albumin over time. • Measure PK parameters after multiple doses of SZN-043, as data allow • Prevalence of ADA for SZN-043 at baseline and incidence of ADA during the study

Objectives	Endpoints
Exploratory Objectives:	**Exploratory Endpoints:**
• To characterize the effect of SZN-043 on serum PD biomarkers	• PD parameters of SZN-043 administration including, but not limited to, the following (as data is available): o Change from baseline in biomarkers of SZN-043 activity including, but not limited to, serum ALP, AFP, and (if tested within a cohort), angiogenin and LECT2. o Change from baseline of the metabolism of ^{13}C-methacetin by the liver-specific cytochrome P450 1A2 system, as measured by the Methacetin Breath Test. o Change from baseline in liver function as measured by the HepQuant DuO test.
• To characterize PK, PD, ADA, and safety relationships as data allow.	• Evaluate PK-PD, PK-ADA, PK-safety, ADA-safety, and ADA-PD relationships, as data allow.
• Explore the change from baseline in clinical condition assessments.	• Change from baseline to Days 7, 28, and 90 of the following items: o mDF (Maddrey's Discriminant Function) o ABIC (age, serum bilirubin, INR, and serum creatinine) • Change from baseline to Days 7 and 28 of the following items: o Albumin o Child-Turcotte-Pugh (CTP) score o Fibrinogen o Liver regeneration markers: alpha-fetoprotein o Hepatocyte damage markers: glutamate dehydrogenase
• Quality of Life Assessments	• Quality of Life measured by CLDQ at Days 28, 60, and 90
• Health Care Utilization Assessments	• Health care utilization including, but not limited to, length of hospital and ICU stays

Abbreviations: ADA=antidrug antibodies; ALP=alkaline phosphatase; ALT=alanine aminotransferase; ALT=alanine aminotransferase; AST=aspartate aminotransferase; CLDQ=Chronic Liver Disease Questionnaire; ECGs=electrocardiograms; GGT=glutamate glutamyltransferase; ICU=intensive care unit; INR= international normalized ratio; IV=intravenous; LECT2=leukocyte cell-derived chemotaxin-2; MAD=multiple ascending dose; PD=pharmacodynamics; PK=pharmacokinetics; TEAE=treatment-emergent adverse events; TESAEs=treatment emergent serious adverse events

3. INVESTIGATIONAL PLAN

3.1. Overall Study Design

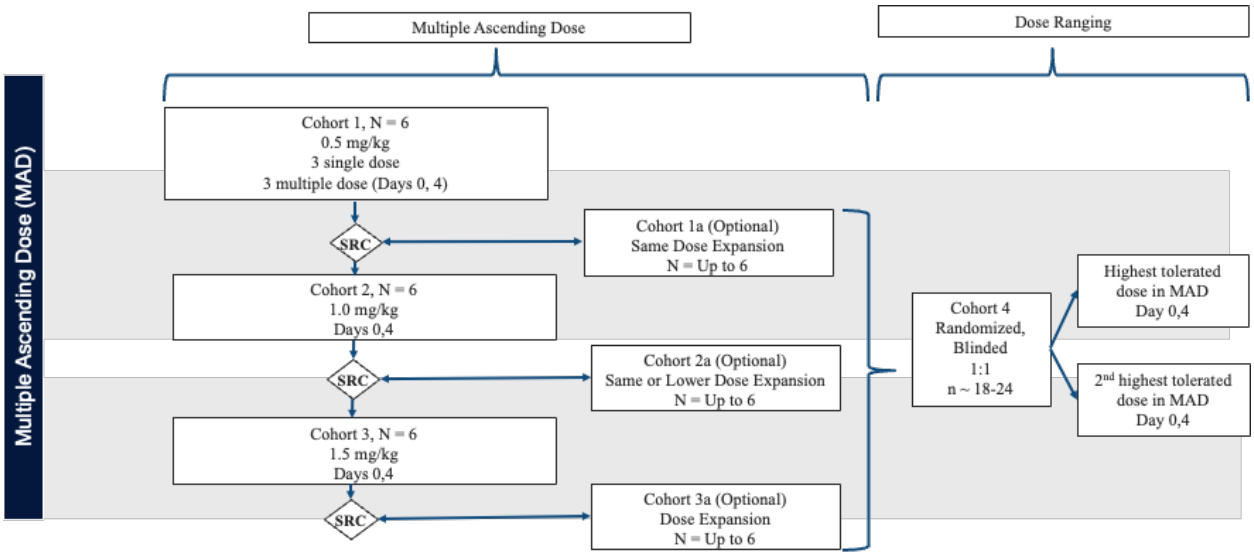
This is a multicentre, multiple ascending dose (MAD), escalation study in participants with sAH. Initial cohorts with escalating doses will be open-label. These will be followed by a cohort inclusive of the highest tolerated dose and a dose below to observe variability in safety across two doses in a blinded setting.

The study will comprise up to 3 Planned Cohorts of escalating doses of SZN-043 dosed at Days 0 and 4 (Primary), 1 planned Dose Expansion Cohort, and 3 Optional Cohorts of variable doses and dosing frequencies in participants with sAH. The use of Optional Cohorts will be determined based on emerging data, and as consequently proposed and agreed by the Sponsor and Safety Review Committee (SRC). Optional cohorts may occur after a planned cohort has completed but are not required and may never be implemented if dosing can progress as described in the planned cohorts. Optional cohorts will have a frequency no higher than previously tested, and the specified dose may be the same, lower, or at a level below the next planned cohort. The dose expansion cohort will repeat the dosing and frequency of a previous cohort. This cohort may occur at any time once the Sponsor and/or SRC have recommended that increasing doses to the next level is not warranted for any reason, and that the dose to be expanded has been determined by the SRC to be safe to use for continued testing in additional participants.

All cohorts will be defined by dose and frequency. The Primary Cohorts are planned as described in Table 5 but may be adjusted based on emerging data as proposed by the Sponsor with agreement by the SRC, and with input from the Investigators Team, as applicable.

A schematic of the study design is presented in Figure 3.

Figure 3: Study Design



Study Participants and Dosing Plan

Participants who provide voluntary documented informed consent will undergo screening evaluations to determine eligibility to become study participants within 1 week before the first dose of SZN-043 (hereafter Day 0). All study visits and assessments will occur as delineated in the Schedule of Assessments (see Appendix 1).

Study participation will be approximately 13 weeks in each cohort: up to a 1-week screening period, a 1-day (sentinel participant) or approximately 1-week (multiple dose participants) treatment period, and a 12-week observation period after treatment completion. The duration of the entire study (first patient screened to last patient last visit) is anticipated to be approximately 18 months but will depend on the enrolment rate. Due to acute nature of the participants in the study and timing of test results, the Sponsor may allow for an extension of the screening period, including the timing of any one or multiple specific screening procedures prior to dosing. Sites will contact the Medical Monitor and obtain prior approval, including which (if any) procedures must be repeated.

All Cohorts will be defined by dose and frequency.

Multiple Ascending Dose Cohorts

The Primary Cohorts are planned as follows; but, may be adjusted based on emerging data (e.g., available safety, data from Optional Cohorts) as proposed by the Sponsor with agreement by the SRC, and with input from the Investigator Team, as applicable. Dosing and dosing frequency for the 3 planned Primary Cohorts are defined in Table 5.

Table 5: Dose and Frequency

Cohort	Dose	No. of Participants	Frequency
1	0.5 mg/kg	6/cohort	Day 0 only (sentinels in Cohort 1) Days 0 and 4 (all other participants)
2	1.0 mg/kg		
3	1.5 mg/kg		

To ensure participant safety, the Primary Cohort 1 will include sentinel dosing. For this study, 3 participants will receive a single dose of SZN-043 before the remainder of the cohort. Sentinel participants will be observed for at least 14 days. The SRC will review available safety data and provide a recommendation on whether multiple doses are supported or if additional action is required before treating the remainder of the cohort.

Optional Cohorts may explore the same or lower doses as completed in a prior Primary Cohort up to a maximum of 1.5 mg/kg in cohorts of up to 6 participants. These cohorts may also explore additional dosing regimens, including changing timing or reducing the frequency. Optional Cohorts will be recommended by the Sponsor and implemented if agreed by the SRC. The proposal must be supported by (at a minimum) emerging safety data from any study with SZN-043 and/or other data about the product that can be made available to SRC to review to make its assessment.

Dose Ranging Cohort

A Dose Ranging Cohort (Cohort 4) will be opened after Multiple Ascending Dose Cohorts have completed dosing, and (based on upon review of available data) the Sponsor is able to

recommend and the SRC is able to endorse two different doses of SZN-043 with the following guidelines:

- Selection of the doses and frequency for Cohort 4 will 1) match the highest dose from the previously completed cohorts cleared for safety by the SRC and 2) a lower dose.
- The number of participants to be included will result in at least 18 participants exposed to the selected dose and frequency in order to better characterize the study endpoints at that dose. Total participants in this Cohort is planned for at least 18, as recommended by the Sponsor and endorsed by the SRC. An additional 6 participants may be added upon recommendation and endorsement from the SRC.
- Dosing frequency is intended to be completed at Days 0 and 4, however, this may be altered upon recommendation of the Sponsor and endorsement of the SRC.

Cohort	Dose	Number of Participants	Frequency
4	TBD mg/kg	18-24	Days 0 and 4 (or as determined by SRC)

Investigators will be informed by memo of the planned dose and dosing frequency.

Dosing Requirements (all cohorts)

While a maximum of 6 participants is planned per cohort, the Sponsor may, at its discretion, allow the entry of additional participants in any one cohort if at the time a 6th participant is identified, more than 1 participant is in screening that may meet eligibility criteria.

Participants will receive each dose of drug under the following conditions:

- Blood ethanol level is less than 50 mg/dL, or 0.05% concentration
- On subsequent doses, safety events observed in the participant that are assessed to be related to SZN-043 (or other safety events that in the Investigator's opinion may undermine the participants' welfare with further discussing regardless of relatedness) are sufficiently resolved or are considered not clinically significant in consideration of the overall clinical status of the participant as assessed by the Investigator.
- Dosing may continue or be delayed beyond the specified endpoint to allow for appropriate resolution of AEs as required if the last dose administered is within 28 days of the first dose.

  NOTE: The Investigator must obtain Sponsor agreement to dose if a related adverse event (AE) is ongoing at the prespecified timepoint. Dosing may continue or be delayed beyond the specified endpoint to allow for appropriate resolution of AEs as required if the last dose administered is within 28 days of the first dose.

In addition to receiving SZN-043, other supportive care, including steroids, will be provided in accordance with local standard-of-care and medical practices.

Participants in any cohort who receive at least one dose of study drug and then request withdrawal from additional treatment and study procedures or are withdrawn by either the

Investigator or Sponsor, will be asked to allow continued contact for vital status at Days 28, 60 and 90. Even after withdrawal, participants will be followed to Day 90 or until their death, whichever comes first. If consent is withdrawn, every effort will be made by the Investigator to check on the participant's vital status on Days 28, 60, and 90.

3.2. Cohort Progression

Cohort progression assessment will proceed 14 days after the required number of participants (see above) have completed dosing:

- The Sponsor, in collaboration with the Investigator Team (comprising the actively recruiting investigators from each participating country) will:
  - propose conditions for an Optional Cohort (in accordance with allowances specified in this protocol) before progressing to the next Planned Cohort, OR
  - propose revised conditions to the next anticipated Planned Cohort (in accordance with allowances specified in this protocol) based on outcomes from an Optional Cohort to the SRC (e.g., expand current dose, proceed to higher dose, change frequency, etc.)
- The SRC will meet to review available safety data to confirm whether the safety data supports the proposed dose escalation for the next Primary or Optional Cohort. The SRC may also propose alternatives to the Sponsor.
- The Sponsor will review the SRC recommendation and will make the final decision on next steps, with the following guidance:
  - If the SRC agrees with the proposal, then recruitment may open.
  - If the SRC is not in agreement with the initial proposal, the Sponsor decision may include accepting any alternative SRC recommendations, proposing other possible revisions within the confines of this protocol that are acceptable to the SRC, or may consider amending and/or terminating the study, if applicable.

A cohort will be considered complete once all participants have completed procedures described in the Schedule of Assessments (Appendix 1), the participant has withdrawn from study (including willingness to allow vital sign check at day 90), had a liver transplant or died.

The study will be considered complete once all planned Cohorts have completed and no further Optional Cohorts are proposed, or the Sponsor with input from the SRC determines that further exploration in multiple doses in any combination of dose and frequency is no longer warranted, regardless of the number of cohorts completed.

3.3. Number of Participants

Up to 36 participants are planned in the Primary Cohorts, Dose Expansion Cohort, and Optional Cohort(s) (if any). The Sponsor may, at its discretion, replace participants who do not receive the planned number of doses, or who withdraw consent prior to day 30. The Sponsor may also allow the inclusion of more than 6 participants per Cohort as specified in the Protocol.

The sample size for this trial is based on safety analyses considerations and not based on any statistical criteria.

3.4. Safety Review Committee

Safety oversight for the study will be supported by an independent SRC, which will be composed of 2 independent specialists in liver disease, at least 1 expert in liver injury assessment, and moderated by the pharmacovigilance representative from the Sponsor.

The SRC may seek external consultation as required (e.g., the Sponsor or clinical research organization medical monitor [MM]) or other applicable specialist relevant to the observed safety signal. The SRC remit is to monitor safety in the study and prespecified timepoints, including on request, to make a recommendation to the Sponsor on study progression up to and including termination of a cohort or the study based on observed safety data. Responsibilities are detailed in the main body of the protocol and the SRC charter. The Sponsor may make proposals developed in collaboration with the Investigator Team, in open session in accordance with the protocol, and have the final decision on whether dosing continues based on the recommendations provided, which may include halting the study sooner than planned even if progression is deemed safe by the SRC. Responsibilities of the SRC are detailed in the SRC charter.

The Investigator Team comprises the actively recruiting Investigators from participating countries and will support the Sponsor in determining appropriate proposals for study progression.

Study Completion

The study will be considered complete once all planned Cohorts have completed and no further Optional Cohorts are proposed, or the Sponsor with input from the SRC determines that further exploration in multiple doses in any combination of dose and frequency is no longer warranted, regardless of the number of cohorts completed.

3.5. Stopping Criteria

Administration of the SZN-043 may be paused, and additional participants will not receive SZN-043, until a consultation has taken place between the Investigator (or designee), the Sponsor's MM, an independent medical representative (e.g., clinical research organization MM), or any additional clinical experts (e.g., DILI expert) as needed under the circumstances outlined below.

3.5.1. Individual Participant Stopping Criteria

All participants will be requested to participate in follow-up safety assessments to the planned end of study (EOS) regardless of having achieved any stopping rules below.

Further dosing will be halted if participants experience any of the following:

1. An AE that (regardless of relationship to SZN-043, including worsening of disease) in the opinion of the investigator would make continuation of the study drug potentially detrimental to the participants' health and well-being.

2. Either of the following:
    a. AST or ALT >500 U/L and >1.5 x highest predose measure
    b. Increase in MELD score of ≥5 points from the prior dose.
3. The participant becomes or is intending to become pregnant, and/or impregnates a partner.
4. Participant does not comply with protocol and in the opinion of the Investigator or Sponsor potentially compromises safety and/or integrity of data collected.
5. Other indicators not mentioned above of overall participant welfare as judged by the Investigator to make continued treatment unsafe.

In the event that after meeting Stopping Criteria 1 or 2, a participant's condition significantly improves such that the Principal Investigator responsible for the participant considers continued dosing may be appropriate, the Principal Investigator may make such a request and must receive approval from both the Sponsor and SRC before another dose is provided.

Should a DILI event be suspected, please see section 9.1.8.11 for additional laboratory tests to be performed.

3.5.2. Cohort Stopping Criteria

Dosing will be halted and the SRC will meet if any of the following criteria are met:

1. If any 1 participant experiences a TEAE ≥Grade 4* (National Cancer Institute- Common Terminology Criteria for Adverse Events [NCI-CTCAE]) (NCI 2017) within 14 days after receiving the last dose of study drug;
2. If 2 or more participants in the same cohort experience the same TEAE ≥Grade 3* (NCI-CTCAE criteria) within 14 days after receiving the last dose of study drug (NCI 2017) considered at least possibly related to study drug, (except for isolated ALP elevations defined as ALP elevations without preceding or concurrent NCI CTCAE ≥ Grade 3 elevations in ALT, AST, or bilirubin.
3. If 2 or more participants in the same cohort experience at least 1 unanticipated TEAE ≥ Grade 3* (NCI-CTCAE) within 14 days after receiving the last dose of study drug (NCI 2017) considered at least possible related to study drug, OR
4. If 2 or more participants experience an AST or ALT (central laboratory) >500 U/L and 1.5 x the highest predose measure

The SRC will make a recommendation for the applicable Cohort, after review of safety and other applicable data, whether to continue the cohort or discontinue any further dosing in the current cohort. The SRC may make further recommendations to the Sponsor on next steps in the study, including but not limited to a change in either the dose or dose frequency and beginning a new cohort up to and including discontinuing the study.

The SRC will be responsible for making the final decision on next steps and may make the decision to discontinue the study at any time.

3.6. Study Termination

The study will be considered complete once all planned Primary Cohorts have completed and no further Optional Cohorts are proposed, or the Sponsor with input from the SRC, determines that further exploration in multiple doses in any combination of dose and frequency is no longer warranted, regardless of the number of cohorts completed.

The study may be discontinued prematurely under the following circumstances:

- New information regarding the safety of the study medication indicates a change in the known risk/benefit profile for the compound, such that the risk/benefit is no longer acceptable for participants in the study. The information may be determined by the Sponsor, the Investigator, the applicable oversight authorities (for the participating country) or regulatory authorities.
- The study is terminated by the Sponsor for administrative reasons.

The Sponsor, Investigator (at each individual site), and the applicable oversight authorities (for the participating country) reserve the right to terminate or suspend the study at any time; however, this should be discussed between the relevant parties beforehand and the reason for such a decision recorded. Should this occur, all data available will also be recorded in the electronic case report forms (eCRFs). If the Sponsor or applicable oversight authority elects to terminate or suspend the study or the participation of the investigational site, a site-specific plan for early termination or suspension will be determined by the Sponsor. The procedure will be followed by the investigational site during termination or study suspension.

The Investigator should notify the relevant Ethics Committee in accordance and timing with applicable requirements in writing of the study's completion or early discontinuation.

3.7. Schedule of Assessments

The Schedule of Assessments for Parts 1 and 2 are presented in Appendix 1.

4. SELECTION AND WITHDRAWAL OF PARTICIPANTS

4.1. Participant Inclusion and Exclusion Criteria

4.1.1. Inclusion Criteria

To be eligible for this study, a participant has to meet ***all*** of the following inclusion criteria:

1. Be a male or female (sex assigned at birth), 18 years of age or older AND considered to be an adult in accordance with local law.
2. Have a body mass index (BMI) between ≥18.0 and ≤ 36.0 kg/m2 at Screening which may be calculated using actual or dry weight for eligible participants with ascites or edema at the Investigator's discretion;
3. Be willing and able to provide written informed consent or have a legally authorized representative who can provide informed consent on behalf of the participant (if approved by the applicable ethics committee and allowed by applicable laws).
4. Have a clinical diagnosis of AH that is anticipated to require inpatient care for a period to encompass at a minimum the first dose of study drug based on typical serum chemistry (as determined by local laboratory) meeting all of the following parameters:
    a. Onset of jaundice within prior 8 weeks to consent;
    b. History of heavy alcohol abuse: >40 (female) or 60 (male) g alcohol/day for ≥6 months;
    c. Consumed alcohol within 8 weeks before study entry;
    d. During Screening: AST >50, AST/ALT >1.5, and both values are: <400 IU/L, and
    e. During Screening: Serum total bilirubin >3.0 mg/dL.

    At the Investigator's discretion, a liver biopsy may be performed to confirm diagnosis in participants who meet criteria a-c above but where other causes of liver disease are not otherwise possible to rule out (viral, drug, autoimmune, etc).
5. MELD score of 21 to 30, inclusive, as calculated as early as Day -1. Participants with a MELD score as high as 33 may be entered into study if approved by the Medical Monitor.
6. Acceptable methods of contraception defined in protocol Section 4.2.3 must be used from Screening until study completion. Surgically sterile males or females (Section 4.2.3) or women who are postmenopausal for ≥12 months do not need additional contraception methods. Postmenopausal status will be confirmed by testing of follicle-stimulating hormone (FSH) levels ≥40 IU/L at Screening for amenorrhoeic female participants.
7. Must have the ability and willingness to attend the necessary visits to the clinical research unit (CRU).

4.1.2. Exclusion Criteria

A participant who meets ***any*** of the following exclusion criteria must be excluded from the study:

1. Previous receipt of antibody or biologic therapy whether licensed or investigational (immunoglobulin products, monoclonal antibodies, or antibody fragments) within the past 6 months.
2. Treatment with:
    a. any experimental drug within 30 days, or within 5 half-lives (whichever is longer), before Day 0 visit (Baseline); or
    b. or are likely to require treatment with dapsone within 7 days of Day 0 and up to 14 or 21 days after last dose (see Section 7 for details); or
    c. or are likely to require treatment with any drug whose elimination could be affected by CYP2E1 within 1 day before Day 0 and up to 14 or 21 days after last dose (see Section 7 for details).
3. Other causes of liver disease including:
    a. Evidence of chronic viral hepatitis (hepatitis B or C)
    b. Biliary obstruction or cholestatic liver disease (e.g., primary biliary sclerosis, sclerosing cholangitis)
    c. Drug-induced hepatotoxicity (e.g., acetaminophen)
    d. Hepatocellular carcinoma
    e. Wilson's disease
    f. Budd Chiari Syndrome
    g. Metabolic dysfunction-associated steatotic liver disease
    h. Metabolic dysfunction-associated steatohepatitis
    i. Auto-immune hepatitis
    j. Acute hepatitis A.
4. Introduction of a new medication with potential hepatotoxicity within 60 days of screening or any anticipated increase in dose or dose regimen of any potential hepatotoxic medication which include but, are not limited to, the following: allopurinol, gold salts, pyrazinamide, amiodarone, halothane, rifampin, anabolic steroids, hydralazine, simvastatin, atorvastatin, isoniazid, sulfamethoxazole/trimethoprim, azathioprine/ 6-mercaptopurine, ketoconazole, sulfasalazine, busulfan, methotrexate, sulfonamides, carbamazepine, minocycline, telithromycin, chlorpromazine, nevirapine, thioguanine disulfiram, nitrofurantoin ticlopidine, erythromycin, phenytoin, valproate, floxuridine, propylthiouracil, flutamide, quinidine, piperacillin, tazobactam.

5. Have a portosystemic shunt or scheduled for transjugular intrahepatic portosystemic shunt placement or highly likely to receive a liver transplant (in the clinical judgment of the Investigator) during the study period.
6. Dependent upon inotropic support or ventilatory or vasopressor support.
7. Multi-system organ failure.
8. Requires renal replacement therapy or creatinine >2.5 mg/dL (or 221 mmol/L) at time of dosing.
9. Uncontrolled hyperthyroidism, history of Paget's disease, osteomalacia, or fracture within 4 weeks of Screening.
10. Uncontrolled bacterial infections, as determined by the investigator's judgment after a minimum of 2 days of antibiotic therapy.
11. History of a previous severe allergic reaction (with generalised urticaria, angioedema, or anaphylaxis) to SZN-043 or any of its components. Participants with known similar allergic reactions relative to other treatments should be approved by the Medical Monitor prior to inclusion.
12. QT duration corrected for heart rate by Fridericia's formula (QTcF) >450 msec for males and >470 msec for females based on either single or averaged QTcF values of triplicate ECGs before study drug administration; OR in the judgement of the Investigator and the Medical Monitor, an abnormal, clinically significant EKG is obtained such that there is concern for participant safety and/or study outcomes.
13. A history of malignant neoplasm, except for adequately treated non-metastatic basal or squamous cell cancers of the skin (>1 year ago) or carcinoma in situ of the uterine cervix (>3 years ago) that has been fully treated and shows no evidence of recurrence. Participants under evaluation for possible malignancy are also not eligible.
14. Significant gastrointestinal (GI) bleeding within 1 week of enrollment requiring transfusion of more than 3 units of blood.
15. Grade 3 or higher encephalopathy by West Haven Criteria. (note: Grade 3 may be acceptable if EC approved process for obtaining legally authorized representative consent/assent is in place)
16. The development of Acute Kidney Injury (AKI) within 7 days prior to dosing as determined by the Investigator. In determining the diagnosis of AKI, the Investigator will consider the following: an increase in serum creatinine (sCr) ≥0.3 mg/dL within 48 h or an increase in sCr ≥50% from Baseline. Baseline sCr is the initial value that per the Investigator’s clinical judgment adequately establishes participant’s kidney function during screening.
17. Presence of portal vein thrombosis.
18. Presence of acute pancreatitis.

19. Cerebral hemorrhage, extensive retinal hemorrhage, acute myocardial infarction (within the last 6 weeks) or severe uncontrolled cardiac arrhythmias (not including atrial fibrillation).
20. Liver imaging within 45 days of dosing shows any lesions consistent with either primary hepatoma or metastatic liver disease (benign lesions, i.e., hemangiomas are permitted).
21. Known infection with HIV or HIV Ab positive at screening.
22. Organ transplantation (such as liver, kidney, lung, heart, bone marrow, or stem cell etc.), other than cornea transplant.
23. Positive urine screen for amphetamines, cocaine, or opiates (i.e., heroin, morphine) at Screening. Participants receiving stable methadone or buprenorphine maintenance treatment for at least 6 months before Screening may be included in the study. Participants with positive cannabis drug screen may be included in the study. Participants with a positive urine drug screen due to prescription opioid or amphetamine-based medication are eligible if the prescription and diagnosis are reviewed and approved by the Investigator.
24. Pregnant or lactating at Screening or planning to become pregnant (self or partner) at any time during the study.
25. Planning to donate sperm (male) or ovum (female) within 90 days after the last dose of study drug.
26. Prior or ongoing medical conditions, medical history, concomitant medication, physical findings, laboratory or EKG abnormalities that, in the Investigator's (or delegate's) opinion, could adversely affect the safety of the participant, make it unlikely the participant will comply with the protocol or complete the study per protocol, lead to premature mortality during the study period, or interfere with the interpretation of the data.
27. Current use of anticoagulants that affect prothrombin time or international normalised ratio (INR).

4.2. Restrictions in the Study

4.2.1. Alcohol

Participants will be required to have a blood ethanol level less than 50 mg/dL or 0.05% concentration before receiving study drug. All participants will be asked to refrain from alcohol use after dosing in line with standard guidelines for treatment of existing disease.

4.2.2. Caffeine

Caffeine consumption should be kept stable throughout study participation.

4.2.3. Contraception

Use of 1 or more highly effective forms of contraception is required for all persons of child-bearing potential and males without a vasectomy from Screening up to 30 days after receiving your last dose.

Persons of child-bearing potential who are surgically sterile are not subject to additional birth control requirements. This includes hysterectomy, bilateral salpingectomy, and bilateral oophorectomy. Males with a vasectomy are only considered surgically sterile if they have received medical assessment of surgical success.

Acceptable highly effective methods of contraception are:

- The use of condoms by the male partner and the use of an effective contraceptive by the female partner that includes combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation (oral, intravaginal, or transdermal), progestogen-only hormonal contraception associated with inhibition of ovulation (oral, injectable or implantable).
- Intrauterine device (IUD)
- Intrauterine hormone-releasing system (IUS)
- Bilateral tubal occlusion
- True Abstinence for 1 month after the last study treatment. True Abstinence is defined as refraining from heterosexual intercourse during the entire period noted. Abstinence must be in line with the preferred and usual lifestyle of the participant. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods), declaration of abstinence for the duration of exposure to IMP, and withdrawal are not acceptable methods of contraception and would not meet study requirements.

Vasectomized partner provided that partner is the sole sexual partner of the participant of childbearing potential and that the partner has received medical assessment of surgical success.

4.2.4. Fasting

Participants will be required to fast up to 8 hours before collection of Fasting Lipid Profile samples at the timepoints indicated in the Schedules of Assessments and procedures described below. Additional fasting requirements of at least 4 hours prior to the Methacetin Breath Test, and at least 5 hours prior to the HepQuant DuO also apply. Water may be consumed ad lib during this period. Investigators should consider requirements for nutrition and determine if fasting can be safely achieved for subject at the time the test is required (e.g. subjects requiring high caloric intake or other medical requirements that preclude fasting as an option at the time the assessments are required). Tests should still be performed, and the Investigator will indicate if done in a fasting or non-fasting state.

4.3. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently dosed in the study. 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 publishing requirements and to respond to queries from regulatory authorities. Minimal information includes screen failure details, eligibility criteria, and any adverse events as described in Section 10.4.2. Individuals who do not meet the criteria for participation in this study (screen failure) may not be rescreened without express permission from the Sponsor.

4.4. Participant Replacement

Participants may be replaced at the discretion of the Sponsor.

4.5. Criteria for Discontinuation or Withdrawal of a Participant

A participant may be discontinued from study drug under the circumstances outlined below irrespective of whether they reach stopping criteria described in Section 3.5. The decision to discontinue a participant from the study by the Investigator should be discussed with the study MM.

- When discontinuation is deemed to be in the best interest of the participant by the Investigator and/or Sponsor (e.g., safety reasons, persistent AEs, or SAEs that, in the Investigator's and/or Sponsor's opinion, compromise the participant's safety or ability to continue study-specific procedures)
- Participant withdrawal of consent
- Persistent lack of adherence to study procedures including use of IP or concomitant medications
- A female participant who desires to become pregnant at the current time, stops contraception, expels her intrauterine device/implant, or becomes pregnant
- If any of the individual stopping rules are met (see Section 3.5)
- Lost to Follow-up
- Death
- If DILI criteria are met, refer to Section 10.2.

4.6. Procedures for Discontinuation or Withdrawal of a Participant

The Investigator or Sponsor may terminate a participant's trial participation with study drug or procedures at any time during the study when the participant meets the discontinuation criteria described in Section 4.5. In addition, a participant may discontinue his or her participation without giving a reason at any time during the study.

Participants in any cohort who receive at least 1 dose of study drug and then request withdrawal or are withdrawn by either the Investigator or Sponsor will be asked to allow continued contact for vital status at Days 28, 60 and 90. If a participant discontinues prematurely from the study or

from study treatment, the reason must be documented in the source document and recorded in the eCRF. Wherever possible, if the participant will no longer participate in study procedures (except for vital status assessment), the tests and evaluations for Early Discontinuation should be performed for all participants who discontinue before the completion of the study. To the extent a participant is willing, the participant will be followed for ongoing adverse event(s), pregnancy, or a confirmed positive ADA finding on study completion, as described in Section 10.5.

5. TREATMENTS

5.1. Treatments Administered

5.1.1. Investigational Product

SZN-043 is supplied in a 10R vial as a colourless to slightly yellow/brown/yellow-brown liquid drug product filled to 10.6 mL with an extractable volume of 10.0 mL containing nominally 350 mg of SZN-043 (at a concentration of 35 mg/mL).

SZN-043 will be administered via IV infusion and dose will be based on participant body weight at Day -1. Planned dose levels are summarised in Table 5.

Participants will be observed for 4 hours during and after SZN-043 infusion.

5.1.2. Reference Product

Participants will be treated as per standard of care as determined by their treating physicians.

5.2. Dosage and Treatment Periods

The SZN-043 dose levels planned are presented in Table 5 and Figure 3. Alternate dose levels may be added, if required (as outlined in Section 3.1).

A maximum single dose of 1.5 mg/kg will be used and SZN-043 will be administered on Day 0 in sentinel participants (Cohort 1) and Days 0 and 4 for all other participants.

- The Investigator must assess participants' clinical presentation before each dose to determine if an additional dose may be administered, ensuring no stopping criteria have been met or other safety considerations exist that preclude additional dosing.
- The Investigator with Sponsor MM must discuss any participant with liver function changes considered potentially related to study drug since the last dose before another dose is administered.

For the Optional Cohorts, the Sponsor, in collaboration with the Investigator Team, will propose dose and frequency combinations based on the review of applicable data. The decision may result in a cohort with decreased or increased dose levels, at the same or different frequency as the previous cohort.

5.3. Method of Assigning Participants to Treatment

5.3.1. Assignment

The Randomisation and Trial Supply Management system (RTSM) will manage the assignment of screening numbers for study participants, control enrollment, and track clinical study supplies at the investigator sites.

Each participant will be provided with a unique screening number entered in the RTSM after documentation of informed consent. Screening numbers for screen failures will not be reused.

5.3.2. Randomisation (Cohort 4 only)

The Randomisation and Trial Supply Management (RTSM) system will manage the randomisation of eligible study participants and assign the study treatment based on a randomisation list prepared using a statistical software package by a Biostatistician in accordance with the investigational plan described in Sections 3.2.

Each participant will be provided with a unique screening number after documentation of informed consent. Once deemed eligible for enrolment in the study, the subject will be assigned a sequential randomisation number prior to first dosing. Subjects who withdraw from the study, for any reason, without completing all necessary screening assessments will be considered screen failures (see Section 4.3) and will be replaced.

5.4. Treatment Compliance

All doses will be administered in the presence of the Investigator or their designee.

5.5. Blinding

Primary Cohorts 1 to 3, including Optional Cohorts are open-label. Dosing and data will not be blinded.

In Cohort 4, a double-blind design will be implemented. Unless considered unblinded based on their role (e.g. clinical supply manager) or as defined in the protocol, the Sponsor, Investigator, MM, study personnel, and subjects are not to make any effort to determine which study drug therapy is being received. Unblinded pharmacy (or other qualified site) personnel will be used in this study to prepare the study drug. Personnel considered unblinded based on their role in the study will not participate in any subject assessments or decisions around relatedness of any adverse events.

When knowledge of whether the subject is on active study drug is essential for the clinical management or welfare of a specific subject (i.e., it is not possible to treat the subject without this information), the Investigator may unblind a subject's treatment assignment. The RTSM retains the information on treatment assignment. If required, the Investigator may access the treatment assignment from the RTSM as described in the instruction manual for the system. If possible (i.e., where the event is not life threatening), prior to any unblinding, the Investigator must discuss options with the MM, Sponsor or appropriate study personnel. The Investigator will record in source documentation, the date and reason for revealing the blinded treatment assignment for that subject and the names and roles of personnel unblinded.

In any case, as soon as possible, and without revealing the subject's study treatment assignment to blinded personnel (unless important to the safety of subjects remaining in the study), the Investigator must notify the Sponsor if the blind is broken for any reason and the Investigator was unable to contact the Sponsor prior to unblinding.

6. STUDY DRUG MATERIALS AND MANAGEMENT

In addition to the information below, the Investigator will adhere to the Pharmacy Manual which contains additional detail on the storage, handling, preparation, administration, and accountability of study drug.

6.1. Study Drug

The Sponsor will supply SZN-043 to the investigational site. The study drug provided for this study was manufactured under current Good Manufacturing Practices (cGMP) and will be suitable for human use.

6.2. Study Drug Packaging and Labelling

The Sponsor is responsible for the manufacturing, including labelling of investigational product (IP) and providing details of batch numbers, safety, and stability data, as requested.

The study drug will be labelled in accordance with local regulatory requirements and will be shipped at a temperature between 2°C and 8°C, inclusive.

6.3. Study Drug Storage

Upon receipt, the study drug must be stored between 2°C and 8°C.

The Investigator or designee will be fully responsible for the security, accessibility, and storage of the study drug while it is at the investigational facility.

6.4. Study Drug Preparation

Study drug will be prepared by the site pharmacy for administration via IV infusion.

6.5. Administration

The Investigator or designee is responsible for the education of study staff and participants as to the correct administration of the study drug. After assessments that have fasting requirements are complete, a light meal may be offered before study drug administration at the discretion of the Investigator.

At each study schedule specified timepoint, participants will be administered an IV infusion of SZN-043. The administration start-stop time and the stop-start times of any infusion interruptions will be recorded, as will the approximate percentage of the planned dose administered (if the entire dose is not administered for any reason).

6.6. Study Drug Accountability

A record will be maintained by the investigational site that will account for all dispensing and return of any used and unused study drug. At the end of the study, the study drug will be reconciled, and a copy of the record given to the study monitor.

6.7. Study Drug Handling and Disposal

On completion of the study, any surplus study drug supplies will be destroyed upon receipt of written approval from the Sponsor. Evidence of the destruction of any surplus study drug will be retained on site and a copy supplied to the study monitor. If no study drug supplies remain, this will be documented in the dispensing record.

7. CONCOMITANT MEDICATION

The following medications are prohibited:

(Note: Any drugs that are listed in more than one category in this section, the Investigator should follow the longest time for prohibition (e.g. halothane))

- Any drug whose metabolism may be affected by induction of CYP2E1 (e.g., Paracetamol (also known as acetaminophen), chlorzoxazone, dapsone, vesnarinone, theophylline, and the inhaled general anesthetics halothane, isoflurane, and enflurane) within 1 day before (with the exception of dapsone, which should be prohibited for 7 days before) and 14 days after last administration.
- Introduction of a new medication with potential hepatotoxicity within 60 days of screening or any anticipated increase in dose or dose regimen of any potential hepatotoxic medication. Potential hepatotoxic medications include, but are not limited to, those presented in Table 6.

Table 6: Potential Hepatotoxic Medications

Potential Hepatotoxic Medications			
allopurinol	amiodarone	anabolic steroids	atorvastatin
azathioprine/6-mercaptopurine	bisulfate	carbamazepine	chlorpromazine
disulfiram	erythromycin	floxuridine	flutamide
gold salts	halothane	herbal/dietary supplements	hydralazine
isoniazid	ketoconazole	methotrexate	minocycline
nevirapine	nitrofurantoin ticlopidine	phenytoin	pyrazinamide
propylthiouracil	quinidine	rifampin	simvastatin
sulfamethoxazone/	sulfasalazine	sulfonamides	telithromycine
trimethoprim	valproate	Piperacillin / Tazobactam	

If a participant that enrols in the study is already taking concomitant therapy, that therapy should be stable (dose and frequency) in accordance with eligibility criteria or, if not specified, local prescription guidelines. On the same days as methacetin breath testing, specific concomitant medications listed below should be administered only after testing has concluded:

- Ciprofloxacin
- Insulin

The Investigator should discuss with the MM any concomitant therapy that is started or requires dose adjustment after study drug administration. Of note, special attention should be paid to any medication or treatment with known hepatotoxic effects that requires adjustment within 14 days before the last dose of study drug.

8. STUDY SCHEDULE

The planned time points for all assessments are provided in the Schedule of Assessments (Appendix 1).

Participants will either be inpatient in a hospital setting or outpatient clinic setting in accordance with the requirements of the treatment plan and disease progression as managed by the treating physician. Study dosing should be conducted in a facility where appropriate emergency medical equipment is available and the participant can remain for the required observation periods.

Procedures for assessments are detailed in Section 9.1 (safety), Section 9.4 (PK), and Section 9.5 (PD biomarkers). Where possible, assessments should be conducted in order of least invasive to most invasive.

8.1. Screening

Screening procedures may not be performed until written informed consent is obtained. The informed consent process can begin before the start of the window for screening procedures (for example, if washout from medications is required).

Screening procedures (including repeated laboratory tests, if required) may be performed at any time during the screening period (within 1 week before the start of study treatment). Due to the acute nature of the participants in the study and timing of test results, the Sponsor may allow for an extension of the screening period, including the timing of any one or multiple specific screening procedures prior to dosing. Sites will contact the Medical Monitor and obtain prior approval, including which (if any) procedures must be repeated. AEs will be recorded for the study starting from the time of signing of informed consent form (see Section 13.3).

8.2. Randomisation Visit (Cohort 4 only)

In Cohort 4, participants will be randomized on a 1:1 basis to one of two doses. Randomisation may occur when all eligibility criteria are confirmed but no earlier than Day -1 after the subject has been admitted to the CRU. If the time elapsed since any of the screening procedures exceeds 28 days (excluding informed consent), only the screening procedure(s) that falls outside the screening window must be repeated.

8.3. Intervention Treatment Period

8.3.1. MAD in Participants with Severe Alcohol-Associated Hepatitis

Dose and frequency are presented in Table 5.

Participants will be confined in accordance with local treatment standards. Participants must be inpatient (defined as a facility where appropriate emergency medical equipment is available and the participant can remain for the required observation periods) for at least 12 hours before and at least 4 hours after dosing for observation. Additional requirements for hospitalization will be according to the treatment requirements specified by the treating physician. Inpatient confinement for study procedures for participant convenience will be at the discretion of the investigator.

Participants will receive study drug on Day 0. Participants will return to the study centre for visits as indicated in Appendix 2. Procedures for EOS will be performed at Day 90, or if the participant discontinues prematurely, the Early Discontinuation procedures will be the EOS procedures.

8.4. Unscheduled Visits

Participants will be instructed to contact the study coordinator/Investigator when any significant change in health status occurs. The participant will be asked to return for an unscheduled clinic visit if clinically indicated. At unscheduled visits, at a minimum, AEs and concomitant medications will be recorded, and results of any study-related procedures deemed appropriate to perform by the Investigator will also be recorded.

If it is determined that the participant should be discontinued from the study at the unscheduled visit, then all the EOS study procedures will be completed, and the visit will be recorded as an EOS visit instead. The participant will be asked to return for a posttreatment follow-up clinic visit 4 weeks after the last study drug dose.

8.5. After Discontinuation or Withdrawal

Participants who are discontinued from the study will not receive any additional treatment from Surrozen, or with SZN-043, after the completion of the study. The long-term care of the participant will remain the responsibility of their primary treating physician(s) as per local standard of care.

For additional details regarding procedures for discontinuation or withdrawal of a participant refer to Section 4.6.

9. STUDY ASSESSMENTS

9.1. Safety and Screening Assessments

Study procedures should be completed as delineated in the Schedule of Assessments (Appendix 1). However, if a participant is unable to attend a visit within the specified window, the Investigator or designee should discuss appropriate scheduling with the Sponsor's MM or appropriate designee. Any unscheduled procedures required for urgent evaluation of safety concerns must take precedence over all routine scheduled procedures.

9.1.1. Demographic/Medical History

Medical history (including caffeine and substance use such as drugs, alcohol, and tobacco), date of birth, age (calculated), sex, ethnicity, and race will be recorded at Screening, and will be rechecked on Day -1.

9.1.2. Vital Signs

Vital signs (including systolic and diastolic blood pressure, pulse rate, respiratory rate, and body temperature) will be measured at the time points specified in the study schedules with participants resting for at least 5 minutes in a semi-supine or supine position. When vital signs measurement timing coincides with a blood collection, the vital signs will be taken before the scheduled collection where possible, ensuring the collection is within the window specified in the protocol.

Additional vital signs may be performed at other times if deemed necessary.

9.1.3. Weight and Height

Body height (cm) and body weight (kg) will be measured at the time points delineated in the study schedules. BMI will be calculated at screening. BMI is calculated by dividing the participant's body weight in kilograms by the participant's height in metres squared (kg/m^2). Body weight and height will be obtained with the participant's shoes and jacket or coat removed.

9.1.4. Physical Examination

Full physical examination will be performed by a licensed healthcare professional at the time points specified in the study schedules.

Full physical examination includes general appearance, head, ears, eyes, nose, throat, thyroid, heart, lungs, abdomen, skin, neurological (including assessments of the cranial nerves, motor and sensory function), extremities, back, neck, musculoskeletal, and lymph nodes.

Symptom-directed physical examinations may be performed at various unscheduled time points if deemed necessary by the Investigator.

9.1.5. Liver Testing

9.1.5.1. Liver Biopsy (optional)

In situations in which viral, drug, or autoimmune causes of liver disease cannot be ruled out, a liver biopsy may be performed to confirm diagnosis, at the Investigator's discretion. Participants must meet the following criteria for diagnosis confirmation:

a. Onset of jaundice within prior 8 weeks, and
b. History of heavy alcohol abuse: >40 (female) or ≥60 (male) g alcohol/day for ≥6 months, AND
c. Consumed alcohol within 8 weeks of study entry.

9.1.5.2. Liver Ultrasound

A liver ultrasound will be performed at Screening to assess lesions indicative of cancer. Any hepatic imaging (ultrasound, CT or MRI) conducted within 45 days of the first dose (Day 0) may also be used for screening purposes. Imaging outside this window may be acceptable after review and approval by the Sponsor Medical Monitor.

9.1.6. Electrocardiograms (ECGs)

9.1.6.1. Routine ECGs

A 12-lead ECG will be taken at the time points delineated in the study schedules. Additional ECG monitoring may be performed at other times if deemed necessary.

ECGs will be performed before vital signs with participants in a supine position for at least 5 minutes prior. ECG on day of dosing will be performed at 5 min (±5 min) and 4 h (±20 min) after end of dose

All ECG tracings will be reviewed by the Principal Investigator or designee.

When the time of ECG monitoring coincides with a blood collection, the ECG will be taken before the scheduled collection while ensuring the blood collection is within the window specified in the protocol.

ECGs may be repeated in triplicate if the abnormality is considered clinically significant by the Investigator. If required, triplicate readings are to be taken at least 1 minute apart, and all 3 ECGs will be recorded.

9.1.7. Serum Alcohol Test/PEth

Both of these tests will be performed at the time points specified in the study schedules. Further details will be provided in the laboratory manual.

9.1.8. Laboratory Assessments

Safety laboratory tests (haematology, serum chemistry, C-reactive protein [CRP], glutamate dehydrogenase [GLDH], coagulation, and urinalysis) and other laboratory tests (lipid profile and thyroid stimulating hormone testing) as described in this section will be performed at the time

points specified in the study schedules (Appendix 1). Participants should be asked to refrain from vigorous exercise at least a day before scheduled blood collection. Urine pregnancy tests will be performed in-house at the Investigator site. If positive, a serum sample will be sent to a local laboratory for confirmation.

Additional (unplanned) clinical laboratory tests may be performed at other times if deemed necessary by the Investigator based on the participant's clinical condition. Medically indicated laboratory tests (emergency or unscheduled tests) should be conducted at the local laboratory.

All samples requiring laboratory analysis in this section will be sent to the central laboratory specified. Where analyses required to perform endpoint calculations are impacted by the icteric nature of the participant, the sample may be analyzed at a secondary central lab location as specified in the lab manual. Where laboratory results are required to make clinical decisions (including those impacting how to progress with the participant in accordance with the protocol) and the central lab cannot provide these results within the required timeframe, samples may additionally be sent to the site local laboratory. For calculating the baseline MELD score as early as Day -1 to determine eligibility, sites will use results obtained from samples sent to the local laboratory, and will record this value in the EDC. Analysis for purposes of the study will be conducted from central laboratory results.

9.1.8.1. Haematology

Haematology parameters tested are:

- Complete blood count
- Haemoglobin
- Haematocrit
- Erythrocytes
- Platelets
- Mean corpuscular volume
- Leukocytes (white blood cells) with differential including eosinophils, neutrophils, basophils, lymphocytes, and monocytes

9.1.8.2. Serum Chemistry

Serum chemistry parameters tested are:

- Blood urea nitrogen
- SCr
- Total Bilirubin and Direct Bilirubin
- AFP (collected as scheduled for PD markers)
- Albumin
- ALT

- ALP (collected as scheduled for PD markers)
- AST
- Creatine kinase
- GGT
- Glucose
- Sodium
- Potassium
- Calcium
- Chloride
- Phosphate
- Bicarbonate
- Phosphatidyl ethanol

9.1.8.3. Coagulation

Coagulation parameters tested are:

- INR
- Activated partial thromboplastin time
- Fibrinogen
- Prothrombin time

9.1.8.4. Additional Laboratory Assessments

- Thyroid-stimulating hormone (Screening only)
- CRP, an inflammation marker
- GLDH activity, an exploratory serum biomarker of hepatocellular injury

9.1.8.5. Lipid Profile

Lipid parameters will be tested after an 8-hour fast and include: total cholesterol, triglycerides, high-density lipoprotein, and low-density lipoprotein.

9.1.8.6. Urinalysis

A urinalysis test (dipstick) will be performed for each participant. Urinary analysis will be performed at Screening and other times according to the study schedule. If an abnormality is noted for protein, blood, nitrite, or leukocyte esterase (and at the discretion of the Investigator) a microscopic examination of red and white blood cells, bacteria, and casts may be performed.

Microscopic urinalysis parameters tested are:

- pH
- Specific gravity
- Urine creatinine
- Protein
- Glucose
- Ketones
- Total bilirubin
- Occult blood
- Nitrite
- Urobilinogen
- Leukocytes

9.1.8.7. Viral Serology

Serology testing include HIV, hepatitis B surface antigen (HBsAg), hepatitis B virus DNA (if HBsAg is positive), hepatitis C virus RNA and will be performed at Screening.

9.1.8.8. Urine Drug Screen

A urine drug screen will be performed at Screening and at admission to the CRU (Day -1). This will include screening for:

- Tetrahydrocannabinol
- Cocaine
- Amphetamines
- Barbiturates
- Benzodiazepines
- Opiates
- Methadone
- Methamphetamines
- Ecstasy
- Phencyclidine

9.1.8.9. Follicle-Stimulating Hormone Testing

Women not of childbearing potential must be postmenopausal (defined as cessation of regular menstrual periods for at least 12 months). Postmenopausal status will be confirmed through testing of FSH levels ≥ 40 IU/L at Screening.

9.1.8.10. Pregnancy Test

Serum (Screening) and urine (screening and other assessments) pregnancy test will be performed for women of childbearing potential only, as indicated in the Schedule of Assessments (Appendix 1). A Urine and Serum sample are drawn at D-1 as the serum pregnancy test may be affected by the level of jaundice.

9.1.8.11. Drug Induced Liver Injury Assessment (DILI)

In the event of a suspected DILI occurrence, the following tests should be performed:

- 5' Nucleotidase
- Alkaline Phosphatase Fractionation (if ALP is elevated) to determine organ source of rise

If possible, analysis will be performed on samples already received at the central laboratory for other pre-defined tests that coincide with the detection of potential DILI (see Section 9). If this is not possible, participants will be asked to return for an unscheduled sample collection. Samples may instead be analysed locally should the local laboratory have the capabilities. Local labs results should also be recorded in the EDC. These tests are intended to be performed at least once, unless agreed between the Investigator and Medical Monitor as necessary to determine additional course of care.

9.2. Efficacy Assessments

9.2.1. Vital Status Assessment (Mortality)

Survival status will be recorded for Days 28, 60 and 90. The actual date of death will be recorded if the participant dies. At the time of consent and when a participant is withdrawn prematurely from study drug or procedures (see Sections 4.5 and 4.6) participants will be requested to provide permission for the investigator to ascertain their vital status through means other than direct contact such as medical records, requesting information from other treating physicians, etc. If at the time of a required vital status assessment, the Investigator is unable to reach the participant directly and they have not withdrawn, the investigator will use these options in addition to any other public sources available in the region of participation to ascertain whether the subject is alive. Substantive efforts will be made to determine vital status and efforts will be made to document them in the source. Each investigator site will work with their monitor to determine the extent to which public records/databases can be used for these purposes and document the level of effort to be used for all participants.

9.2.2. Lille Model

The Lille Model is a medical modeling tool for predicting mortality in patients with alcohol-associated hepatitis (Louvet 2007). Originally designed to predict mortality in patients who are not responding to steroids, it stratifies participants already receiving steroids for AH treatment to predict which will not improve and should be considered for other management strategies.

Lille model score = (exp(−R))/(1 + exp(−R)), where R = 3.19 − (0.10 × age) + (0.147 × baseline albumin) + (0.0165 × change in bilirubin level) − (0.206 × creatinine) − (0.0065 × baseline bilirubin) − (0.0096 × prothrombin time) using total serum bilirubin values on the days of assessment.

9.2.3. Model for End-Stage Liver Disease (MELD) Score

The MELD Score has been validated as predictor of survival in participants with cirrhosis, AH, acute liver failure, and in participants with acute hepatitis (Singal 2013; Kim 2021). The MELD score used to determine eligibility will be calculated from local laboratory samples drawn at Day -1.

The MELD score for purposes of qualification will be calculated using serum bilirubin, serum creatinine, and INR applying the following formula:

9.57 loge (creatinine) + 3.78 × loge (total bilirubin) + 11.2 × Loge (INR) + 6.43

Applying the following United Network for Organ Sharing (UNOS) modifications:

- If the patient has been dialyzed twice within the last 7 days, then the value of serum creatinine should be 4.0 mg/dL
- Any value less than one is given a value of 1 (i.e. if bilirubin is 0.8 a value of 1.0 is used) to prevent subtraction from any of the three factors, since the natural logarithm of a positive number below 1 (greater than 0 and less than 1) yields a negative value.

9.3. Other Exploratory Assessments

9.3.1. Maddrey's Discriminant Function Score (mDF)

The Maddrey score uses 2 blood tests to determine the extent of liver damage, bilirubin and prothrombin time (Maddrey 1978). The equation used to calculate the Maddrey Score is:

Bilirubin (mg/dL) + 4.6 times (prothrombin time in seconds minus control). (Note –"control" is a calculation that the lab uses to determine what "normal" results are at that particular facility, and is not a lab result from the participant's blood.)

9.3.2. Child-Turcotte-Pugh Score

The Child-Turcotte-Pugh (CTP) score is used to assess the severity of cirrhosis based on assessment of bilirubin, albumin, INR, ascites, and encephalopathy (Child 1964).

9.3.3. Chronic Liver Disease Questionnaire (CLDQ)

The CLDQ is short, easy to administer, produces both a summary score and domain scores, and correlates with the severity of liver disease (Younossia 1999).

9.3.4. Health Care Utilization

Information on health services provided related to the disease under study, such as hospital length of stay related to illness, concomitant treatments required, etc. will be collected. No financial information, such as insurance, reimbursement, etc. will be obtained and the information will be limited to details around their clinical care while in participating in this study.

9.4. Pharmacokinetic and Antidrug Antibodies Assessments

9.4.1. Blood Sample Collection

Blood samples for PK and ADA analyses will be obtained, according to the site's standard operating procedures, at the timepoints specified. The actual collection time of each sample must be recorded in the source data documentation, on the collection tube and in the eCRF. The allowed time deviation window for blood sample collection before a deviation is recorded is indicated in the Schedule of Assessments (Appendix 1).

9.4.2. Sample Analysis

Serum PK and ADA sample analysis will be performed using validated procedures and methods. If a sample confirms positive for ADA to SZN-043, it will be assessed for titer and for specificity to recombinant human RSPO2. If a participant has a positive response to any ADA test at the EOS visit, the participant will be asked to consent to quarterly visits for up to 1 year to assess AEs and changes in ADA response (see Section 10.5.3).

Complete written instructions for handling, processing, storage, and shipping of samples are available in the Laboratory Manual.

9.5. Pharmacodynamic Assessments

Applicable to all assessments described in this section, the Sponsor may determine from on-going data collection during the study that results from any or all do not provide value to understanding of SZN-043 pharmacodynamic effect. Upon such determination to reduce burden and risk to patients related to the additional blood drawn for these assessments, the Sponsor will inform investigators to discontinue the applicable test via a Protocol Clarification and applicable addendum or update to the Laboratory manual.

9.5.1. Serum Pharmacodynamic Biomarkers

Blood samples for serum PD biomarker analysis will be obtained, at the timepoints specified in the Schedule of Assessments (Appendix 1).

Blood PD biomarker sample analysis will be performed at a central laboratory according to qualified procedures and methods.

Concentrations of serum biomarkers of SZN-043 pharmacology are predicted to transiently increase following dosing. PD biomarkers of interest include, but are not limited to, the following:

- Changes in concentrations of biomarkers in blood samples, including but not limited to: AFP and ALP
- Changes in concentrations of angiogenin and LECT2
    - Blood samples for these biomarkers will be drawn in Cohort 1
    - Sponsor will evaluate whether continued analysis and consequently blood draws are necessary for these biomarkers after each completed cohort, and may, at its discretion, eliminate the inclusion of this biomarker based on lack of utility. If this test is removed, Sponsor will notify sites via a written Protocol Clarification.

The actual collection time of each sample must be recorded in the source data documentation, on the collection tube, and in the eCRF. The allowed time deviation window for blood sample collection before a deviation is recorded is indicated in the Schedule of Assessments (Appendix 1).

PD measurements described in this section may be removed in whole during the study if data does not indicate utility. Sites will be notified by Protocol Clarification if this occurs.

9.5.2. Methacetin Breath Test

The ^{13}C-methacetin breath test (MBT) is a semi-quantitative, non-invasive, hepatic metabolic function test, specifically of cytochrome P450 1A2 (CYP1A2) activity (Festi 2005). Metabolism of ^{13}C-labelled methacetin by CYP1A2 results in $^{13}CO_2$ enrichment in breath. MBT may be a useful dynamic measure of global hepatic function as a change in activity via serial measurements may reflect hepatocyte regeneration after acute injury (Fontana 2021).

Participants will be required to fast for a minimum of 4 hours before undertaking the MBT (water permitted ad lib). If the participant is taking insulin or ciprofloxacin, these medications should be taken after the MBT is complete.

The MBT will involve:

- Collection of exhalation in 2 tubes (baseline samples), approximately -10 and -5 minutes before administering the ^{13}C-methacetin dose, followed by
- Intake of isotope (^{13}C-methacetin),
- Collection of exhalation in 1 tube every 10 minutes (± 5 minutes) post-isotope intake for up to 60 minutes.

The MBT will be performed as delineated in the Schedule of Assessments (Appendix 1). Further details will be provided in the applicable laboratory manual. All appropriate approvals for the local country and/or region must be in place before the kits will be shipped and the procedure is performed. Tests beyond baseline are only performed if a baseline test has been completed.

9.5.3. HepQuant DuO Test

The HepQuant DuO test is designed to detect and quantify liver disease severity in participants with underlying liver disease (Wieland 2021). Longitudinal assessment of the HepQuant DuO test will explore the potential impact of SZN-043 driven hepatocyte regeneration in participants with AH.

The evaluation will involve:

- Oral ingestion of 40 mg d4-cholate
- Timed 5 mL blood sample collection

Further instructions are provided in the Instructions for Use (IFU) located in the laboratory manual.

The HepQuant DuO will be performed as delineated in the Schedule of Assessments (Appendix 1), in consideration of the following:

- This test will only be required if kits are available at site for use by a participant at the time of their baseline. Tests beyond baseline do not need to be performed, if a baseline measure is not available.
- Participants taking contraindicated medications who are unable or unwilling to accommodate dosing schedule modifications listed in the IFU, or those with contraindicated conditions listed in the IFU will NOT have the HepQuant Test performed.
- This test is only to be conducted if approval for the use of the test is in place in accordance with local regulations (i.e., where additional approval is required in addition to implementation of the protocol) at the time of any participant's baseline assessment.

All appropriate approvals for the local country and/or region must be in place before the kits will be shipped and the procedure is performed.

10. ADVERSE EVENTS

10.1. Definition of Adverse Events

An AE is any event, side-effect, or other untoward medical occurrence that occurs during the study. An AE can, therefore, be any unfavourable and unintended sign, symptom, or disease temporally associated with IP use, whether or not considered related to the IP.

Examples of events meeting the definition of an AE include:

- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition
- New conditions detected or diagnosed after study drug administration that occur during the reporting periods, even though it may have been present prior to the start of the study
- Signs, symptoms, or the clinical sequelae of a suspected interaction
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study drug or concomitant medications (overdose per se will not be reported as an AE/SAE).

Examples of events that **do not** meet the definition of an AE include:

- Medical or surgical procedure (e.g., endoscopy, appendectomy); the condition that leads to the procedure should be reported as an AE if it meets the criteria of an AE
- Situations where an untoward medical occurrence did not occur (e.g., 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
- **For this study**, as SZN-043 reduces ASGR1, a cell surface protein on hepatocytes important for ALP clearance, isolated elevations in ALP *are expected* and should not be considered an AE.

10.2. Drug-Induced Liver Injury (DILI) Criteria

Suspected drug-induced liver injury (DILI) will be based on the presence of the following criteria (FDA 2009). As all participants are anticipated to have abnormal liver tests before starting treatment with SZN-043, ULN is replaced by the mean baseline values (MBV) as determined by the mean values observed on Day -1 and Day 0) obtained before study treatment and increases should be proportionate to this modified baseline.

- ALT or AST ≥8× MBV
- ALT or AST ≥5× MBV for more than 2 weeks
- ALT or AST ≥3× MBV and total bilirubin ≥2× MBV
- ALT or AST ≥3× MBV and INR > 1.5

- ALT or AST ≥3× MBV with the appearance of fatigue, nausea, vomiting, right upper-quadrant pain or tenderness, fever, rash, and/or eosinophilia (absolute eosinophil count >5%)

Hy's law can be considered to have been met when no other cause to explain the elevated ALT or AST and total bilirubin has been identified upon completion of a comprehensive diagnostic evaluation.

Investigator or Medical Monitor may consider other indicators of potential liver damage (e.g, elevated GGT, ALP) in assessing whether to report a potential DILI event.

Should a DILI event be suspected, please see section 9.1.8.11 for additional laboratory tests to be performed.

The SRC will adjudicate events meeting DILI criteria. Hepatologists and experts in the assessment of DILI will support the assessment, analysis, and adjudication of DILI events, as further described in the SRC charter. Participants who are confirmed to have met DILI criteria will discontinue further dosing but will continue in study.

Investigators will be required to report any participants meeting Section 10.2 criteria as outlined below (Section 10.4.6).

10.3. Definition of Serious Adverse Events

SAEs are a subset of adverse events. An SAE is an AE occurring during any study phase (i.e., baseline, treatment, washout, or follow-up), and at any dose of the study drug, that fulfils one or more of the following:

- Results in death
- Is immediately life-threatening
- Requires in-patient hospitalisation or prolongation of existing hospitalisation
- Results in persistent or significant disability or incapacity
- Results in a congenital abnormality or birth defect

Important medical events that do not result in one of the above seriousness criteria, may be considered an SAE by the Investigator when, based upon appropriate medical judgement, they are considered clinically significant and may jeopardise the participant, or may require medical or surgical intervention to prevent one of the outcomes listed above.

An AE is considered "life-threatening" if, in the opinion of either the Investigator or the Sponsor, its occurrence places the participant at immediate risk of death. It does not include an AE that, had it occurred in a more severe form, might have caused death.

10.4. Adverse and Serious Adverse Event Reporting

10.4.1. Reporting Requirements

In this study, AEs (including those classified as SAEs) will be reported for all participants from the time of consent until the completion of the EOS visit as described in this section.

Investigators will be required to report any TEAE ≥Grade 3, infusion reactions, DILI diagnosis, pregnancy, and SAEs within 24 hours of discovery.

AEs reported from the time of consent to the first administration of study drug will be recorded as pretreatment AEs. AEs from the first administration of study drug until the EOS visit will be recorded as treatment-emergent AEs (TEAEs). AEs will be followed as described in Section 10.5.1.

Adverse events that are ongoing at the EOS visit will be marked as Not Recovered/Not resolved on the AE eCRF page (see Section 10.4.2.4).

Pregnancy reporting is not required prior to receipt of first dose. Participants who are pregnant are not eligible for the study.

10.4.2. Recording Adverse Events

Adverse events spontaneously reported by the participant and/or in response to an open question from the study personnel or revealed by observation will be recorded in accordance with the Investigator's normal clinical practice and on the AE page of the eCRF during the study at the investigational site.

The AE term should be reported in standard medical terminology when possible. A diagnosis should be used. If no diagnosis is known, then clinical signs and symptoms may be recorded. If no diagnosis is known and clinical signs or symptoms are not present, then the abnormal finding may be recorded.

For each AE, the Investigator will evaluate and report the onset (date and time), resolution (date and time), severity, seriousness, causality, action taken, and outcome. In addition, the Investigator will also record if the AE is related to a study procedure; this will also be captured in the electronic data capture (EDC).

For participants who screen fail, only adverse events related to study procedures and SAEs will be recorded in the EDC.

In addition, if the AE meets the criteria for being serious, the SAE report form must also be completed (Section 10.4.3).

All spontaneously volunteered and enquired for, as well as observed AEs, will be recorded in the participant's medical records and the eCRF.

10.4.2.1. Severity of an Adverse Event

Severity of AEs will be graded by the Investigator or designee as one of:

- **Mild (Grade 1)**: A type of AE that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.
- **Moderate (Grade 2)**: A type of AE that is usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the research participant.

- **Severe (Grade 3)**: A type of AE that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.
- **Life-threatening (Grade 4)**: A type of AE that places the participant at immediate risk of death.
- **Death (Grade 5)**: Events that result in death.

TEAEs will be graded according to the Common Terminology Criteria for Adverse Events (CTCAE V5.0) (NCI 2017).

Investigators will be required to report any TEAE ≥Grade 3 within 24 hours of discovery, as detailed below (Section 10.4.4).

10.4.2.2. Causal Relationship of an Adverse Event

The Investigator will assess the relationship between the occurrence of each AE and study drug. The Investigator's assessment of this relationship will be recorded in the source documents and the eCRF. Alternative causes, such as medical history, concomitant therapy, other risk factors, and the temporal relationship of the event to the study drug should be considered and investigated, if appropriate. The following definitions are general guidelines to help assign grade of attribution:

- **Not related:** The event is clearly related to other factors such as the participant's environment or clinical state, therapeutic interventions or concomitant drugs administered to the participant. This is especially so when an event occurs prior to the commencement of treatment with the study drug.
- **Unlikely:** The temporal association, participant history, and/or circumstances are such that the study drug is not likely to have had an association with the observed event. Other conditions, including concurrent illness, progression, or expression of the disease state, or reaction to a concomitant drug administered appear to explain the event.
- **Possible:** The event follows a reasonable temporal sequence from the time of study drug administration or follows a known response to the study drug but could have been produced by other factors such as the participant's clinical state, other therapeutic interventions, or concomitant drugs administered to the participant.
- **Probable:** The event follows a reasonable temporal sequence from the time of study drug administration and follows a known response to the study drug and cannot be reasonably explained by other factors such as the participant's clinical state, other therapeutic interventions, or concomitant drugs administered to the participant.
- **Definite:** There is evidence to suggest a causal relationship between the study drug and the adverse event. For example, the event follows a reasonable temporal sequence from the time of study drug administration or control abates upon discontinuation or cannot be explained by known characteristics of the participant's clinical state.

10.4.2.3. Action Taken with Investigational Product

Should the Investigator need to alter the administration of the study drug from the procedures described in the protocol for the well-being and safety of the participant, then the action taken will be recorded on the AE eCRF page, as one of the following options:

- Dose Delayed
- Drug Interrupted
- Drug Withdrawn
- Not Applicable
- Other

10.4.2.4. Outcome

- Recovered / Resolved
- Recovering / Resolving
- Recovered / Resolved with Sequelae
- Not Recovered / Not Resolving
- Fatal
- Unknown

10.4.3. Recording Serious Adverse Events

All SAEs, regardless of relationship to the study drug, during the period starting from the time the participant signed the Informed Consent Form (ICF) to the EOS should be recorded in the EDC/eCRF within 24 hours of knowledge of the event. SAEs that are recorded in the EDC will immediately notify the Sponsor and MM. A paper SAE form may be completed if the EDC system is non-functional and emailed to the Surrozen Safety Team at clinicalsafety@surrozen.com. The Investigator may also provide the notification by phone, but this must be followed by a written notification. The SAE along with all details recorded on the paper SAE form must be entered into EDC once the system is functional.

The SAE report will include a full description of the event including the below parameters:

- Diagnosis or description of event
- Onset date
- Severity assessment
- Causal relationship to the IP
- Assessment of seriousness of the event
- Treatment administered for the SAE
- Action taken related to study drug including the following: dose delay, dose reduction, dose interruption, or study drug withdrawn

- Outcome of event and end date
- Pertinent information such as laboratory data, preferably with baseline values and copies of laboratory reports.

If requested, supporting de-identified source documents (e.g., hospital discharge summary, autopsy report when available, results of relevant diagnostic tests completed to evaluate the event) will be sent to clinicalsafety@surrozen.com.

The Sponsor is responsible for notifying the relevant regulatory authorities of events as required by local regulations. It is the Investigator's responsibility to notify the Ethics Committees of all SAEs in accordance with the Ethics Committees SAE reporting policy. The Investigator will also be notified of all unexpected, serious, drug-related events that occur during the clinical trial. The investigational site is responsible for notifying its Ethics Committees of these additional SAEs.

10.4.4. Recording TEAEs ≥Grade 3

TEAEs will be recorded on the AE eCRF. Once the Investigator becomes aware of a TEAE ≥Grade 3, he/she must record it in the EDC within 24 hours of knowledge of the event. TEAEs ≥Grade 3 that are recorded in the EDC will immediately notify the Sponsor and MM. If the TEAE is also an SAE, this must be reported in accordance with Section 10.4.3.

To meet the reporting requirements if the EDC system is non-functional, the details of the event may be emailed to the Surrozen Safety Team at clinicalsafety@surrozen.com either in narrative form or if an SAE, using the paper SAE form. The Investigator may also provide the notification by phone, but this must be followed by a written notification. The event must be entered into EDC once the system is functional.

Regardless of how the initial report is provided, the Investigator should include a description of the event, the date of onset, and the Investigator's assessment of the causal relationship to IP.

If requested, supporting de-identified source documents (e.g., results of relevant diagnostic tests completed to evaluate the event) will be sent to the Sponsor and MM at clinicalsafety@surrozen.com.

10.4.5. Recording Details for Infusion Reactions

An infusion reaction is any adverse event that occurs during or within the first day after study drug administration and is thought to be related to the infusion of a medication. A guidance for managing infusion reactions is included in Appendix 3.

Once the Investigator becomes aware of an infusion reaction, he/she must record it in the EDC within 24 hours of knowledge of the event. Infusion reactions recorded in the EDC will immediately notify the Sponsor and MM. Infusion reactions will be recorded on the AE eCRF. If the infusion reaction is also an SAE, this must be reported in accordance with Section 10.4.3.

To meet the reporting requirements if the EDC system is non-functional, the details of the event may be emailed to the Surrozen Safety Team at clinicalsafety@surrozen.com using the paper AE/SAE form. The Investigator may also provide the notification by phone, but this must be

followed by a written notification. The event must be entered into EDC once the system is functional.

Regardless of how the initial report is provided, the Investigator should include a description of the event, the date of onset, and the Investigator's assessment of the causal relationship to IP.

If requested, supporting de-identified source documents (e.g., results of relevant diagnostic tests completed to evaluate the event) will be sent to the Sponsor and MM at clinicalsafety@surrozen.com.

10.4.6. Recording Details for DILI Events

While performing protocol-required assessments, the Investigator will review lab results that might lead to identification of a DILI event. Once the Investigator becomes aware of a DILI event, he/she must record it in the EDC within 24 hours of knowledge of the event. DILIs recorded in the EDC will immediately notify the Sponsor and MM.

For participants who meet the protocol-defined criteria for DILI, the following information may be requested:

- Information on laboratory abnormalities
- Clinical symptoms
- Potential cause of any hepatic illness
- Time of start of illness
- Complete description of the injury, including systemic symptoms, other organ involvement, rash, fever, and eosinophilia.
- Information on outcomes reported as consequences of DILI such as hospitalization, recovery, treatment, liver transplant, and/or death.
- Free text describing the course of illness, including pertinent physical examination findings, such as hepatomegaly, splenomegaly, right-upper quadrant tenderness, the time course of abnormalities of aminotransferases, ALP, total bilirubin with dates of testing, normal ranges, and results for tests done in addition to those specified in the original protocol, and tests done during any unscheduled visits. These additional laboratory test results, including reference ranges, should also become part of the overall database. Supportive tabular and/or graphical display of serial laboratory data is often desirable in addition to narrative information. Prestudy transaminase values should be sought, which may suggest chronic liver disease and/or an acute process that may have preceded exposure to the investigational drug.
- Risk factors, especially history of alcohol use; risk factors for metabolic dysfunction-associated steatotic liver disease such as diabetes, obesity, and hypertriglyceridemia, which may prompt ultrasound examination of the liver to detect steatosis.

- All concomitant drugs (dose, start and stop dates, whether they are known to be hepatotoxic, information on rechallenge or dechallenge with drugs with the same or similar structure).
- Evaluation of nondrug causes: recent hepatitis A, B, and C serology; evidence for biliary obstruction; imaging study results; acute AH (recent drinking and AST >2 x ALT are supportive); recent history of severe hypotension or congestive heart failure; other underlying viral disease.
- All supplemental information, including consultation reports, narrative information, and special studies.

If requested, supporting de-identified source documents (e.g., results of relevant diagnostic tests completed to evaluate the event) will also be sent to the Sponsor and MM at clinicalsafety@surrozen.com.

The SRC will review all available information.

10.4.7. Recording Pregnancy

If a participant becomes pregnant or if a male participant's female partner becomes pregnant during the clinical trial, the Investigator will report the details on a Pregnancy Notification and Outcome Form in the EDC system **within 24 hours of knowledge of the pregnancy**. The paper Pregnancy Notification and Outcome Form should be completed if the EDC system is not functional and emailed to the Surrozen Safety Team at clinicalsafety@surrozen.com. Information from the paper form must be entered into EDC once the EDC system is functional. Even though participants agree to withdraw or terminate participation in the clinical trial, the Investigator should follow-up and document the outcome of all pregnancies. When possible, all pregnancies should be followed to term.

Abortions (spontaneous, accidental, or therapeutic) must also be reported to the Surrozen Safety Team. Congenital anomalies/birth defects always meet SAE criteria, and should therefore, be expeditiously reported as an SAE, using the above-described process (Section 10.4.3) for SAE reporting. In this case, a Pregnancy Notification and Outcome Form should have been previously completed and will need to be updated to reflect the outcome of the pregnancy.

10.5. Follow-up of Participants After Study Completion

10.5.1. Adverse Events and Serious Adverse Events

At a minimum, all AEs and SAEs that are deemed definitely related, possibly related or probably related to the study drug must be followed until resolution, until the condition stabilises, until the event is otherwise explained, or until the participant dies or is lost to follow-up. The Investigator is responsible for ensuring that follow-up includes any supplemental investigations as may be indicated to elucidate as completely as practical the nature and/or causality of the AE/SAE. This may include additional laboratory tests or investigations or consultation with other health care professionals.

The Sponsor may request that the Investigator perform or arrange for the conduct of supplemental measurements and/or evaluations. If a participant dies during participation in the study or during a recognised follow-up period, the Sponsor should be provided with a copy of any post-mortem findings, including histopathology.

10.5.2. Pregnancy

Investigators should follow participants and partners of participants (with consent) who become pregnant after receiving study drug through the outcome of the pregnancy and will be requested to report the outcome of the pregnancy as described in Section 10.4.7.

10.5.3. End of Study ADA Positive Cases

If a participant, upon completion of the study, is confirmed positive for ADAs and/or ADAs that cross react with RSPO2, the titre value will be assessed approximately every 3 months after the EOS visit. Changes related to timing of assessment will not be considered deviations to protocol if approved by Sponsor. The participant must separately consent to this follow-up. The follow-up period will end when the participant's ADA is negative or returns to Baseline (i.e., is equal or less than the Baseline quantified titre value), when the participant withdraws consent or a maximum of 1 year after the EOS visit, whichever comes first. During this period, the Investigator will report to the Sponsor any adverse events that could be related to the presence of ADA.

11. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

11.1. Study Monitoring

Before an investigational site can enter a participant into the study, a representative of the Sponsor will evaluate the investigational study site to:

- Determine the adequacy of the facilities
- Discuss with the Investigator(s) and other personnel their responsibilities regarding protocol adherence, and the responsibilities of the Sponsor or its representatives.

A study monitor will be identified and will be responsible to liaison with and support the investigational site.

The study monitor and regulatory authority inspectors are responsible for contacting and visiting the investigative site for the purpose of inspecting the facilities and, upon request, inspecting the various records of the study (e.g., eCRFs, essential documentation, and other pertinent data) provided that participant confidentiality is respected.

During the study, the monitor will have regular contact with the investigational site for the following as further defined in the study monitoring plan:

- Provide information and support to the Investigator(s).
- Confirm that facilities remain acceptable.
- Confirm that the investigational team is adhering to the protocol, that data are being accurately recorded in the eCRFs, and that study drug accountability checks are being performed.
- Perform source data verification as specified in the study plans. This may include a comparison of the data in the eCRFs with the participant's medical records at the hospital or practice, and other records relevant to the study. This will require access to all original records for each participant (e.g., clinic charts).
- Record and report any protocol deviations not previously sent to the Sponsor.
- Confirm AEs and SAEs have been properly documented on eCRFs.
- Confirm any SAEs have been forwarded to the Sponsor and those SAEs that met criteria for reporting have been forwarded to the Ethics Committees.

The monitor will be available between visits if the Investigator(s) or other staff needs information or advice.

11.2. Data Management

The Investigator (or designee) will maintain individual records for each participant. These records constitute source data. An eCRF will be created by the data management group for recording the required data in the study database. All eCRF information is to be filled in by site staff unless otherwise specified in the completion guidelines. If required data are not available or

are not applicable, this fact should be indicated. Blank spaces should not be present unless otherwise directed.

The study monitor will perform source data verification of data entered in the eCRF and raise queries for correction by the site. The data entered in the eCRF will be participant to data validation checks for consistency and completeness by the data management group. Data queries will then be generated and sent to the investigational site for response before the database is locked and released for statistical analysis.

The EDC system used for study data entry is fully 21 CRF Part 11 compliant. All creation, modification, or deletion of electronic study records will be captured by an automated Audit Trail of system activities.

11.3. Audits and Inspections

Authorised representatives of the Sponsor, or oversight bodies (i.e., a regulatory authority, or an Ethics Committee may visit the site to perform audits or inspections, including source data verification. The purpose of an audit or inspection is to systematically and independently examine all study-related activities and documents to determine whether these activities were conducted, and data were recorded, analysed, and accurately reported according to the protocol, International Council for Harmonisation Good Clinical Practices (ICH GCP) guidelines, and any applicable laws and regulatory requirements. The Investigator should contact the Sponsor immediately if contacted by a regulatory agency about an inspection.

12. STATISTICS

This section summarises the planned statistical analysis strategy and procedures for the study. Statistical methods will be further outlined in a Statistical Analysis Plan (SAP). The SAP will be approved by the Sponsor before the database lock for the participants enroled for their respective parts of the study. If, after the study has begun, changes are made to primary and/or key secondary objectives/hypotheses or the statistical methods related to those hypotheses, then the protocol will be amended (consistent with *ICH Guideline E9*). Changes to other secondary or exploratory analyses made after the protocol has been finalized, along with an explanation as to when and why they occurred, will be listed in the SAP or CSR for the study. Ad hoc exploratory analyses, if any, will be clearly identified in the CSR. Methods outlined in the SAP will supersede protocol-specified statistical methods in the event of divergence.

12.1. Sample Size

The sample size for this trial is based on safety analysis considerations and not any statistical criteria.

12.2. Analysis Populations

Participant inclusion into each population will be determined before the final analysis, and any interim analyses. The analysis populations are presented in Table 7.

Table 7: Analysis Populations

Population	Definition
Intent to Treat (ITT)	All participants who consent to participate in the study, regardless of whether they receive study drug or not.
Safety	All participants who receive any amount of study drug
Pharmacokinetic (PK)	All participants who receive any amount of active study drug and have at least 1 measurable SZN-043 serum concentration postdose to allow determination of at least 1 serum PK parameter. An evaluable PK profile will be determined at the discretion of the pharmacokineticist after examination of participants with dosing or protocol deviations that could potentially affect the PK profile.
Immunogenicity	All participants who receive any amount of active study drug and have at least 1 ADA sample will be included in the immunogenicity population.
Pharmacodynamic (PD)	All participants who receive any amount of study drug and who have at least 1 evaluable postdose PD measurement. PD population which will be used for the summaries of that PD biomarker's data.

Note: All participant data listings will be presented for the ITT population unless otherwise noted. The safety population will be used for safety summaries, the PK population will be used for PK summaries, the immunogenicity population will be used for antidrug antibody summaries, and the PD population will be used for PD biomarker summaries.

12.3. Interim Analyses and Data Monitoring

A formal interim analysis is not planned, however group and other analyses may be conducted at the ends of each cohort for purpose of data cleaning and monitoring.

The full database will be locked following study completion for all participants. Data from each part will be summarised separately.

12.4. Statistical Methods

Statistical analyses will be primarily descriptive; no formal hypothesis testing will be conducted. Analyses will be performed according to SAS® (Version 9.4 or higher).

Data will be summarised by cohort and treatment group. In general, continuous variables will be summarised with descriptive statistics (number of participants with available data, mean, standard deviation, minimum, median, and maximum). For PK and PD parameters, coefficient of variation (CV) and geometric mean will also be presented, as appropriate. Categorical endpoints will be summarised with frequency counts and percentages within each category.

Unless otherwise specified, baseline will be defined as the last value before the administration of SZN-043.

All data in the database will be presented in by-participant data listings.

12.4.1. Participant Disposition

Participant disposition will be analysed with counts and percentages. The number and percentage of screened participants, enroled participants, treated participants, participants discontinued from the study and SZN-043, as well as the primary reason for discontinuation will be summarised by cohort and treatment group.

12.4.2. Demographics, Medical History, and Baseline Characteristics

Demographics and baseline characteristics data will be summarised by cohort and treatment group with descriptive statistics for the different populations.

Medical history terms will be coded according to MedDRA® Version 22.0 or higher. Medical history will be summarised for each cohort and treatment group by MedDRA® system organ class and Preferred Term for the Safety Population.

12.4.3. Prior and Concomitant Medication

Prior and concomitant medications will be coded from the current version of the World Health Organisation drug dictionary available at the start of the study. Prior and concomitant medications will be summarised by cohort and treatment group according to the Anatomical Therapeutic Chemical classification and preferred name for the Safety Population.

12.4.4. Treatment Compliance and Exposure

Treatment compliance and exposure will be summarised and listed by cohort and treatment group for all participants in the Safety Population. The duration of exposure will be presented in days and calculated as the date of last dose of study drug minus the date of first dose of study

drug, plus one. Duration of exposure and total dose received (mg/kg) will be summarised with descriptive statistics.

12.4.5. Safety Analyses

All safety assessments, including concomitant medications, AEs, laboratory evaluations, vital signs, ECGs, and other safety assessments will be analysed by cohort and treatment group using the Safety Population.

12.4.5.1. Adverse Events

Adverse events will be coded from the current version of the MedDRA® Version 22.0 or higher and will be graded according to the CTCAE V5.0 (NCI 2017). The number and percentage of participants reporting TEAEs and serious TEAEs will be summarised by System Organ Class and Preferred Term. Separate summaries will be provided for all TEAEs, TEAEs by toxicity grade, TEAEs by relationship to study drug, treatment-emergent serious adverse events, and treatment-emergent serious adverse events by relationship to study treatment.

Separate by-participant data listings will be provided for deaths, SAEs, participants meeting DILI criteria, and AEs leading to discontinuation of the study.

12.4.5.2. Laboratory Evaluations

Laboratory evaluations (including haematology, serum chemistry, lipid profiles, and coagulation) will be summarised by cohort, treatment group, and protocol-specified collection time point. Observed values and change from baseline clinical laboratory data will be summarised with descriptive statistics and presented for each protocol-specified time point.

Abnormal urinalysis results (dipstick and microscopy), if applicable, will be listed only.

The cumulative number and percentage of participants with liver function test abnormalities meeting DILI criteria as defined in Section 10.2 will be summarised by treatment group.

12.4.5.3. Vital Signs

Vital signs (blood pressure [systolic and diastolic], pulse rate, respiratory rate, and body temperature) will be summarised by cohort, treatment group, and protocol-specified collection time point. Observed values and change from baseline will be summarised with descriptive statistics and presented for each protocol-specified time point.

12.4.5.4. Electrocardiograms

ECG values will be summarised by clinical assessment (normal, abnormal but not clinically significant or abnormal and clinically significant) by cohort, treatment group, and by protocol-specified collection time point. Shift from baseline for ECG clinical assessments will be presented by cohort and treatment group.

12.4.6. Pharmacokinetics, Immunogenicity, and Pharmacodynamic Biomarkers Assessments

Serum concentrations and actual blood sampling times will be listed by treatment, dose level and protocol-specified time point and summarised using descriptive statistics at each protocol-specified time point. Individual and mean serum concentration-time profiles will also be presented graphically for each treatment and dose level.

PK parameters will be computed from the individual serum concentrations using a non-compartmental and/or compartmental approach as data allow.

PK parameters will be estimated, as data allow, as presented in Table 8.

Table 8: Estimated Pharmacokinetic Parameters

Parameter	Definition
C_{max}	Maximum observed serum concentration
C_{last}	Last measurable plasma concentration
C_{tau}	Concentration at the end of the dosing interval
T_{max}	Time to maximum concentration
$AUC_{0\text{-}last}$	Area under the drug concentration-time curve, from time 0 to the last measurable concentration
AUC_{tau}	rea under the plasma concentration-time curve for a dosing interval
$AUC_{0\text{-}inf}$	Area under the drug concentration-time curve, from time 0 to infinity
CL	Clearance
CL_{ss}	Clearance at steady state
$t_{½}$	Apparent terminal half-life
K_{el}	Apparent terminal elimination rate constant
V_d	Apparent volume of distribution
V_{ss}	Volume of distribution at steady state
V_z	Volume of distribution in the terminal state
MRT	Mean residence time
R_{ac}	Accumulation ratio

Values for K_{el}, $t_{½}$, $AUC_{0\text{-}inf}$, CL, or V_z will not be reported for cases that do not exhibit a terminal log-linear phase in the concentration versus time profile. Additional analyses will be performed as deemed necessary upon review of the data.

The relationship between PK levels and ECG interval results will be analysed.

Observed values for ADA levels/status will be summarised with descriptive statistics by cohort and treatment group. If data permit, the relationship between ADA levels and PK endpoints may be explored. A full description of planned analyses for immunogenicity data will be described in the SAP.

MBT data will be expressed as percentages of the $^{13}CO_2$ recovery per hour using an area under curve (AUC) method and observed values and changes from baseline will be summarised by treatment, time point, and dose level.

If performed, HepQuant DuO test results (observed and changes from baseline) will be summarised by cohort, treatment group, and protocol-specified time point using descriptive statistics.

Serum concentrations of biomarkers (observed and changes from baseline) will be summarised by cohort, treatment group, and protocol-specified time point using descriptive statistics.

Individual and mean serum concentrations may also be presented graphically for each treatment and dose level, if appropriate.

13. ETHICS

13.1. Ethics Review

The final study protocol, including the final version of the ICF, must be approved or given a favourable opinion in writing by an Ethics Committees as appropriate. The Investigator and Sponsor must have received the written approval before any participant into the study may be enroled.

The Ethics Committees must approve any amendment to the protocol in accordance with local requirements. In addition, the Ethics Committees must approve all advertising used to recruit participants for the study. The protocol must be re-approved by the Ethics Committees upon receipt of amendments and annually, as local regulations require. The Principal Investigator or Sponsor/Designee will be responsible for submitting any amendments depending on the requirements of the local Ethics Committees.

The Principal Investigator (or CRO if so delegated) is responsible for providing the Ethics Committees with reports of any reportable serious adverse drug reactions from any other study conducted with the SZN-043. The Sponsor will provide this information to the PI and the CRO as appropriate.

Progress reports and notifications of serious adverse drug reactions will be provided to the Ethics Committees according to local regulations and guidelines.

13.2. Ethical Conduct of the Study

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki (Ethical Principles for Medical Research Involving Human Subjects) and are consistent with ICH GCP, and any other applicable laws and regulatory requirements.

13.3. Written Informed Consent

The Principal Investigator will ensure that the participant is given full and adequate oral and written information about the nature, purpose, possible risk, and benefit of the study. Participants must also be notified that they are free to discontinue from the study at any time without prejudice. The participant should be given the opportunity to ask questions and allowed time to consider the information provided before voluntarily signing the written ICF. Note: A legally authorized representative may consent on behalf of the participant where allowed by local regulations and if approved by the applicable ethics committee.

The participant’s signed and dated informed consent must be obtained before conducting any study procedures. The participants will be informed of their rights to privacy but will be made aware that the study data will be submitted to the Sponsor and possibly to drug regulatory authorities for review and evaluation. They will be informed also that the study monitor may inspect their medical records to verify the accuracy and completeness of the study records and results.

The acquisition of informed consent should be documented in the participant's medical records, as required, and the ICF will be signed and personally dated by the participant and by the person who conducted the informed consent discussion. In instances when participants are unable to provide written informed consent themselves, a legally authorized representative may sign on their behalf as permitted by local law.

The Principal Investigator must maintain the original, signed ICF. A copy of the signed ICF must be given to the participant or legal representative. The date that informed consent was signed will be recorded on the eCRF.

13.4. Data Protection

The Sponsor or its designee will conduct this study in compliance with all applicable data protection regulations.

Participants will be informed that data will be held on file by the Sponsor and that these data may be viewed by staff including the study monitor and by external auditors in accordance with local data protection law. Additionally, participants will be informed that their medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate ethics or institutional committee members, and by inspectors from regulatory authorities. The level of disclosure will also be explained to participants who will give consent for the usage of their data as described in the informed consent. Participants will be assigned by a unique identifier. Any participant records or datasets that are transferred to the Sponsor will contain the identifier only; participant names or any personal information which could identify the participant will not be transferred.

In the event of a data security breach, notification to the supervisory authority and to the data participant will be managed as applicable and in accordance with Articles 33 and 34 of the General Data Protection Regulation.

Participants will also be informed that a study report will be prepared and may be submitted to regulatory authorities and for publication. Regulatory authorities may also require publications of a summary report on public registries (e.g., layperson summary publication required under the Clinical Trial Regulation) as required by applicable regulations. However, participants will be identified in such reports only by study identification number, gender and age. All participant data will be held in strict confidence.

By signing this protocol, the Investigator agrees to treat all participant data used and disclosed in connection with this study in accordance with all applicable privacy laws, rules and regulations. Data generated by this study will be considered confidential by the Investigator, except to the extent that it is included in a publication as provided in the publications section of this protocol.

13.5. Long-term Storage

All samples may be stored for up to 10 years. The Sponsor anticipates analysis of remaining samples in the future that relate directly to the objectives of this protocol. These objectives include additional serum protein mechanistic or PD biomarkers, comprehensive proteomic analyses, microRNAs, extracellular vesicles, and comprehensive mass spectrometry analyses. Participants will be asked for consent at the start of this study (CL-0043-1002) for this extension

of use. Additional consent may be requested before testing if required by local regulations and laws applicable to the person and where the sample was originally obtained. Samples may be destroyed before the 10-year period elapses at the discretion of the Sponsor without notification. Participants may request to have their samples destroyed at any time before analysis.

14. REGULATORY INFORMATION RELATED TO REGIONAL SPONSOR REQUIREMENTS

Novotech will act as the legal Australia, New Zealand, and South Korean Sponsor for the study and will fulfil the obligations that this role entails. The Sponsor or designee shall, to the extent required by the applicable laws and regulations, interact with the regulators on behalf of the Sponsor in connection with this study. The Sponsor or designee will prepare a required submission document and submit these to the applicable regulators for each of the countries.

Surrozen will retain its role as sole Sponsor for all other regions.

15. DATA HANDLING AND RECORDKEEPING

15.1. Inspection of Records

The Sponsor, or its delegated representative, will be allowed to conduct site visits to the investigation facilities for the purpose of monitoring any aspect of the study. The Investigator agrees to allow the monitor to inspect the drug storage area, study drug stocks, drug accountability records, participant charts and study source documents, and other records relative to study conduct.

15.2. Retention of Records

All source data, clinical records and laboratory data relating to the study will be archived for at least 15 years after the completion of the study. All data will be available for retrospective review or audit.

Source documents are original documents, data, and records from which the participant's eCRF data are obtained. These include, but are not limited to: hospital records, clinical and office charts, laboratory and pharmacy records, diaries, microfiches, radiographs, angiograms, study drug accountability logs, and correspondence.

The Investigator and study staff are responsible for maintaining a comprehensive filing system of all study-related (essential) documentation. These include, but are not limited to: Ethics Committee correspondence, study drug accountability logs, and curricula vitae of all personnel participating in the study. These files must be suitable for inspection at any time by the Sponsor, monitor, and/or applicable regulatory authorities. All essential documentation should be retained by the institution as required by local laws and regulations.

No study document should be destroyed without prior written agreement between the Sponsor and the Investigator. If the Investigator wishes to assign the study records to another party or move them to another location, the Principal Investigator must notify the Sponsor in writing of the new responsible person and/or the new location.

15.3. Liability/Indemnity/Insurance

The Sponsor will ensure sufficient insurance is available to enable it to indemnify and hold the Investigator(s) and relevant staff as well as any hospital, institution, ethics committee or the like, harmless from any claims for damages for unexpected injuries, including death, that may be caused by the study drug but only to the extent that the claim is not caused by the fault or negligence of the participants or Investigator(s).

16. PUBLICATION POLICY

16.1. Publication of Results

The publication, presentation, or other public disclosure of study results (each, a "Publication") will be accurate and honest, undertaken with integrity and transparency and in accordance with the Sponsor's approval.

Publication of results will be subjected to fair peer-review. Authorship will be discussed between researchers prior to study commencement (or as soon as possible thereafter) and reviewed whenever there are changes in participation.

All conflicts arising through disputes about authorship will be reviewed by the Sponsor.

Acknowledgement will be given to collaborating institutions and hospitals and other individuals and organizations providing finance or facilities. Participant confidentiality will be maintained by referring to individual participants by their identifying code used in the trial. Public release of data is not acceptable before scientific conference embargos or publication of the manuscript unless agreed upon with the Sponsor. In the case of no publication, information will only be released to the public and media in accordance with the Sponsor's approval.

Study data that have not been published, presented, or otherwise disclosed in accordance with the clinical trial agreement shall remain confidential information of the Sponsor, the Investigator may not disclose or permit the disclosure of such unpublished data to any third party, nor may they disclose or permit the disclosure of any study data to any third party in greater detail than the same have been disclosed in any permitted publication, presentation or other disclosure.

The results summary will be posted to an applicable clinical trial registry as required by legal agreement, local law, or regulation.

16.2. Disclosure and Confidentiality

By signing this protocol, the Investigator agrees to keep all information provided by the Sponsor in strict confidence and to request similar confidentiality from site staff and the local Ethics Committees. Study documents provided by the Sponsor (protocols, IBs, eCRFs, etc.) will be stored appropriately to ensure their confidentiality. The information provided by the Sponsor to the Investigator may not be disclosed to others without direct written authorisation from the Sponsor, except to the extent necessary to obtain informed consent from participants who wish to participate in the study.

The Investigator must ensure that the participant's anonymity is also maintained. Participants should only be identified by their initials and a participant study number on the eCRFs and other source documents. Other study-related documents (e.g., signed ICFs) should be kept in strict confidence by the Investigator.

17. QUALITY CONTROL AND QUALITY ASSURANCE

17.1. Compliance with Good Clinical Practice

To ensure compliance with GCP and all applicable regulatory requirements, the Sponsor may conduct a quality assurance audit. Please see Section 11.3 for more details regarding the audit process.

The study will be carried out in accordance with the current version of the Declaration of Helsinki (Ethical Principles for Medical Research Involving Human Subjects), and with the Guideline for GCP E6 (R2) (EMA/CHMP/ICH/135/1995), as adopted by regulatory authorities for participating regions and/or countries.

17.2. Archiving and Regulatory Inspection

All study-related documents and records are to be retained for a minimum of 15 years after trial completion. Written agreement from the Sponsor must precede destruction of the same.

In accordance with ICH GCP, this study may be selected for audit. Inspection of site facilities (e.g., pharmacy, medication storage areas, laboratories) and review of study-related records may occur by the Sponsor, the Sponsor's representative(s), or regulatory authority to evaluate the study conduct and compliance with the protocol, ICH GCP, and applicable regulatory requirements.

18. CLINICAL STUDY REPORT

A clinical study report (CSR) will be prepared with reference to the Tripartite Harmonised ICH Guideline: Structure and Content of Clinical Study Reports E3 (November 1995).

19. SPONSOR AND INVESTIGATOR OBLIGATIONS

19.1. Protocol Amendments

Neither the Investigator nor the Sponsor will modify or alter this protocol without the agreement of the other. All agreed protocol amendments will be clearly recorded on a protocol amendment form and will be signed and dated by the original protocol approving signatories. All protocol amendments will be submitted to the relevant institutional Ethics Committees for approval before implementation, as required by local regulations. The only exception will be when the amendment is necessary to eliminate an immediate hazard to the trial participants. In this case, the necessary action will be taken first, with the relevant protocol amendment following shortly thereafter.

19.2. Protocol Deviations

Should any protocol deviation occur, it must be reported to the study monitor as soon as is reasonably practical. The deviation and the reason for its occurrence must be documented, reported to the relevant Ethics Committees or applicable Regulatory Authority (if required), and included in the CSR.

A Serious Breach is a type of deviation that must be reported to the Sponsor within 1 business day of the investigator becoming aware of such a deviation. A Serious Breach is defined as a deviation which is likely to effect to a significant degree – (a) the safety or physical or mental integrity of the subjects of the trial; or (b) the scientific value of the trial". When in doubt whether an event meets this criteria, the Investigator should contact the CRA and/or medical monitor within the 1 business day timeframe to confirm action to be taken. Sponsor, or its CRO where so delegated, will be responsible for ensuring suspected or confirmed Serious Breaches are reported to applicable regulatory authorities within required timeframes.

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21. APPENDICES

Appendix 1: Schedule of Assessments

Appendix Table 1a: Schedule of Assessments for MAD in Severe Alcohol-Associated Hepatitis Participants (Dosing Day 0 (Single Dose Cohort Component), and Day 0, 4)

Procedure	**Screening**		**Treatment and Observation Period**																**EOS**	**E/D**
			W1							W2				W3		W4	W5	W9	W13	
Study Day	Pre-D–1	D–1	**D0** [a]	D1	D2	D3	**D4** [a]	D5	D6	D7	D8	D9	D11	**D14**	D18	**D21**	**D28**	D60	D90	
Visit Window														*±1d*			***+4d***	*±3d*	*±3d*	**NA**
Dose Day 0 Participants	X	X	X	X	X	X	X	X	X	X			X	X			X	X	X	X
Dose Day 0/4 Participant	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Informed consent	X																			
Inclusion/exclusion criteria	X [b]																			
Demography	X																			
Physical examination	X	X																	X	X
Height	X																			
Weight	X	X																	X	X
Medical history	X	X																		
Chronic liver disease questionnaire (CLDQ)		X [d]															X	X	X	X
Serum Alcohol Test			X [d] PEth				X [d]										PEth	PEth	PEth	PEth
Liver Ultrasound	X																			
FSH (postmenopausal women only)	X																			
Serum HCG (WOCBP)		X																		
Urine Pregnancy test (WOCBP)	X	X					X										X	X	X	X
Urine Drug Screen	X	X																		
Laboratory assessments [c]	X	X	X [d]	X[e]	X[e]	X[e]	X[d]	X[e]	X[e]	X	X	X[e]	X[e]	X	X	X[e]	X	X	X	X

Procedure	Screening		Treatment and Observation Period															EOS	E/D
			W1							W2				W3		W4	W5	W9	W13	
Study Day	Pre-D–1	D–1	**D0** [a]	D1	D2	D3	**D4** [a]	D5	D6	D7	D8	D9	D11	**D14**	D18	**D21**	**D28**	D60	D90	
Visit Window														*±1d*			***+4d***	*±3d*	*±3d*	**NA**
TSH	X																			
GLDH			X[d]	X	X	X	X[d]	X	X	X	X	X	X	X	X	X	X	X	X	X
CRP			X [d]				X [d]			X				X	X				X	X
Fasting Lipid Profile [c]			X [d]											X	X				X	X
Urinalysis [f]	X		X [d]											X	X				X	X
HIV, HBsAg, HBV DNA (if HBsAg positive), HCV RNA	X																			
12-lead ECG [g]	X	X	X				X												X	X
Vital signs [h]	X	X	X [h1]				X [h1]			X							X	X	X	X
Lille score [i]			X				X			X										X
MELD score [j]	X	X					X			X							X	X	X	X
Randomisation		X																		
SZN-043 administration [l]			X				X													
Methacetin breath test [n]		X				X[n1]				X[n1]							X			X [n2]
HepQuant DuO test [o]		X								X							X			X
Ascites and Encephalopathy Score		X								X							X			
Vital Status Assessment																	X	X	X	
AE/SAE review [p]	X	X	←													→			X	X
Concomitant medication review	X	X	←													→			X	X
For Serum PK [l],Blood PD biomarkers [m], and Anti-SZN-043 antibodies refer to Appendix Table 2																				

FOOTNOTES for SOA 1B

[a] The extent of time the patient is inpatient in a hospital setting is in accordance with standard of care and as directed by the treating physician. On dosing days participants should be in seen in a setting that can provide appropriate medical support and ability to perform the required assessments.

[b] Recheck clinical status before randomisation and first dose of study drug.

[c] Participants are required to fast for 8 hours before collection of Fasting Lipid Profile blood samples. Fasting prior to other blood samples is at the discretion of the Investigator based on the health requirements of the participant.

[d] Assessments that fall on a dosing day should be performed once before dose administration.

[e] Chemistry and coagulation panel only.

[f] Urinalysis includes specific gravity, pH, glucose, protein, blood, and ketones by dipstick. Microscopic examination may be conducted if blood or protein is abnormal (and at the discretion of the Investigator).

[g] ECGs will be performed before vital signs with participants in a supine position for at least 5 min prior. ECGs may be repeated in triplicate if abnormality is considered clinically significant by the Investigator. If required, triplicate readings to be taken at least 1 min apart, and all 3 ECGs will be recorded. **ECG on day of dosing will be performed at 5 min (±5 min) and 4 h (±20 min) after end of dose.**

[h] Vital signs (including systolic and diastolic blood pressure, pulse rate, respiratory rate, and body temperature) will be measured after the participant has rested for at least 5 min in a semi-supine or supine position.

h1: On days of dosing, vital signs will be measured 60 min before treatment administration, at 15-min intervals for the first hour after end of administration, and every 30 min thereafter during the 4-hour observation period (within ±10 min).

[i] Lille scores for study purpose will be calculated by the central laboratory. Lille score will only be calculated for the E/D visit if on or prior to Day 7.

[j] MELD score will be calculated by the central laboratory. For eligibility, the sites will calculate the MELD score using results from additional blood samples sent to the local lab on Day -1 (see Section 9.1.8 last paragraph), and record the value obtained in the EDC. Sites may not include results for components of the MELD from blood drawn on different days. Only one qualifying MELD scores is required for participants to be eligible.

[k] Study drug will be administered described in Section 5, including dosing schedules that apply.

[l] On dosing days, PK samples will be drawn from the opposite arm of dosing.

[m] Blood PD biomarkers include AFP and ALP. These will also include LECT2 and angiogenin unless Sponsor provides written documentation to cease collection for this purpose (see Section 9.5.1).

[n] The methacetin breath test requires fasting of at least 4 hours (water allowed). The methacetin breath test will involve collection of exhalation in 2 tubes before isotope intake, and 1 tube every 10 min (±5 min) after isotope intake for up to 60 min, as further described in the laboratory manual.

n1: The MBT for Day 0 only participants will be performed at Day 3, and for Day 0 and 4 participants on Day 7, not both.

n2: Methacetin breath test may be performed once up to 48 hours prior to dosing on D0.

n3: Methacetin breath test will be performed at the early discontinuation visit if it occurs after Day 7 and before Day 28.

[o] The HepQuant DuO test is performed after at least a 5 h fast; 3 mL blood samples are obtained 20 min (±2 min), and 60 min (±5 min) after the end of oral dose administration with the cholate solutions (See Appendix 2). The HepQuant DuO test may be performed once up to 48 hours prior to dosing on Day 0. HepQuant Duo test will be performed at the early discontinuation visit if it occurs before Day 28. Participants unable to meet the requirements listed in the IFU are still eligible for the study but should not participate in the HepQuant Test.

[p] Adverse event assessment will include evaluation for infusion reactions, which may include photographs of the affected area at the discretion of the Investigator.

Note:

PEth (where indicated for the alcohol serum test) indicates testing the level of phosphatidyl ethanol.

When the time of vital signs measurement and/or 12-lead ECG coincides with a blood draw, the vital signs and/or 12-lead ECG will be taken before the scheduled blood draw where possible, ensuring the blood draw is within the window specified.

PD measurements may be removed during the study if data does not indicate utility. Sites will be notified by Protocol Clarification if this occurs.

Vital Status to be recorded needs to be known about the participant at the timepoints indicated. However, the assessment thereof can be made AFTER that date if the participant was not available at the time. For example, if they do not return for a Day 28 but return at Day 60, their Day 28 vital status will be inferred.

Appendix Table 2: Day 0 and Day 0/4 Dosing Schedule for PK, PD, and Anti-SZN-043 Antibody Assessment Timing for SOA

Cohorts 1 to 3, including Optional Cohorts	**PK, PD Biomarker, and Anti-SZN-043 Antibody Sampling Windows**	
	SZN-043 Administration	
Timing of Dose	**Days 0 and 4**	**Day 0**
Anti-SZN antibody testing		
Day 0 predose	X	X
Days 14, 28, 60, 90 (anytime ±1 day)	X	X
Every 3 months after EOS/ED if positive	X until baseline or negative results or 1-year post-EOS	X until baseline or negative results or 1-year post-EOS
Pharmacodynamic Testing **(Note: Applicable to all Pharmacodynamic Tests, the Sponsor may determine from on-going data collection during the study that results from any or all do not provide value to understanding of SZN-043 pharmacodynamic effect. Upon such determination to reduce burden and risk to patients related to the additional blood drawn for these assessments, the Sponsor will inform investigators to discontinue the applicable test via a Protocol Clarification and applicable addendum or update to the Laboratory manual.)**		
Day 0 predose (anytime)	X	X
Day 1 (±1h postdose Day 0)	X	X
Day 2, 3 (anytime)	X	X
Day 4 (predose)	X	
Day 5 (±1h postdose)	X	X
Day 6 (anytime)	X	
Day 7 (anytime)	X	X
Day 9 (anytime)	X	
Day 11 (anytime)	X	X
Days 14, 21, 28 (anytime ±1 day)	X	X
EOS/ED	X	X
Pharmacokinetic Testing **(Note: On the day of dose administration, samples will be collected from the opposite arm.**		
Day 0 Predose [a] Post-dose 5 min (±5 min) Post-dose 30 min (±5 min) Post-dose 1 h (±5 min) Post-dose 2 h (±5 min) Post-dose 4 h (±10 min) Post-dose 8 h (±10 min) Post-dose 12 h (±10 min)	X (all)	X (all)
Day 1 (±1h post-dose on Day 0)	X	X
Days 2 and 3 (±4h postdose Day 0)	X	X

Cohorts 1 to 3, including Optional Cohorts	**PK, PD Biomarker, and Anti-SZN-043 Antibody Sampling Windows**		
	SZN-043 Administration		
Timing of Dose	**Days 0 and 4**		**Day 0**
Day 4 Predose [a] Post-dose 5 min (±5 min) Post-dose 30 min (±5 min) Post-dose 1 h (±5 min) Post-dose 2 h (±5 min) Post-dose 4 h (±10 min) Post-dose 8 h (±10 min) Post-dose 12 h (±10 min)	X (All)		X (±4h post-dose Day 0)
Day 5	X ±1 h post-dose Day 4		X (±4h post-dose Day 0)
Day 6	X (anytime)		
Day 7	X (anytime)		X (anytime)
Day 8		X	
Day 9		X (anytime)	
Day 11		X (anytime)	X(anytime)
Day 14, 21, 28 (anytime ±1 day)		X	X

[a] Participants must be supine for 10 minutes predose and 5 minutes post-dose.

Cohort 4	**PK, PD Biomarker, and Anti-SZN-043 Antibody Sampling Windows**	
	SZN-043 Administration	
Timing of Dose	**Days 0 and 4**	**Day 0**
Anti-SZN antibody testing		
Day 0 predose	X	X
Days 14, 28, 60, 90 (anytime ±1 day)	X	X
Every 3 months after EOS/ED if positive	X until baseline or negative results or 1-year post-EOS	X until baseline or negative results or 1-year post-EOS
Pharmacodynamic Testing **(Note: Applicable to all Pharmacodynamic Tests, the Sponsor may determine from on-going data collection during the study that results from any or all do not provide value to understanding of SZN-043 pharmacodynamic effect. Upon such determination to reduce burden and risk to patients related to the additional blood drawn for these assessments, the Sponsor will inform investigators to discontinue the applicable test via a Protocol Clarification and applicable addendum or update to the Laboratory manual.)**		
Day 0 predose (anytime)	X	X
Day 1 (±1h postdose Day 0)	X	X
Day 2, 3 (anytime)	X	X
Day 4 (predose)	X	
Day 5 (±1h postdose)	X	X
Day 6 (anytime)	X	
Day 7 (anytime)	X	X
Day 9 (anytime)	X	
Day 11 (anytime)	X	X
Days 14, 21, 28 (anytime ±1 day)	X	X
EOS/ED	X	X
Pharmacokinetic Testing (Cohorts 1 to 3, and optional Cohorts) **(Note: On the day of dose administration, samples will be collected from the opposite arm.)**		
Day 0 Predose [a] Post-dose 5 min (±5 min) Post-dose 1 h (±5 min) Post-dose 4 h (±5 min) Post-dose 8 h (±10 min)	X (all)	X (all)
Day 1 (±1h post-dose on Day 0)	X	X
Days 2 and 3 (±4h postdose Day 0)	X	X
Day 4 Predose [a] Post-dose 5 min (±5 min) Post-dose 1 h (±5 min) Post-dose 4 h (±5 min) Post-dose 8 h (±10 min)	X (All)	X (±4h post-dose Day 0)

Cohort 4	**PK, PD Biomarker, and Anti-SZN-043 Antibody Sampling Windows**		
	SZN-043 Administration		
Timing of Dose	**Days 0 and 4**		**Day 0**
Day 5	X ±1 h post-dose Day 4		X (±4h post-dose Day 0)
Day 6	X (anytime)		
Day 7	X (anytime)		X (anytime)
Day 9		X (anytime)	
Day 11		X (anytime)	X(anytime)

[a] Participants must be supine for 10 minutes predose and 5 minutes post-dose.

Appendix 2: HepQuant DuO Test to Measure Liver Function Disease and Treatment Effects

NOTE: Detail in this section are given for reference only. The current version of the HepQuant DuO Instructions For Use (IFU) located within the laboratory manual should be considered the primary source of information regarding contraindicated medications and conditions.

The HepQuant DuO test is currently available in the U.S. as a Laboratory Developed Test (LDT) and is used in this study as an exploratory endpoint of an investigational assay. This Appendix describes the HepQuant DuO test and its use for assessing liver disease and treatment effects in this study.

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Background

With progression, liver diseases alters hepatocyte function and the portal circulation which manifests as portal hypertension and portal-systemic shunting. The clinical consequences are coagulopathy, jaundice, varices, ascites, and encephalopathy. HepQuant DuO test quantifies the changes in liver function and the portal circulation from early through late stages of disease.

The HepQuant DuO test is a simplified version of the HepQuant SHUNT test, which is a blood-based, non-invasive test that is well tolerated by participants, simple to administer, and does not require expensive equipment or technology. Over 2000 HepQuant SHUNT tests have been performed in over 1200 participants.

HepQuant test experience encompasses healthy participant controls, and patients with chronic hepatitis C, metabolic dysfunction-associated steatotic liver disease/metabolic dysfunction-associated steatohepatitis, primary sclerosing cholangitis (PSC), hepatocellular carcinoma (HCC), polycystic liver disease, and spans the spectrum from minimal to advanced fibrosis and compensated to decompensated disease (Alkhouri 2019, Asrani 2021, Burton 2015, Everson 2007-2022, Fallahzadeh 2021, Helmke 2013-2022, Hoteit 2020, Kim 2021, Lawitz 2021, Lemmer 2019, O'Leary 2014, Rahimi 2021, Shiffman 2021-2022, Shrestha 1997, Wieland 2021).

Cholates

The HepQuant DuO test measures the clearance of cholate labelled with the molecular probe deuterium [D] ([2,2,4,4-d] cholate (d4-CA)). Cholates are naturally occurring endogenous compounds found in the human body and deuterium is also a naturally occurring non-radioactive cold stable isotope.

Cholates labelled with stable isotopes in the amounts administered in the HepQuant tests have no known harmful effects. Because clearance of cholate from the blood is a liver-specific flow-dependent function, measuring cholate clearance is a non-invasive method for assessing the severity of liver disease in intact humans.

HepQuant DuO Test Collection Kits

Test kits are shipped to clinical sites which function as testing centres. In brief, the HepQuant DuO Liver Diagnostic Kit contains the following items applicable to this protocol:

- Sealed vial of sterile solution of d4-CA (40 mg) in sodium bicarbonate for oral use
- Transfer tubes and pipettes (for transport of serum to HepQuant designated lab)
- Labels
- Instructions for Use
- Test requisition form
- Supplies and labels for returning the samples for analysis

Test Administration

The HepQuant DuO test is performed after at least 5 hours of fasting, usually after an overnight fast and requires venous access via peripheral direct venipuncture (or through an IV line if applicable). 3 mL blood samples are obtained at 20 and 60 minutes after ingestion of the oral d4-cholate solution; and ≥1 mL serum per sample is shipped at ambient temperature to the HepQuant laboratory for analysis of cholate concentrations.

The participant may be in a bed seated upright or in a recliner chair – the participant should be seated in an upright position, or if in bed, have the head of the bed elevated by at least 30 degrees to aid gastric emptying of the orally administered dose of d4-CA solution.

Prior to administration, the HepQuant DuO Test Collection Kits are kept at ambient temperature. For the oral d4-CA dose, the full contents of the d4-CA solution are poured into a >40 mL cup and flavouring added. The d4-cholate/flavouring mixture is administered orally in one gulp. Time 0 is the time at which the patient starts drinking the oral cholate solution.

If the participant were to experience an anaphylactic or hypersensitivity reaction to the compound, administration should be stopped, and the participant should be treated in accordance with standard of care. The participant should not undergo any future HepQuant tests but may remain enroled in the main study at the discretion of the Investigator.

Additional instructions are supplied with the kits.

Known Potential Risks

Risks from the Test Compounds

Allergic reaction to the oral d4-cholate compound (theoretical – none yet reported)

Reactions could include:

- Rash
- Difficulty breathing
- Wheezing when breathing
- Sudden drop in blood pressure
- Swelling around the mouth, throat, or eyes
- Fast pulse

Severe reactions are very rare, but a severe reaction (called anaphylaxis) can lead to profoundly low blood pressure and even death

Sweating

Risk of Phlebotomy

Localized pain

Bruising

Occasional lightheadedness

Fainting

Infection at the site (rare)

Risk of Fasting

Dizziness

Headache

Stomach discomfort

Fainting

Test Compound

Cholates, labelled with stable (nonradioactive) isotopes, occur naturally and are not known to have any deleterious or adverse effects when given orally in the dose used in HepQuant tests. The serum cholate concentrations that are achieved by oral doses are similar to the serum concentrations of bile acids that occur after the ingestion of a fatty meal. Because cholates are naturally occurring with a pool size in humans of 1 to 5 g, the labelled d4-cholate used in the HepQuant DuO test is unlikely to be harmful to a foetus.

However, the effects of this compound on the foetus is not definitively known. As the protocol for the main study contains provisions ensuring that no pregnant females are enroled in the study, there are no additional warnings related to pregnancy and the HepQuant DuO test.

The d4-cholate used in the HepQuant DuO test for this study is labelled with a stable (non-radioactive) form of hydrogen that is found in nature and can be measured in blood. This form of cholate was used under U.S. FDA IND (65123) from 2002 to 2017, and in numerous studies under U.S. Investigational Device Exemptions since 2017. Its use in humans has been monitored since that time. To date, the d4-cholate used in this study has not been associated with any allergic reactions or side effects. However, there may be unknown risks.

Contraindicated Medications and Conditions

Non-selective beta-blockers and angiotensin-converting enzyme or angiotensin II receptor blocker inhibitors could affect the blood flow to the liver, so participants who are currently taking these medications will be asked to delay taking their normal dose the morning of their testing and until their test is completed. Delaying these medications could cause a temporary elevation in blood pressure but the risk would be minimal, similar to that of participants that miss doses of medications in everyday life.

GLP-1 agonists (e.g., semaglutide, Ozempic®, Wegovy® and others), narcotics, and other medications may slow gastric emptying. Although the effects on HepQuant DuO are unknown,

GLP-1 agonists and other medications affecting gastric emptying should be withheld for at least 5 days prior to DuO™ testing.

All over-the-counter dietary supplements (including, but not limited to, psyllium husk powder [Metamucil®], wheat dextrin [Benefiber®], and cyclodextrin products) and prescription bile acid sequestrants or binding resins (e.g., cholestyramine [Prevalite® or Questran®], colestipol [Colestid®], colesevelam [Welchol®]) for at least 24 hours prior to taking the test. Certain over-the-counter supplements and prescriptive medications may alter bile acid absorption from the intestine and affect the HepQuant DuO results.

Ursodeoxycholic acid (e.g., Ursodiol, Actigall), cholic acid (e.g., CholBam), or other bile acids might alter intestinal absorption of the d4-cholateand should be withheld on the morning of testing.

Resection of large segments of small intestine (short gut) or severe gastroparesis could potentially affect absorption of the orally administered d4-cholate. Therefore, participants with these conditions will be excluded.

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Appendix 3. Management of Infusion Reactions

The following outlines recommended assessment and management considerations when a participant experiences an infusion reaction in response to receiving IP. Investigators are responsible to ensure they follow local guidance and treatment protocols as applicable.

An IR is any adverse sign or symptom that occurs during the infusion of a medication or within the first day of administration. IRs commonly occur with biologics, ranging in severity from mild flushing to severe anaphylaxis-type symptoms. These reactions are not always predictable or associated with a drug's mechanism of action. Most IRs occur within 30 to 120 minutes after the start of administration and occur during the first or second infusion; therefore, careful monitoring during and shortly after infusion is necessary to detect potential IRs and manage them accordingly.

IRs are either allergic reactions to foreign proteins [generally immunoglobulin E-mediated allergic responses] or non-immune-mediated reactions. Most IRs are mild with symptoms such as chills, fever, nausea, headache, skin rash, pruritus, etc. Severe reactions are less frequent and may be fatal without appropriate intervention.

Typical manifestations include generalised symptoms (rash, fever, chills), mucocutaneous (flushing, urticaria, pruritus), respiratory (wheezing, shortness of breath), circulatory (hypotension) and abdominal symptoms (nausea, vomiting, cramps, diarrhoea), minutes to hours after exposure to the drug. Prompt recognition of the infusion reaction and assessment of the reaction severity is required.

Classification of Infusion Reaction

The CTCAE grading scale for grading the severity of infusion reactions is as follows.

NCI CTCAE v5.0 infusion-related reactions

Adverse event	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Infusion related reaction	Mild transient reaction; infusion interruption not indicated; intervention not indicated	Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDs, narcotics [opioids], IV fluids); prophylactic medication indicated for ≤24 h	Prolonged (e.g., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae	Life-threatening consequences; urgent intervention indicated	Death

NCI 2017

General guideline for initial management of an IR of grade 2 or higher severity (local practice and treatment protocols should supersede)

- Stop infusion
- Call for help
- Maintain IV access
- Assess vitals and consciousness regularly
- Position participant appropriately (Trendelenburg if hypotensive)
- Supplemental oxygen, as required
- Administer medication for symptom relief, examples include:
  - diphenhydramine and ranitidine
  - NSAID
- Escalate therapy to appropriately and adequately manage acute symptoms, examples include:
  - Corticosteroids
  - Epinephrine

Rechallenge

The severity and nature of the reaction will determine the decision to restart the treatment. After all symptoms have resolved and discussion with Sponsor, rechallenge with a reduced infusion rate and additional premedication (such as corticosteroids and antihistamines) may be attempted. However, rechallenge in IRs with CTCAE severity grade 3 or higher should not be attempted (NCI 2017).

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If you decide to receive notices and disclosures from us electronically, you may at any time change your mind and tell us that thereafter you want to receive required notices and disclosures only in paper format. How you must inform us of your decision to receive future notices and disclosure in paper format and withdraw your consent to receive notices and disclosures electronically is described below.

Consequences of changing your mind

If you elect to receive required notices and disclosures only in paper format, it will slow the speed at which we can complete certain steps in transactions with you and delivering services to you because we will need first to send the required notices or disclosures to you in paper format, and then wait until we receive back from you your acknowledgment of your receipt of such paper notices or disclosures. Further, you will no longer be able to use the DocuSign system to receive required notices and consents electronically from us or to sign electronically documents from us.

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How to contact Surrozen - Part 11:

You may contact us to let us know of your changes as to how we may contact you electronically, to request paper copies of certain information from us, and to withdraw your prior consent to receive notices and disclosures electronically as follows:
To contact us by email send messages to: dave@surrozen.com

To advise Surrozen - Part 11 of your new email address

To let us know of a change in your email address where we should send notices and disclosures electronically to you, you must send an email message to us at dave@surrozen.com and in the body of such request you must state: your previous email address, your new email address. We do not require any other information from you to change your email address.

If you created a DocuSign account, you may update it with your new email address through your account preferences.

To request paper copies from Surrozen - Part 11

To request delivery from us of paper copies of the notices and disclosures previously provided by us to you electronically, you must send us an email to dave@surrozen.com and in the body of such request you must state your email address, full name, mailing address, and telephone number. We will bill you for any fees at that time, if any.

To withdraw your consent with Surrozen - Part 11

To inform us that you no longer wish to receive future notices and disclosures in electronic format you may:

i. decline to sign a document from within your signing session, and on the subsequent page, select the check-box indicating you wish to withdraw your consent, or you may;

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- Until or unless you notify Surrozen - Part 11 as described above, you consent to receive exclusively through electronic means all notices, disclosures, authorizations, acknowledgements, and other documents that are required to be provided or made available to you by Surrozen - Part 11 during the course of your relationship with Surrozen - Part 11.