CLINICAL STUDY PROTOCOL

Protocol Title:	A Multi-Center, Randomized, Double-Blind, Dose-Ranging, Placebo-Controlled, Proof of Concept, Adaptive, Phase 1b Clinical Study to Evaluate the Safety, Pharmacokinetics, Pharmacodynamics, and Efficacy of Orally Administered TERN-201 in Patients with Presumed Non-Cirrhotic Non-Alcoholic Steatohepatitis (NASH)
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Compound:	TERN-201
Study Phase:	1b
Sponsor Name:	Terns Inc.
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Regulatory Agency Identifier Number(s)	
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CONFIDENTIAL

Sponsor Signatory:

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Signing Reason: I approve this document
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17-Aug-2021

[redacted]
President and Chief Medical Officer
Terns, Inc.

Date

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1. Protocol Summary

1.1. Synopsis

Protocol Title:

A Multi-Center, Randomized, Double-Blind, Dose-Ranging, Placebo-Controlled, Proof of Concept, Adaptive, Phase 1b Clinical Study to Evaluate the Safety, Pharmacokinetics, Pharmacodynamics, and Preliminary Efficacy of Orally Administered TERN-201 in Patients with Presumed Non-Cirrhotic Non-Alcoholic Steatohepatitis (NASH)

Objectives:

Primary Objective:

- To characterize the safety and tolerability of TERN-201 versus placebo for 12 weeks in non-cirrhotic presumed NASH patients, with clinical or histological NASH diagnosis

Secondary Objectives:

- To assess the plasma and urine PK of TERN-201 for 12 weeks in non-cirrhotic presumed NASH patients
- To assess the PD effect of TERN-201 versus placebo for 12 weeks on plasma VAP-1/SSAO activity in non-cirrhotic presumed NASH patients

Exploratory Objectives:

- To assess the plasma and urine PK of TERN-201 metabolites (including TRN-001021 and TRN-001744) at steady state
- To assess the effect of TERN-201 versus placebo on imaging assessments and blood biomarkers of NASH activity
- To assess the effect of TERN-201 versus placebo on biomarkers of inflammation
- To explore the potential for TERN-201 to improve proteinuria due to endothelial effects
- To explore other PD markers, and overall exposure-response and dose-response relationship of TERN-201, as applicable
- To explore the exposure-response and dose-response relationship, as applicable, of TERN-201 and baseline patient characteristics such as soluble VAP-1 (sVAP-1), body mass index (BMI), diabetes mellitus, and others

Endpoints:

Primary Endpoint:

- Overall safety assessed by treatment emergent AEs (TEAEs) and treatment emergent clinical safety laboratory abnormalities

Secondary Endpoints:

- Plasma and urine PK parameters for TERN-201

- Percent change from baseline in plasma VAP-1/SSAO activity

Exploratory Endpoints:

- Plasma and urine PK parameters for TERN-201 metabolites (including TRN-001021 and TRN-001744)
- Change from baseline in corrected T1 (cT1) by magnetic resonance imaging (MRI)
- Change from baseline in liver fat content by magnetic resonance imaging-proton density fat fraction (MRI-PDFF)
- Change from baseline in stiffness by transient elastography
- Change from baseline in alanine aminotransferase (ALT)
- Change from baseline in gamma-glutamyl transpeptidase (GGT)
- Change from baseline in aspartate aminotransferase (AST)
- Change from baseline in NASH and fibrosis biomarkers including cytokeratin-18 (CK-18) (M30 and M65), procollagen III n-terminal propeptide (PIIINP), tissue inhibitor of metalloproteinases-1 (TIMP-1), hyaluronic acid (HA), pro-peptide of type III collagen (PRO-C3), and type III collagen (C3M). Other non-invasive tests for NASH fibrosis may also be assessed including the fibrosis-4 (FIB-4) index, enhanced liver fibrosis (ELF) test, NAFLD fibrosis score (NFS), and PRO-C3/C3M ratio.
- Change from baseline in inflammatory biomarkers including high sensitivity C-reactive protein (hs-CRP), interleukin-6 (IL-6), intercellular adhesion molecule-1 (ICAM-1), and vascular cell adhesion molecule-1 (VCAM-1)
- Change from baseline in estimated glomerular filtration rate (eGFR), urine protein including urine protein-to-creatinine ratio (UPCR), and urine albumin-to-creatinine ratio (UACR)
- Change from baseline in plasma methylamine levels (PD marker of VAP-1/SSAO inhibition)
- Exposure-response and dose-response relationship of TERN-201 over 12 weeks, as applicable
- Exposure-response and dose-response relationship, as applicable, of TERN-201 and baseline patient characteristics such as sVAP-1, BMI, diabetes mellitus, and others

Overall Design:

The study is a multi-center, randomized, double-blind, placebo-controlled, adaptive study.

Approximately 80 clinically or histologically diagnosed adult non-cirrhotic presumed NASH patients who meet study eligibility criteria will be enrolled and randomized at an overall ratio of 2:1 into 3 dose groups and placebo across 2 parts of the study.

Part 1

In Part 1, approximately 30 patients will receive 10 mg TERN-201 (n = 20) or matching placebo (n = 10) orally once daily, for 12 weeks.

In Part 1 of the study, approximately 12 randomized patients will take part in an intensive PK and PD collection after the first dose (Week 0/Day 1), at Week 6, and after the last dose of study drug (Week 12). Randomization will ensure approximately 8 patients in the TERN-201 group and approximately 4 patients in the placebo group are assigned to the PK/PD sub-study. Patients who are not participating in the PK/PD sub-study will have trough PK/PD sampling only.

Part 2 may be enrolled based on an interim analysis, as follows:

An interim analysis will be performed after all patients in Part 1 have completed Week 6 assessments. Interim PK and PD data will be assessed. Blinded safety data will also be reviewed. Enrollment of cohorts to assess 4 mg and up to 20 mg TERN-201 may be initiated per the following criteria:

- TERN-201 4 mg:
    - If robust VAP-1/SSAO activity suppression is observed and available PK from Part 1 suggests that a lower dose may also possibly lead to robust VAP-1/SSAO activity suppression, enrollment in Part 2 with 4 mg TERN-201 may be initiated.
- TERN-201 up to 20 mg:
    - If safety data indicates 10 mg TERN-201 is overall safe and well-tolerated, and available PK from Part 1 predicts that targeted exposures for a dose up to 20 mg will be below an upper limit of 5400 ng•hr/mL for $AUC_{0\text{-}24hr}$ and 768 ng/mL for C_{max}, enrollment in Part 2 with a dose up to 20 mg TERN-201 may be initiated.

Part 2

In Part 2, if initiated, approximately 50 patients will receive 4 mg TERN-201 (n = 20), and/or up to 20 mg TERN-201 (n = 20), or matching placebo (n = 10) orally once daily, for 12 weeks.

In Part 2 of the study, approximately 15 randomized patients will take part in an intensive PK and PD collection after the first dose (Week 0/Day 1), at Week 6, and after the last dose of study drug (Week 12). Randomization will ensure approximately 6 patients at each TERN-201 dose level and approximately 3 patients in the placebo group are assigned to the PK/PD sub-study. Patients who are not participating in the PK/PD sub-study will have trough PK/PD sampling only.

The total duration of study participation will be approximately 22 weeks, consisting of a 6-week Screening Period, a 12-week Treatment Period and a 4-week Follow-up Period.

Number of Patients:

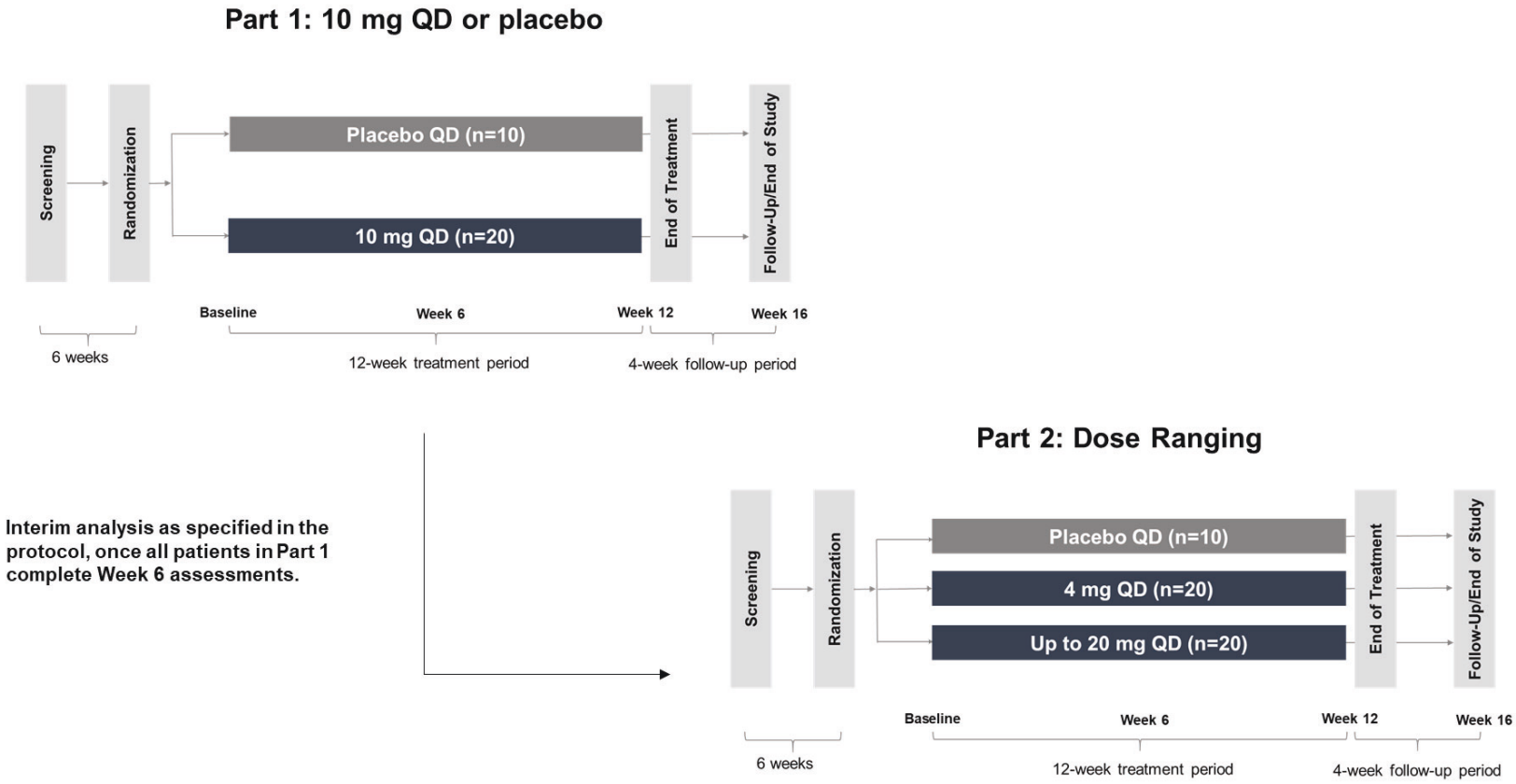
Approximately 80 patients will be randomly assigned to treatment with TERN-201 capsule or matching placebo.

Patients who are randomized but do not receive study drug for any reason may be replaced. In addition, patients who discontinue treatment early for reasons other than safety (i.e., withdrawal of consent, lost to follow-up, patient relocated, etc.) may also be replaced. Replacement patients will receive the same treatment assignment as the patient that discontinued treatment early.

Study Centers Planned:

Up to 15 centers in the United States.

1.2. Schema


Part 1: 10 mg QD or placebo
Screening
Randomization
Placebo QD (n=10)
10 mg QD (n=20)
End of Treatment
Follow-Up/End of Study
Baseline
Week 6
Week 12
Week 16
6 weeks
12-week treatment period
4-week follow-up period
Interim analysis as specified in the protocol, once all patients in Part 1 complete Week 6 assessments.
Part 2: Dose Ranging
Screening
Randomization
Placebo QD (n=10)
4 mg QD (n=20)
Up to 20 mg QD (n=20)
End of Treatment
Follow-Up/End of Study
Baseline
Week 6
Week 12
Week 16
6 weeks
12-week treatment period
4-week follow-up period

1.3. Schedule of Activities

	Screening	Treatment Period[a]						ET[b]	Follow-Up[c]	Notes
Visit	**Screening**	**Week 0**	**Week 2**	**Week 4**	**Week 6**	**Week 8**	**Week 12**		**Week 16**	
Study Day	**-42 to Day -1**	**Day 1**	**15**	**29**	**43**	**57**	**85**		**113**	Visit windows post-randomization through Week 12: ± 3 days from the specified study day. Visit window Week 16: 1 week prior/+2 days from the specified study day.
Procedures										
Written Informed Consent	X									Written informed consent may be obtained via telephone in accordance with Section 10.1.2. Screening may be initiated via telephone.
Patient Fasting	X	X	X	X	X	X	X	X	X	Patients must be in fasted state for at least 8 hours prior to blood collection and study drug administration, where applicable.
Randomization		X								
Review Inclusion and Exclusion Criteria	X	X								Recheck clinical status before randomization and first dose of study drug.
Demographics	X									Includes age, sex, and race/ethnicity.
Height and Weight	X	X	X	X	X	X	X	X	X	Height and weight are collected at Screening and will be used to calculate BMI for eligibility. Waist circumference is also measured at Screening. Only weight is collected on other days indicated.
Medical History	X	X								Includes details of illnesses and allergies, date(s) of onset, whether condition(s) is currently ongoing, and medication history, including alcohol use.

	Screening	Treatment Period[a]						ET[b]	Follow-Up[c]	Notes
Visit	**Screening**	**Week 0**	**Week 2**	**Week 4**	**Week 6**	**Week 8**	**Week 12**		**Week 16**	
Study Day	**-42 to Day -1**	**Day 1**	**15**	**29**	**43**	**57**	**85**		**113**	Visit windows post-randomization through Week 12: ± 3 days from the specified study day. Visit window Week 16: 1 week prior/+2 days from the specified study day.
Physical Examination	X	X	X	X	X	X	X	X	X	A complete physical examination will be performed at Screening and Week 16. A targeted physical examination will be performed at all other visits, as needed.
Vital Signs	X	X	X	X	X	X	X	X	X	Includes temperature, pulse rate, respiratory rate, and blood pressure.
Chemistry[d]	X	X	X	X	X	X	X	X	X	Specific analytes are listed in Appendix 1. ALT and AST stability may be evaluated prior to randomization per Section 5. Increased monitoring criteria for elevated ALT and/or AST above 2 × Baseline or above 5 × ULN for < 1 week is outlined in Appendix 3. Refer to Appendix 5 for the eGFR formula, to be calculated by central lab.
Hematology[d]	X	X	X	X	X	X	X	X	X	Specific analytes are listed in Appendix 1.
Coagulation[d]	X	X								Specific analytes are listed in Appendix 1. PT/INR will be tested at Screening, Week 0, and if significant abnormal liver function tests are observed.
Fasting Lipid Profile[d]		X			X		X	X		Specific analytes are listed in Appendix 1.
Serology	X									Includes HBsAg, anti-HCV, and anti-HIV.

	Screening	Treatment Period[a]						ET[b]	Follow-Up[c]	Notes
Visit	**Screening**	**Week 0**	**Week 2**	**Week 4**	**Week 6**	**Week 8**	**Week 12**		**Week 16**	
Study Day	**-42 to Day -1**	**Day 1**	**15**	**29**	**43**	**57**	**85**		**113**	Visit windows post-randomization through Week 12: ± 3 days from the specified study day. Visit window Week 16: 1 week prior/+2 days from the specified study day.
COVID-19 Assessment[d,e]	X	X			X		X			Screening and on-study COVID-19 assessments should be conducted in accordance with Appendix 8.
Serum pregnancy test[d]	X	X		X		X	X	X		WOCBP only.
Serum FSH	X									To confirm postmenopausal status, as outlined in Appendix 7.
Blood Alcohol Test	X									
Urinalysis[d]	X	X			X		X	X	X	Specific analytes are listed in Appendix 1. Microscopic examination is required if blood or protein is abnormal.
Urine Drug Screen[d]	X	X		X		X	X	X	X	
Total Urine Collection *(PK/PD Sub-Study only)*		X			X					Total urine collection from 0-8 hours post dose as specified in Appendix 2.
Intensive PK and PD Sampling *(PK/PD Sub-Study only)*		X			X		X			Intensive PK sampling will be performed pre-dose and 0.5, 1, 2, 4, 6, 8 and 24 hours after the first dose of study drug on Week 0/Day 1 and Week 6, and at pre-dose and 0.5, 1, 2, 4, 6, 8, 24, 48 and 72 hours after the last dose of study drug at Week 12. Refer to Appendix 2 for additional detail.

	Screening	Treatment Period[a]						ET[b]	Follow-Up[c]	Notes
Visit	**Screening**	**Week 0**	**Week 2**	**Week 4**	**Week 6**	**Week 8**	**Week 12**		**Week 16**	
Study Day	**-42 to Day -1**	**Day 1**	**15**	**29**	**43**	**57**	**85**		**113**	Visit windows post-randomization through Week 12: ± 3 days from the specified study day. Visit window Week 16: 1 week prior/+2 days from the specified study day.
Trough PK and PD Sampling[d]		X	X	X	X	X	X	X		Only one sample will be collected at each visit prior to drug administration on the visit day. Patients discontinuing the study at any time for any reason will have one sample collected at the ET visit. Refer to Appendix 2 for additional detail.
Baseline sVAP-1[f]		X								
NASH/Fibrosis Biomarkers[d]		X			X		X	X		Includes CK-18 (M30 and M65), PIIINP, TIMP-1, HA, PRO-C3, and C3M.
Inflammation Biomarkers[d]		X	X	X	X	X	X	X		Includes hs-CRP, IL-6, ICAM-1, and VCAM-1.
12-lead ECG	X	X			X		X			In addition to the scheduled timepoints, perform ad-hoc ECG in the instance of patient-reported symptoms considered potentially cardiac in nature such as chest pain/pressure, palpitations, dizziness, shortness of breath, or report of patient recently seeking medical care for such symptoms (e.g., emergency room visit); obtain cardiology consult based on the clinical judgement of the Investigator.

	Screening	Treatment Period[a]						ET[b]	Follow-Up[c]	Notes
Visit	**Screening**	**Week 0**	**Week 2**	**Week 4**	**Week 6**	**Week 8**	**Week 12**		**Week 16**	
Study Day	**-42 to Day -1**	**Day 1**	**15**	**29**	**43**	**57**	**85**		**113**	Visit windows post-randomization through Week 12: ± 3 days from the specified study day. Visit window Week 16: 1 week prior/+2 days from the specified study day.
Transient Elastography	X						X	X		A historical transient elastography report within 3 months of Screening may be used to determine eligibility for this study. See inclusion/exclusion criteria for details.
MRI cT1[g]	X				X		X	X		A Screening MRI cT1 may proceed on the basis of the initial ALT and AST levels at Screening, given all other eligibility criteria are met, but randomization should not occur prior to confirmation of ALT and AST stability, as necessary. An MRI cT1 should be performed at ET if the patient has had at least 4 weeks of dosing.
Dispense Study Drug[h]		X		X		X				Study drug will be assigned via the IWRS. Patients will be supplied with enough study capsules for 4-week use.
Drug Accountability			X	X	X	X	X	X		
Lifestyle Counseling		X	X	X	X	X	X	X	X	Guidance should be provided on key elements of a healthy lifestyle at each visit including diet, exercise, weight loss, and avoidance of alcohol per standard of care management for a NASH patient population.

	Screening	Treatment Period[a]						ET[b]	Follow-Up[c]	Notes
Visit	**Screening**	**Week 0**	**Week 2**	**Week 4**	**Week 6**	**Week 8**	**Week 12**		**Week 16**	
Study Day	**-42 to Day -1**	**Day 1**	**15**	**29**	**43**	**57**	**85**		**113**	Visit windows post-randomization through Week 12: ± 3 days from the specified study day. Visit window Week 16: 1 week prior/+2 days from the specified study day.
Adverse Events Review	X	←==========→						X	X	After informed consent but prior to initiation of study drug, all AEs and SAEs related to protocol-mandated procedures should be reported. All AEs and SAEs, regardless of cause or relationship, will be collected from the start of study drug through the Follow-Up Period.
Concomitant Medications Review		←==========→						X	X	
Take Study Drug Capsules		←==========→								Patients must be in fasted state for at least 8 hours prior to study drug administration. At all study visits, study drug administration will be observed at the study site. Patients should be instructed to hold their dose of study drug on visit days until all visit procedures have been completed. On all other days, patients will self-administer the study drug orally once daily in the morning on an empty stomach, after an 8 hour fast.

a. If a patient requires home quarantine due to SARS-CoV-2 infection or exposure, or due to COVID-19 symptoms or other associated concern with attending an in-person study visit, home health care visits may be conducted to continue study assessments in the patient's home where feasible, and/or remote visits via telephone, telemedicine, or other appropriate virtual communication may be substituted for a visit to the site.

b. Patients discontinuing the study at any time for any reason prior to Week 12 (Early Termination) should complete the ET visit as soon as feasible and return for a Follow-Up 4 weeks (-1 week /+2 days) after the last dose of study drug.
c. The Follow-Up may take place at Week 16 (-1 week /+2 days) or 4 weeks (-1 week /+2 days) after the last dose of study drug if patients discontinue the study at any time for any reason prior to Week 12 (Early Termination).
d. Samples collected during the treatment period should be collected pre-dose.
e. In the event of symptoms suggestive of COVID-19, ad hoc testing (including molecular test such as PCR or viral antigen serology, and/or antibody testing), may be completed at Investigator's discretion.
f. sVAP-1 will be collected along with trough PD sampling.
g. MRI-PDFF data will be collected along with MRI cT1.
h. If a patient is required to be quarantined due to active infection of COVID-19 or exposure to COVID-19, or is otherwise unable to visit the site due COVID-19, study drug may be mailed to the patient or made available via another appropriate mechanism (i.e., curbside pickup, etc.). See Section 6.8.1 for additional guidance in the event of hospitalization for COVID-19.

Abbreviations: AE = adverse event; ALT = alanine transaminase; AST = aspartate transaminase; BMI = body mass index; CK-18 = cytokeratin-18; COVID-19 = coronavirus disease 2019; cT1 = corrected T1; ECG = electrocardiogram; ET = early termination; eGFR = estimated glomerular filtration rate;; FSH = follicle stimulating hormone; HA = hyaluronic acid; HbA1c = hemoglobin A1c; HBsAg = hepatitis B surface antigen; HCV = hepatitis C virus; HIV = human immunodeficiency virus; hsCRP = high sensitivity C-reactive protein; ICAM-1= intercellular adhesion molecule 1; INR = international normalized ratio; IWRS = interactive web response system; MRI = magnetic resonance imaging; MRI-PDFF = MRI-proton density fat fraction; PCR = polymerase chain reaction; PD = pharmacodynamics; PIIINP = Procollagen III N-Terminal Propeptide; PK = pharmacokinetics; PRO-C3 = pro-peptide of type III collagen; ULN = upper limit of normal; SAE = serious adverse event; sVAP-1= soluble vascular adhesion protein-1; TIMP-1 = tissue inhibitor of metalloproteinases-1; VCAM-1 = vascular cell adhesion molecule 1; WOCBP = women of childbearing potential.

2. Introduction

2.1. Overview of NASH and Role of VAP-1/SSAO in Disease

Terns is developing TERN-201, an investigational, potent, and highly selective, irreversible covalent inhibitor of human vascular adhesion protein-1(VAP-1)/semicarbazide-sensitive amine oxidase for the treatment of patients with non-alcoholic steatohepatitis (NASH).

NASH is an advanced form of non-alcoholic fatty liver disease (NAFLD), the most common cause of chronic liver disease in North America (Chalasani 2018). NASH is characterized by the presence of hepatic inflammation and hepatocellular ballooning, with or without fibrosis. NASH is a progressive condition that can lead to cirrhosis, decompensated liver disease, and increased risk for hepatic carcinoma and liver-related mortality (Ekstedt 2015). Currently, there are no approved therapies for the treatment of NASH. With an aging population and the emergence of overlapping epidemics of obesity, diabetes, and dyslipidemia/metabolic syndrome, NAFLD and NASH have increased greatly in prevalence (Andronescu 2018), posing a significant healthcare challenge.

VAP-1/SSAO is a cellular adhesion protein and ectoenzyme expressed on the vascular endothelium that has long been recognized as a mediator of leukocyte adhesion and extravasation in the setting of inflammation (Salmi 2019). The enzymatic activity of VAP-1 further contributes to inflammation and oxidative stress by converting primary amines to aldehyde, ammonia, and hydrogen peroxide. VAP-1 levels are increased in the liver tissue and blood of patients with NASH and circulating VAP-1, termed soluble VAP-1 (sVAP-1), is independently associated with fibrosis stage (Weston 2015). Genetic and pharmacology studies indicate VAP-1 deficiency or inhibition attenuate steatosis, inflammation, and fibrosis in NASH models. VAP-1 deficiency attenuates carbon tetrachloride (CCl4)-induced hepatic fibrosis and VAP-1 knockout mice exhibit reduced hepatic steatosis and fibrosis when fed a western lifestyle diet. Moreover, treatment with a VAP-1 antibody reduces inflammation, steatosis, and fibrosis in a methionine choline–deficient diet mouse model of NASH (Weston 2015).

Based on these observations, VAP-1 inhibition is anticipated to reduce inflammation and fibrosis in NASH patients. This novel mechanism provides a potential opportunity to treat NASH, a disease with significant unmet medical needs.

Of note, historically, VAP-1 has also been referred to as SSAO due to its sensitivity to inhibition by semicarbazide, a property that distinguishes it from flavin adenine dinucleotide (FAD)-containing monoamine oxidases (e.g., MAO-A and MAO-B) (Smith 1998). In this document, the

terms VAP-1 and SSAO (or VAP-1/SSAO) are used interchangeably. Additional information on nomenclature is available in the Investigator's Brochure.

2.2. VAP-1/SSAO Inhibition in NASH and TERN-201 Background

VAP-1 has been identified as a target for NASH due to the inflammatory component of NASH pathogenesis, association of increased VAP-1 levels in NASH patients, and nonclinical studies supporting potential benefit in NASH from VAP-1/SSAO deficiency or suppression (Section 2.1). One other VAP-1/SSAO inhibitor has been studied in NASH patients (ClinicalTrials.gov Identifier: NCT03166735). Pharmaxis (Frenchs Forest, AUS) identified an oral VAP-1 inhibitor, BI 1467335 (formerly PXS-4728A), which was advanced into clinical development for NASH by Boehringer Ingelheim. Preliminary data suggest dose-dependent reductions in alanine aminotransferase (ALT) and CK-18 with 12-weeks of treatment with BI 1467335, and an overall reassuring safety profile in NASH patients (ClinicalTrials.gov Identifier: NCT03166735). In addition to its activity against VAP-1, BI 1467335 also inhibits monoamine oxidase B (MAO-B) (Schilter 2015), albeit to a lesser extent, with potential implications for drug-drug interactions associated with monoamine oxidase inhibition. In addition to NASH, VAP-1 inhibitors have also been explored for other indications including kidney disease. In a phase 2 study (ALBUM, ClinicalTrials.gov Identifier: NCT02358096), the VAP-1 inhibitor ASP8232 (Astellas Pharma) was effective at reducing albuminuria in patients with diabetic kidney disease, suggesting the possibility of benefit outside of liver, perhaps attributable to endothelial effects (de Zeeuw 2018).

TERN-201 is a potent, irreversible, highly specific inhibitor of VAP-1/SSAO, formulated for oral administration in a capsule form. Nonclinical studies have demonstrated that TERN-201 is efficacious in models of liver fibrosis and NASH, and does not have activity against monoamine oxidase A or B.

TERN-201 has been evaluated in an extensive nonclinical program, including PK, safety pharmacology, genotoxicity, and repeat dose toxicology/toxicokinetic studies of up to 13 weeks in duration. TERN-201 has also been evaluated in a first-in-human (FIH) study (N=61), where it was found to be overall safe and well-tolerated.

Below is a brief summary of these studies. Detailed results are available in the TERN-201 Investigator's Brochure.

2.2.1. Summary of Nonclinical Studies

[redacted]

[redacted]

2.2.2. Clinical Studies of TERN-201

The initial, FIH Phase 1 clinical study, TERN201-US-A101, was a double-blind, randomized, placebo-controlled study to investigate the safety, tolerability, pharmacokinetics (PK), and pharmacodynamics (PD) of single and multiple ascending oral doses of TERN-201 in healthy participants. The study was also designed to investigate the effect of food (high-fat/high-calorie meal) on the PK of TERN-201. Study TERN201-US-A101 was comprised of 3 parts. In Part A, 4 single-ascending dose (SAD) cohorts (8 participants each [6 TERN-201, 2 placebo]) were completed, in which participants received oral TERN-201 or matching placebo doses of 1, 3, 6, or 10 mg. A fifth SAD cohort (20 mg) was planned but not enrolled due to public health restrictions resulting from the Coronavirus Disease 2019 (COVID-19) pandemic. In Part B, 3 multiple-ascending dose (MAD) cohorts (8 participants each [6 TERN-201, 2 placebo]) were completed, in which participants received oral TERN-201 or matching placebo daily doses of 1 mg for 7 days, 4 mg for 7 days, or 10 mg for 14 days. Part C, the Food Effect cohort, was initiated with 5 of the 16 planned participants enrolled; however, enrollment was discontinued early due to the -19 pandemic. The 5 participants enrolled in Part C received both doses of TERN-201 10 mg (single doses on Days 1 and 8, fed and fasted) as planned in the study protocol.

During the study, no safety or tolerability concerns were identified, and no predefined stopping criteria were met. All AEs were Grade 1 or 2 (National Cancer Institute [NCI] Common Terminology Criteria for Adverse Events [CTCAE] Version 5.0) in severity. All AEs in participants who received TERN-201 were reported to be mild in severity. With exception of mild contact dermatitis at the site of electrocardiogram (ECG) leads that was considered unrelated to study drug, and headache (2 participants), all AE types were isolated to a single participant. There were no serious AEs, deaths, or AEs that led to discontinuation of study drug

in any cohort. Laboratory, vital signs, and other safety assessments including EEG monitoring showed no notable findings across individual participants or cohorts.

Plasma exposures to TERN-201 were greater than dose proportional. TERN-201 was rapidly cleared from plasma. Steady state was achieved in the highest dose group (10 mg) after Day 7 of dosing. The half-life of TERN-201 increased with dose, suggesting saturable, target-mediated clearance.

Single and multiple doses of TERN-201 significantly suppressed plasma total amine oxidase activity at all doses studied. Using an exploratory assay to assess the effect of TERN-201 on VAP-1/SSAO-specific amine oxidase activity in the plasma, near complete inhibition (>80% with 1 mg, > 90% with 10 mg) was observed after only a single dose on Day 1 (achieved within 4 hours after dosing) with sustained suppression over the dosing period in MAD cohorts. Dose-dependent increases in methylamine, an endogenous substrate of VAP-1/SSAO predicted to increase upon VAP-1/SSAO inhibition, were observed after the first dose of TERN-201 and continued to increase in a dose-dependent manner after multiple doses of TERN-201.

Based on the exploratory assessment on plasma PK of two TERN-201 metabolites, TRN-001021 and TRN-001744, the percentages of either metabolite AUC relative to the total TERN-201-related plasma AUC (sum of TERN-201, TRN-001021, and TRN-001744) were calculated. Median TRN-001021 AUC was <10% and 13.7% of the total plasma AUC associated with TERN-201 in the 4 mg and 10 mg groups, respectively. Median TRN-001744 AUC was 11.5% and <10% of the total plasma AUC associated with TERN-201 in the 4 mg and 10 mg groups, respectively.

Additional details on Study TERN201-US-A101 are available in the Investigator's Brochure.

2.3. Benefit/Risk Assessment

The protocol has been designed to minimize the risk to patients. Patients will be monitored to detect AEs during the study and will be followed appropriately to ensure resolution of AEs. Standard hematology, chemistry, urinalysis, lipid levels, and ECGs will be obtained and monitored for abnormalities. Prior to administration of a dose up to 20 mg TERN-201, available PK from the 10 mg cohort will be assessed to predict that projected exposures are below the limits noted above.

Taking into account the measures taken to minimize risk to patients in this study, the potential risks identified in association with TERN-201 are justified by the anticipated benefits that may be afforded to patients with NASH.

Please refer to the Investigator's Brochure for a summary of data on TERN-201 and guidance for Investigators.

3. Objectives and Endpoints

Primary Objective:

- To characterize the safety and tolerability of TERN-201 versus placebo for 12 weeks in non-cirrhotic presumed NASH patients, with a clinical or histological NASH diagnosis

Secondary Objectives:

- To assess the plasma and urine PK of TERN-201 for 12 weeks in non-cirrhotic presumed NASH patients
- To assess the PD effect of TERN-201 versus placebo for 12 weeks on plasma VAP-1/SSAO activity in non-cirrhotic presumed NASH patients

Exploratory Objectives:

- To assess the plasma and urine PK of TERN-201 metabolites (including TRN-001021 and TRN-001744) at steady state
- To assess the effect of TERN-201 versus placebo on imaging assessments and blood biomarkers of NASH activity
- To assess the effect of TERN-201 versus placebo on biomarkers of inflammation
- To explore the potential for TERN-201 to improve proteinuria due to endothelial effects
- To explore other PD markers, and overall exposure-response and dose-response relationship of TERN-201, as applicable
- To explore the exposure-response and dose-response relationship, as applicable, of TERN-201 and baseline patient characteristics such as soluble VAP-1 (sVAP-1), body mass index (BMI), diabetes mellitus, and others

Endpoints:

Primary Endpoint:

- Overall safety assessed by treatment emergent AEs (TEAEs), and treatment emergent clinical safety laboratory abnormalities

Secondary Endpoints:

- Plasma and urine PK parameters for TERN-201

- Percent change from baseline in plasma VAP-1/SSAO activity

Exploratory Endpoints:

- Plasma and urine PK parameters for TERN-201 metabolites (including TRN-001021 and TRN-001744)
- Change from baseline in corrected T1 (cT1) by magnetic resonance imaging (MRI)
- Change from baseline in liver fat content by magnetic resonance imaging-proton density fat fraction (MRI-PDFF)
- Change from baseline in stiffness by transient elastography
- Change from baseline in alanine aminotransferase (ALT)
- Change from baseline in gamma-glutamyl transpeptidase (GGT)
- Change from baseline in aspartate aminotransferase (AST)
- Change from baseline in NASH and fibrosis biomarkers including cytokeratin-18 (CK-18) (M30 and M65), procollagen III n-terminal propeptide (PIIINP), tissue inhibitor of metalloproteinases-1 (TIMP-1), hyaluronic acid (HA), pro-peptide of type III collagen (PRO-C3), and type III collagen (C3M). Other non-invasive tests for NASH fibrosis may also be assessed including the fibrosis-4 (FIB-4) index, enhanced liver fibrosis (ELF) test, NAFLD fibrosis score (NFS), and PRO-C3/C3M ratio.
- Change from baseline in inflammatory biomarkers including high sensitivity C-reactive protein (hs-CRP), interleukin-6 (IL-6), intercellular adhesion molecule-1 (ICAM-1), and vascular cell adhesion molecule-1 (VCAM-1)
- Change from baseline in estimated glomerular filtration rate (eGFR), urine protein including urine protein-to-creatinine ratio (UPCR), and urine albumin-to-creatinine ratio (UACR)
- Change from baseline in plasma methylamine levels (PD marker of VAP-1/SSAO inhibition)
- Exposure-response and dose-response relationship of TERN-201 over 12 weeks, as applicable
- Exposure-response and dose-response relationship, as applicable, of TERN-201 and baseline patient characteristics such as sVAP-1, BMI, diabetes mellitus, and others

4. Study Design

4.1. Overall Design

The study is a multi-center, randomized, double-blind, placebo-controlled, adaptive study.

Approximately 80 clinically or histologically diagnosed adult non-cirrhotic presumed NASH patients who meet study eligibility criteria will be enrolled and randomized at an overall ratio of 2:1 in up to 3 dose groups and placebo across 2 parts of the study.

Part 1

In Part 1, approximately 30 patients will receive 10 mg TERN-201 (n = 20) or matching placebo (n = 10) orally once daily, for 12 weeks. Part 2 may be enrolled based on an interim analysis, as follows:

In Part 1 of the study, approximately 12 randomized patients will take part in an intensive PK and PD collection after the first dose (Week 0/Day 1), at Week 6, and after the last dose of study drug (Week 12). Randomization will ensure approximately 8 patients in the TERN-201 group and approximately 4 patients in the placebo group are assigned to the PK/PD sub-study. Patients who are not participating in the PK/PD sub-study will have trough PK/PD sampling only.

An interim analysis will be performed after all patients in Part 1 have completed Week 6 assessments. Interim PK and PD data will be assessed. Blinded safety data will also be reviewed. Enrollment of cohorts to assess 4 mg and up to 20 mg TERN-201 may be initiated per the following criteria:

- TERN-201 4 mg:
    - If robust VAP-1/SSAO activity suppression is observed and available PK from Part 1 suggests that a lower dose may also possibly lead to robust VAP-1/SSAO activity suppression, enrollment in Part 2 with 4 mg TERN-201 may be initiated.
- TERN-201 up to 20 mg:
    - If safety data indicates 10 mg TERN-201 is overall safe and well-tolerated, and available PK from Part 1 predicts that targeted exposures for a dose up to 20 mg will be below an upper limit of 5400 ng•hr/mL for $AUC_{0\text{-}24hr}$ and 768 ng/mL for C_{max}, enrollment in Part 2 with a dose up to 20 mg TERN-201 may be initiated.

Part 2

In Part 2, if initiated, approximately 50 patients will receive 4 mg TERN-201 (n = 20), and/or up to 20 mg TERN-201 (n = 20), or matching placebo (n = 10) orally once daily, for 12 weeks.

In Part 2 of the study, approximately 15 randomized patients will take part in an intensive PK and PD collection after the first dose (Week 0/Day 1), at Week 6, and after the last dose of study drug (Week 12). Randomization will ensure approximately 6 patients at each TERN-201 dose level and approximately 3 patients in the placebo group are assigned to the PK/PD sub-study.

The total duration of study participation will be approximately 22 weeks, consisting of a 6-week Screening Period, a 12-week Treatment Period and a 4-week Follow-up Period.

4.2. Scientific Rationale for Study Design

Collectively, results from nonclinical studies and FIH study, TERN201-US-A101, support the development of TERN-201 as an orally administered VAP-1/SSAO inhibitor to reduce inflammation and fibrosis in the liver of patients with NASH. TERN-201 provides a promising potential treatment for NASH, a disease with significant unmet medical need. [redacted]

The initiation of Part 1 of the study will evaluate the highest dose studied in the FIH study (10 mg TERN-201), which was safe and well-tolerated and will allow for the PD effect of TERN-201 (e.g., inhibition of plasma VAP-1/SSAO activity) to be assessed in the NASH population. [redacted]

The placebo-controlled nature of the study will allow for a control group to characterize the safety and preliminary efficacy of TERN-201 in a NASH population. Given the efficacy of TERN-201 has not yet been confirmed, there is no clear detriment to patients who may be randomized to receive placebo rather than active treatment in this study.

The study will enroll a non-cirrhotic presumed NASH population based on clinical characteristics and imaging (without a requirement for liver biopsy), to characterize safety and efficacy in this population. While there is not an expected risk of neurological toxicity at the clinical doses proposed based nonclinical toxicity studies and the FIH study, patients with a history of seizures and select other co-morbidities will be excluded to avoid interference from disease processes in the safety assessment of TERN-201 in this study.

4.3. Justification for Dose

Doses for this study were based on results from the FIH Phase 1 study, TERN201-US-A101, which evaluated 4 SAD cohorts of TERN-201 or matching placebo at 1 mg, 3 mg, 6 mg, or 10 mg, and 3 MAD cohorts of TERN-201 or matching placebo at 1 mg for 7 days, 4 mg for 7 days, or 10 mg for 14 days.

In the FIH study, single or multiple doses of TERN-201 resulted in rapid inhibition of plasma amine oxidase activity, with sustained inhibition during 14 days of dosing. TERN-201 demonstrated a favorable safety profile and was overall well-tolerated at all doses studied (Section 2.2.2).

Part 1 of this study assesses 10 mg of TERN-201, the highest dose studied in the FIH study. In the FIH study, this dose led to >90% suppression of plasma VAP-1/SSAO-specific amine oxidase activity in healthy participants. NASH patients are expected to have a higher baseline level of VAP-1, and thus the PD effect of TERN-201 in NASH patients may differ from healthy participants. A higher dose of up to 20 mg may be enrolled based on assessment of safety and PK with the 10 mg dose, and a lower dose of 4 mg may be enrolled based on observation of a robust PD effect of TERN-201 on plasma VAP-1/SSAO activity in the 10 mg cohort, thus minimizing the number of patients exposed until the PK and PD effects of TERN-201 can be confirmed in Part 1 of the study.

Toxicity and safety pharmacology studies support starting with the 10 mg dose and enrolling a higher dose up to 20 mg. [redacted]

Additional details on available data from Study TERN201-US-A101 are provided in the TERN-201 Investigator's Brochure.

5. Study Population

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1. Inclusion Criteria

Patients are eligible to be included in the study only if all of the following criteria apply at Screening:

1. Must be 18 to 75 years of age inclusive, at the time of signing the informed consent

2. Male or female, willing to follow contraception requirements defined by study protocol (Appendix 7); female patients of childbearing potential must also have negative serum pregnancy test, not be breastfeeding, and not plan to become pregnant during the study or within 30 days after last dose of study drug

3. Overweight or obese with a BMI ≥ 25 kg/m^2

4. NASH by clinical diagnosis or biopsy as follows:
    a. For clinical diagnosis:
        i. Step 1: Liver stiffness measured by transient elastography of 6.5 - 21 kPa and controlled attenuation parameter (CAP) > 280 dB/m within 3 months prior to Screening (if results available within this timeframe, assessment does not need to be repeated at Screening).
        ii. Step 2: Patients meeting these and all other eligibility criteria will undergo MRI cT1 and must have a cT1 value > 800 ms for randomization.
    b. For biopsy diagnosis:
        i. Step 1: Fibrotic NASH (NASH CRN F1, F2, or F3) without cirrhosis diagnosed by biopsy within 2 years prior to randomization, with no subsequent treatment for NASH and stable weight (< 5% weight loss) since the time of the biopsy. Results from a previous study end of treatment biopsy are permissible if drug was deemed non-therapeutic or patient received placebo.
        ii. Step 2: Patients meeting these and all other eligibility criteria will undergo MRI cT1 and must have a cT1 value > 800 ms for randomization.

5. All patients must have:
    - ALT ≥ 43 U/L for men and ≥ 28 U/L for women
    - MRI-cT1 liver inflammation > 800 ms

6. Capable of giving signed informed consent as described in Section 10.1.2 which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol

5.2. Exclusion Criteria

Patients are excluded from the study if any of the following criteria apply at Screening:

Medical Conditions

1. History or clinical evidence of chronic liver diseases other than NAFLD or NASH including but not limited to:

    - Active hepatitis B virus (HBV) infection defined as positive HBV surface antigen at screening
    - Active hepatitis C virus (HCV) infection defined as positive HCV antibody (anti-HCV) and HCV ribonucleic acid (RNA). Patients with anti-HCV but negative HCV RNA will be eligible for participation if HCV RNA has been negative for at least 1 year.
    - Autoimmune liver disease
    - Primary biliary cirrhosis
    - Primary sclerosing cholangitis
    - Wilson's disease (history should include normal serum ceruloplasmin and 24-hour urinary copper)
    - Gilbert's syndrome
    - Hemochromatosis or other iron overload
    - Alpha-1-antitrypsin (AAT) deficiency (history should include normal AAT genotype and serum AAT level)
    - Alcoholic liver disease
    - Prior known drug-induced hepatotoxicity
    - Known bile duct obstruction
    - Suspected or proven liver cancer

2. History or clinical evidence of cirrhosis, hepatic decompensation, or other severe liver impairment, including ascites, hepatic encephalopathy, and variceal bleeding

3. History of liver transplant, or current placement on a liver transplant list

4. ALT or AST > 5 × upper limit of normal (ULN)

5. Unstable elevated ALT or AST. Patients with ALT or AST > 60 IU/L must have evidence of a stable ALT and AST over at least a 2-week time period prior to randomization as evidenced by one of the following:

- Comparison to prior ALT and AST (historical values) obtained within 2-12 weeks prior to the Screening visit: Screening ALT and AST values should be ≤ 30% higher than a documented prior result, OR
- Repeat ALT and AST values at least 2 weeks after the Screening visit: Repeat ALT and AST should be ≤ 30% higher than the values from the Screening visit, and the repeat values must be ≤ 5 × ULN
- If the Investigator has clinical suspicion for acute liver injury in a patient for other reasons, the patient should be excluded after discussion with the Medical Monitor.
- The MRI cT1 may proceed on the basis of the initial ALT and AST values at Screening, given all other eligibility criteria are met, but randomization should not occur prior to confirmation of ALT and AST stability, as necessary.

6. Total bilirubin > 1.2 mg/dL

7. Albumin < 3.3 g/dL

8. International normalized ratio (INR) > 1.3

9. Alkaline phosphatase (ALP) > 159 IU/L

10. Platelet count < 150,000 /mm^3

11. eGFR < 60 mL/min/1.73m^2

12. Weight loss of > 5% total body weight within 3 months prior to Screening

13. History of a malignancy within 2 years of Screening, with the following exceptions:

    a) Adequately treated carcinoma in situ of the cervix

    b) Adequately treated basal or squamous cell cancer or other localized non-melanoma skin cancer

14. Uncontrolled diabetes with hemoglobin A1c (HbA1c) > 9.5% or actively undergoing anti-diabetes medication titration (see Exclusions 35, 36, and 39 for additional details). Note: Patients with or without diabetes may be enrolled provided all eligibility criteria are met.

15. Average weekly alcohol consumption of > 21 standard drinks for males and > 14 standard drinks for females over a period of more than 3 consecutive months in the year prior to Screening. Remote history of alcoholism with abstinence > 12 months prior to Screening and no history of alcoholic liver disease is permissible.

Note: A standard drink is defined as 12 oz (360 ml) beer, 1.5 oz (45 ml) liquor, or 5 oz (150 ml) wine.

16. Illicit substance/chemical abuse in the 12 months prior to Screening
17. Cannabis use (tetrahydrocannabinol [THC] and cannabidiol [CBD]) within 14 days of randomization
18. Unwilling to abstain from excessive alcohol use (defined in #15 above), cannabis use, and illicit substance use during study participation
19. Positive for human immunodeficiency virus (HIV) infection
20. QTcF > 450 ms for males, > 470 ms for females
21. Unstable cardiovascular disease defined as myocardial infarction, unstable angina, percutaneous intervention, coronary artery bypass graft, or stroke within 6 months prior to randomization
22. New York Heart Association class III or IV heart failure, or know left ventricular ejection fraction < 30%
23. Uncontrolled hypertension defined as systolic blood pressure > 160 mmHg or a diastolic blood pressure > 100 mmHg (treated or untreated) on at least two occasions more than 10 minutes apart
24. History of hypotension including orthostatic or postprandial hypotension
25. History of seizure disorder
26. History of known or suspected serotonin syndrome
27. Schizophrenia or bipolar disorder
28. Parkinson's disease
29. Known or suspected pheochromocytoma
30. Known allergy to study drug
31. Clinically significant multiple or severe drug allergies, or severe post-treatment hypersensitivity reactions
32. Laboratory or clinical evidence of current infection with Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), i.e., COVID-19

33. Presence of any condition that could, in the opinion of the Investigator, compromise the patient's ability to participate in the study

Prior Therapy

34. Use within 6 months prior to Screening: Treatment with monoamine oxidase inhibitors including but not limited to isoniazid, linezolid, methylene blue, tranylcypromine, isorboxazid, phenelzine, selegiline, rasagiline, safinamide; these therapies are also prohibited from randomization through end of study follow-up per Section 6.6

35. Use within 3 months prior to Screening: obeticholic acid, pioglitazone or other PPARγ agonists, or high-dose vitamin E (> 400 IU/day); these therapies are also prohibited from randomization through end of study follow-up per Section 6.6

36. Initiation or dose adjustment within 3 months prior to Screening (i.e., must be on stable dose for 3 months prior to Screening):
    - GLP-1 analogues, DPP-4 inhibitors, and SGLT2 inhibitors
    - Vitamin E ≤ 400 IU/day

37. Use within 3 months prior to Randomization:
    - Medications potentially impacting steatohepatitis, including but not limited to systemic corticosteroids (prednisone equivalent of > 10 mg/day for > 2 weeks), amiodarone, tamoxifen, and methotrexate; these therapies are also prohibited from randomization through end of study follow-up per Section 6.6

38. Initiation or dose titration within 3 months prior to Randomization:
    - Hormonal contraceptives

39. Initiation or dose titration within 2 months prior to Randomization (i.e., must be on stable dose for 2 months prior to Randomization):
    - Metformin and other antidiabetic drugs not described above.

40. Use within 2 weeks prior to Randomization:
    - Oral creatine supplementation; this is also prohibited from randomization through end of study follow-up per Section 6.6
    - Vaccination for influenza, COVID-19, or other routine vaccinations
    - Potent CYP3A inducers or inhibitors; these therapies are also prohibited from randomization through end of study follow-up per Section 6.6

Prior Clinical Study Experience

41. Participation in another clinical trial within 3 months or 5 half-lives of the other investigational agent (whichever is longer) prior to randomization. Patients who can demonstrate they did not receive active drug or who received an investigational treatment that was deemed non-therapeutic during clinical trial participation are eligible for enrollment

5.3. Lifestyle Considerations

Contraceptives or other means of birth control are required for patients of childbearing potential during study participation (see Appendix 7).

5.3.1. Lifestyle Counseling

Guidance should be provided on key elements of a healthy lifestyle at each visit including diet, exercise, weight loss, and avoidance of alcohol per standard of care management for this patient population.

5.3.2. Meals and Dietary Restrictions

Patients should arrive at the clinic fasting for assessments and study drug administration as defined in the Schedule of Activities (Section 1.3). This includes at least an 8-hour fast prior to the visit, during which food and drink is restricted. Water is allowed ad libitum.

On all other days, patients will self-administer the study drug orally once daily in the morning on an empty stomach, after an 8-hour fast.

Patients participating in the PK/PD sub-study at Week 0/Day 1, Week 6, and Week 12 should arrive at the clinic fasting (an 8-hour fast prior to the visit) and restrict food and drink until 2 hours post-dose. Food and drink may resume after this timepoint. Patients participating in the PK/PD sub-study do not need to be fasting for blood collection at 24, 48, or 72 hours post last dose of study drug at Week 12.

5.3.3. Alcohol, Cannabis, and Illicit Drug Use

Patients must agree to not consume > 21 standard drinks per week for males and > 14 standard drinks per week for females. A standard drink is defined as 12 oz (360 ml) beer, 1.5 oz (45 ml) liquor, or 5 oz (150 ml) wine.

Patients must abstain from THC (cannabis) and illicit drug use during study participation.

Patients must abstain from CBD use during study participation. Short term topical CBD use (< 14 days) is acceptable.

5.4. Screen Failures

Screen failures are defined as patients who consent to participate in the clinical study but are not subsequently randomized. A minimal set of screen failure information is required and will be documented to ensure transparent reporting of screen failure patients to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any serious adverse event (SAE).

An otherwise eligible patient who is completing a vaccination series prior to enrollment may have the Screening window extended to allow for vaccination completion; laboratory assessments to confirm eligibility should be repeated if the Screening window has been exceeded. An otherwise eligible patient who screen fails due to SARS-CoV-2 testing or clinical status may re-screen at the discretion of the Investigator once SARS-CoV-2 infection has resolved. Any other requests for re-screening must be discussed with the Sponsor.

6. Study Drug

Study drug is defined as any investigational intervention(s), marketed product(s), or placebo intended to be administered to a study patient according to the study protocol.

6.1. Study Drug(s) Administered

Investigational Medicinal Product	TERN-201 capsules	Placebo-to-match (identical in shape, size, appearance, and color to TERN-201 capsules)
Type	Drug	Drug
Dose Formulation	Capsule	Capsule
Unit Dose Strength(s)	1, 3, or 10 mg per capsule	Matching placebo per capsule
Route of Administration	Oral	Oral
Use	Experimental	Placebo
IMP/NIMP	IMP	IMP
Sourcing	Provided centrally by the Sponsor	Provided centrally by the Sponsor
Packaging and Labeling	Study drug will be provided in a labeled carton that contains HDPE bottle(s). In Part 1, each carton will contain one bottle for 4-week usage. In Part 2, each carton will contain two bottles for 4-week usage. Each bottle will be labeled as required per country requirements.	Study drug will be provided in a labeled carton that contains HDPE bottle(s). In Part 1, each carton will contain one bottle for 4-week usage. In Part 2, each carton will contain two bottles for 4-week usage. Each bottle will be labeled as required per country requirements.

Abbreviations: HDPE = High-density polyethylene; IMP = investigational medicinal product; NIMP = non investigational medicinal product

6.2. Study Drug Administration

Patients will be instructed to take capsules as shown in Table 1.

Table 1 Study Drug by Dose Group

Dose Group	TERN-201 Capsules	Placebo-to-Match
Part 1 – 10 mg	One 10-mg capsule QD	One placebo capsule QD
Part 2 – 4 mg	One 1-mg capsule and one 3 mg capsule QD	Two placebo capsules QD
Part 2 – 20 mg	Two 10-mg capsules QD	Two placebo capsules QD

Abbreviations: QD = once per day

6.3. Preparation/Handling/Storage/Accountability

The Investigator or designee must provide acknowledgement of receipt of each shipment of study drug including appropriate temperature conditions have been maintained during transit for all study drug received and any discrepancies are reported and resolved before use of the study drug.

Only patients enrolled in the study may receive study drug and only authorized site staff may supply or administer study drug. All study drug must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the Investigator and authorized site staff.

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

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

6.4. Measures to Minimize Bias: Randomization and Blinding

Patients will be randomized to TERN-201 or placebo using an Interactive Web Response System (IWRS). Before the study is initiated, the log-in information and directions for the IWRS will be provided to each site.

Approximately 80 patients will be enrolled in this study. In Part 1, approximately 30 patients will be randomized at a ratio of 2:1 to receive 10 mg TERN-201 (n = 20) or matching placebo (n = 10). In Part 2, if initiated, approximately 50 patients will be randomized at a ratio of 2:1 to receive 4 mg TERN-201 (n = 20), and/or 20 mg TERN-201 (n = 20), or matching placebo (n = 10). Randomization will be stratified by Screening MRI cT1 values ≤ 900 ms versus > 900 ms.

In Part 1 of the study, approximately 12 randomized patients will take part in an intensive PK and PD collection after the first dose and after the last dose of study drug. Randomization will ensure approximately 6 patients in the TERN-201 group and approximately 6 patients in the placebo group are assigned to the PK/PD sub-study. Patients who are not participating in the PK/PD sub-study will have trough PK/PD sampling only.

In Part 2 of the study, approximately 15 randomized patients will take part in an intensive PK and PD collection after the first dose and after the last dose of study drug. Randomization will ensure approximately 6 patients at each TERN-201 dose level and approximately 3 patients in the placebo group are assigned to the PK/PD sub-study. Patients who are not participating in the PK/PD sub-study will have trough PK/PD sampling only.

Investigators, patients, all study personnel, and the Sponsor will remain blinded to each patient's assigned dose group throughout the course of the study, unless otherwise specified in Section 6.4.1. Study drug will be dispensed at the study visits as summarized in Schedule of Activities. Returned study drug should not be re-dispensed to patients.

A planned interim analysis will be conducted after all patients in Part 1 have completed Week 6 assessments, and an administrative interim analysis may be conducted after the completion of Part 1 of the study. For these analyses, the study team will be blinded at the individual patient level, with designated personnel responsible for producing the summary results. The details will be addressed in a separate plan.

6.4.1. Unblinding

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

Any unblinding of Sponsor personnel for expedited reporting of suspected unexpected serious adverse reactions (SUSARs) or other reasons including planned interim analyses will be addressed in a separate plan.

6.4.2. Patient Enrollment and Study Drug Assignment

It is the responsibility of the Investigator to ensure that patient eligibility is confirmed prior to randomization. Documentation of the personally signed and dated informed consent of each patient, using the study-specific ICF, is required before initiating the Screening Period.

After written informed consent has been obtained, the patient's identification number will be obtained from the IWRS. Once eligibility to participate has been established, the randomized treatment assignment will be obtained from the IWRS.

6.5. Study Drug Compliance

Patients will be dispensed study during their study visits and will self-administer study drug at home. Patients must be in fasted state for at least 8 hours prior to study drug administration. At all study visits, study drug administration will be observed at the study site. Patients should be instructed to hold their dose of study drug on visit days until all visit procedures have been completed. On all other days, patients will self-administer the study drug orally once daily in the morning on an empty stomach, after an 8 hour fast.

Compliance will be assessed by direct questioning and counting returned capsules during the study visits and documented in the source documents and electronic case report form (eCRF). Deviation(s) from the prescribed dosage regimen should be recorded in the eCRF.

If a patient is required to be quarantined due to active infection of COVID-19 or exposure to COVID-19, or is otherwise unable to visit the site due to COVID-19, study drug may be mailed to the patient or made available via another appropriate mechanism (i.e., curbside pickup, etc).

Patients will be asked to maintain records of self-administered drug on non-study visit days. A record of the number of study drug capsules dispensed to and taken by each patient must be maintained and reconciled with study drug and compliance records at the site. Study drug start and stop dates, including dates for delays will also be recorded in the eCRF.

6.6. Concomitant Therapy

Any medication or vaccine (including over-the-counter or prescription medicines, vitamins and/or herbal supplements) that the patient is receiving at the time of randomization or receives during the study must be recorded at each study visit along with:

- Reason for use
- Dates of administration including start and end dates
- Dosage information including dose and frequency

Medications prohibited from randomization through end of study follow-up:

- Monoamine oxidase inhibitors including isoniazid, linezolid, methylene blue, tranylcypromine, isorboxazid, phenelzine, selegiline, rasagiline, safinamide
- Medications with potential impact on NASH outcome, including obeticholic acid, pioglitazone or other PPARγ agonists, or high-dose vitamin E (> 400 IU/day)
    - Patients receiving ≤ 400 IU/day prior to study should not have dose adjustment on-study
- Medications potentially impacting steatohepatitis, including but not limited to systemic corticosteroids (prednisone equivalent of > 10 mg/day for > 2 weeks), amiodarone, tamoxifen, and methotrexate. Use of systemic corticosteroids for < 2 weeks within 3 months prior to randomization and while on study is allowed.
- Oral creatine supplementation
- Potent inducers or inhibitors of CYP3A; a noncomprehensive list for known CYP3A strong inducers and inhibitors is provided below:
    - Potent CYP3A inhibitors prohibited on study include but are not limited to: boceprevir, cobicistat, ritonavir, grapefruit juice, itraconazole, ketoconazole, posaconazole, telaprevir, telithromycin, troleandomycin, voriconazole, clarithromycin, idelalisib, nefazodone, and nelfinavir
    - Potent CYP3A inducers prohibited on study include but are not limited to: apalutamide, carbamazepine, enzalutamide, mitotane, phenytoin, rifampin, and St. John's wort
    - Patients who require initiation of potent CYP3A inducers and inhibitors during the study should discontinue study drug. For patients who subsequently discontinue prohibited medications, study drug administration may not be resumed unless discussed with the Medical Monitor. Patients who do not resume study drug should continue in the study for Follow-Up.
- Other investigational agents

All other medications not listed above are acceptable for use from randomization through end of study follow-up. The Medical Monitor should be contacted if there are any questions regarding concomitant therapy.

6.7. Dose Modifications

Dose modifications of study drug are not permitted.

6.8. Dose Interruptions

On all non-study visit days, patients will self-administer the study drug orally once daily in the morning, on an empty stomach, after an 8 hour fast. If a patient forgets to self-administer study drug in the morning on a given day, the dose can be taken on the same day when the patient remembers, with the exception below:

- For patients participating in the PK/PD sub-study, drug must be self-administered the morning of the day prior to the Week 6 and Week 12 visits. If not, the visit should be re-scheduled for the following day.

If a patient forgets to self-administer study drug on a given day, it will be designated a missed dose. Dosing may continue orally once daily according to the protocol schedule after a missed dose.

If study drug is discontinued or suspended for safety reasons considered related to study drug, dosing should not be resumed without consultation with the Medical Monitor. Information on stopping study drug for patients due to safety/other reasons is detailed in Section 7.

6.8.1. Dose Interruptions due to COVID-19

If a patient requires home quarantine due to SARS-CoV-2 infection or exposure, or due to COVID-19 symptoms, the patient may continue study drug provided that appropriate safety follow-up is possible, and that hospitalization is not required. Home health care visits may be conducted to continue study assessments in the patient's home where feasible, and/or remote visits via telephone, telemedicine, or other appropriate virtual communication may be substituted for a visit to the site. Sites should discuss the mechanism for safety follow-up with the Medical Monitor.

If a patient has symptoms of COVID-19 requiring hospitalization, study drug must be discontinued during hospitalization. A case-by-case assessment of whether to resume study drug can be done upon discharge. Dosing should not be resumed without consultation with the Medical Monitor. The patient should be encouraged to remain in the study to be evaluated during the Follow-Up Period.

6.9. Intervention after the End of the Study

No further interventions are planned after the end of the study.

7. Discontinuation of Study Drug and Patient Discontinuation/Withdrawal

7.1. Discontinuation of Study Drug

Study drug must be discontinued for an individual patient in the following instances:

- If an AE of Grade 3 or above (National Cancer Institute (NCI) CTCAE 5.0) occurs and is considered related to study drug as judged by the Investigator per the guidance in Appendix 6
- Symptoms of COVID-19 requiring hospitalization
- Change in clinical status that, in the judgement of the Investigator compromises the patient's ability to continue treatment or is not considered to be in the patient's best interest
- Patient request to discontinue study drug for any reason
- Pregnancy during the study (refer to Appendix 7)
- Sponsor discretion
- Discontinuation of the study at the request of the Sponsor, a regulatory agency, or Institutional Review Board (IRB)/Independent Ethics Committee (IEC)

Resumption of study drug may be considered in discussion with the Medical Monitor and Sponsor.

If one of the following situations occurs and is considered related to the study drug without alternative etiology, study drug may be discontinued at the discretion of the Investigator and the Medical Monitor should be informed (with repeat test performed within 48-72 hours once initial abnormality is detected):

- ALT or AST > 8 × ULN
- ALT or AST > 5 × ULN for more than 1 week, confirmed with a repeat assessment
- ALT or AST > 2 × Baseline with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia > 5%
- ALT or AST > 2 × Baseline and total bilirubin > 2 × ULN or INR > 1.5 for more than 1 week, confirmed with a repeat assessment

In addition, Investigators may permanently discontinue study drug at their discretion due to patient non-compliance with study drug or study assessments.

If study drug is permanently discontinued, the patient will remain in the study to be evaluated during the Follow-Up Period. See the Schedule of Activities for data to be collected at the time of discontinuation of study drug and follow-up and for any further evaluations that need to be completed.

7.2. Patient Discontinuation/Withdrawal from the Study

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

Patients discontinuing the study at any time for any reason prior to Week 12 (Early Termination) should complete the early termination (ET) visit as soon as feasible and return for a Follow-Up approximately 4 weeks after the last dose of study drug. See the Schedule of Activities for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.

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

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

7.3. Lost to Follow up

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

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

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

Discontinuation of specific sites or of the study as a whole are addressed in Section 10.1.8.

8. Study Assessments and Procedures

Study procedures and their timing are summarized in the Schedule of Activities. Protocol waivers or exemptions are not allowed.

Adherence to the study design requirements, including those specified in the Schedule of Activities, is essential and required for study conduct.

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

The maximum amount of blood collected from each patient over the duration of the study is not expected to exceed 650 mL. Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

If a patient requires home quarantine due to SARS-CoV-2 infection or exposure, or due to COVID-19 symptoms or other associated concern with attending an in-person study visit; home health care visits may be conducted to continue study assessments in the patient's home where feasible, and/or remote visits via telephone, telemedicine, or other appropriate virtual communication may be substituted for a visit to the site.

8.1. Study Assessments

Planned time points for all safety assessments are provided in the Schedule of Activities.

8.1.1. Demographics

Demographic data includes age, sex, and race/ethnicity.

8.1.2. Height and Weight

Height and weight are collected at Screening and will be used to calculate BMI. Waist circumference is also measured at Screening. Only weight is collected on other days specified in the Schedule of Activities.

Waist (abdominal) circumference is measured with measuring-tape position as follows (National Heart, Lung, and Blood Institute 2000): The upper hip bone and the top of the right iliac crest should be located and measuring tape placed in a horizontal plane around the abdomen at the level of the iliac crest. The tape should be snug but should not compress the skin, and should be parallel to the floor, at the time of measurement. The measurement should be taken at the end of a normal expiration.

8.1.3. Medical History

Medical and surgical history, including details of illnesses and allergies, date(s) of onset, whether condition(s) is currently ongoing, and medication history, including alcohol use, will be collected for all patients at Screening.

8.1.4. Physical Examinations

A complete physical examination will include assessments of general appearance, cardiovascular, respiratory, abdomen, head and neck (including ears, eyes, nose, throat, and thyroid), lymph nodes, musculoskeletal systems, and neurological exam.

A targeted physical examination may be conducted to evaluate reported current or prior AEs, symptoms reported by the patient, or abnormal laboratory readouts.

Investigators should pay special attention to clinical signs related to previous serious illnesses.

8.1.5. Vital Signs

Temperature, pulse rate, respiratory rate, and blood pressure will be assessed and maintained in source documentation.

Blood pressure and pulse measurements will be assessed with a completely automated device. Manual techniques will be used only if an automated device is not available.

Blood pressure and pulse measurements should be preceded by at least 5 minutes of rest for the patient in a quiet setting without distractions (e.g., television, cell phones).

8.1.6. Electrocardiograms

Single 12-lead ECGs will be obtained as outlined in the Schedule of Activities using an ECG machine that automatically calculates the heart rate and measures PR, QRS, and QT intervals. QTc will be calculated using the formula outlined in Appendix 4.

An ad hoc ECG should be performed in the instance of patient-reported symptoms considered potentially cardiac in nature such as chest pain/pressure, palpitations, dizziness, shortness of breath, or report of patient recently seeking medical care for such symptoms (e.g., emergency room visit); cardiology consult should be obtained based on the clinical judgement of the Investigator.

The Investigator will review the ECGs for any clinically significant abnormalities.

8.1.7. Clinical Laboratory Assessments

See Appendix 1 for the list of clinical laboratory tests to be performed and the Schedule of Activities for the timing and frequency.

The Investigator must review the laboratory report, document this review, and record any AEs per the guidance in Appendix 6. The laboratory reports must be filed with the source documents.

Clinically significant laboratory shifts, or any clinically significant abnormalities considered possibly related to study drug in the opinion of the Investigator, should be repeated within 48-72 hours and followed to resolution or until stable.

All protocol-required laboratory assessments, as defined in Appendix 1, must be conducted in accordance with the laboratory manual and the Schedule of Activities.

8.1.7.1. Liver Function Tests

In order to be eligible for this study, patients must have an ALT ≥ 43 U/L for men or ≥ 28 U/L for women. ALT and AST stability may be evaluated prior to randomization per Section 5.

During the course of the study, liver function tests (LFTs) will be monitored per the Schedule of Activities. Refer to Appendix 1 for a list of tests to be performed, and to Appendix 3 for additional information on criteria for increased liver chemistry monitoring.

8.1.8. Transient Elastography and Controlled Attenuation Parameter

Liver stiffness will be assessed by vibration-controlled transient elastography (via FibroScan®) at Screening to determine study eligibility. If results from transient elastography measurement within 3 months of Screening are available, these values can be used to assess eligibility and do not need to be repeated.

The transient elastography requirement is intended to select for patients likely to have at least F1 fibrosis. The protocol excludes patients with cirrhosis based on medical history or clinical signs or symptoms (Exclusion criteria #2). Prior studies indicate variability in the ranges of liver stiffness measured by transient elastography in NASH patients with fibrosis or cirrhosis. In STELLAR-3, which enrolled patients with bridging fibrosis, median liver stiffness at baseline was approximately 13 kPa, with an interquartile range between 10 and 17 kPa (Harrison 2020). In STELLAR-4, which enrolled patients with cirrhosis, median liver stiffness at baseline was approximately 20-21 kPa, with an interquartile range between 14 and 30 kPa (Harrison 2020). The utility of transient elastography to diagnose cirrhosis in the setting of NASH also appears limited based on the low positive predictive value (PPV) of even relatively high kPa thresholds. For a threshold of 21 kPa, the upper limit for this study, the PPV for F4 fibrosis (i.e., cirrhosis) in the setting of NASH is 0.37 (which may be even lower in a population with low prevalence of

cirrhosis, such as one in which cirrhosis is excluded on clinical grounds), with a negative predictive value of 0.96 (Eddowes 2019). This threshold has a sensitivity of 0.59 and a specificity of 0.90 for a diagnosis of cirrhosis in the setting of NASH (Eddowes 2019).

CAP is an assessment of liver steatosis and is generally used to complement the assessment of liver stiffness by transient elastography for evidence of NASH (Eddowes 2019). CAP estimates the total ultrasonic attenuation (go-and-return path), expressed in dB/m, based on the postulate that fat affects ultrasound propagation. A CAP threshold of 274 dB/m has sensitivity of 0.9 and specificity of 0.6 for identification of liver steatosis of ≥ 5% (Eddowes 2019). The threshold of 280 dB/m was chosen to identify patients who are likely to have elevated liver steatosis, in conjunction with the other imaging assessments at screening, including cT1.

Patients who meet NASH entry criteria based on a liver biopsy (Inclusion Criteria #4) should still undergo transient elastography at Screening to enable assessment of change from baseline in stiffness by transient elastography.

Transient elastography will also be conducted at Week 12, and at ET.

8.1.9. Magnetic Resonance Imaging: Correct T1 and Proton Density Fat Fraction

MRI cT1 will be conducted as specified in the Schedule of Activities.

MRI cT1 is a novel MRI-based quantitative metric for assessing a composite of liver inflammation and fibrosis. This assessment is based on multiparametric MRI data, measuring relaxation time that varies based on extracellular tissue fluid attributed to inflammation and fibrosis, with a longer relaxation time occurring with more extracellular fluid; the measurement is corrected for elevated iron content, which has an opposing effect on relaxation time (Banerjee 2014). Values for cT1 have been shown to correlate with the NAFLD Activity Score (NAS) and its components, as well as with degree of fibrosis by liver histology (Banerjee 2014; Dennis 2021). A population at low risk for NAFLD was found to have values ranging from 573 to 852 ms with a median of 666 ms and interquartile range from 643 to 694 ms, with high cT1 values (e.g. > 875 ms) having been shown to strongly predict liver-related clinical outcomes (e.g., hepatic encephalopathy, variceal bleeding, ascites, death) (Mojtahed 2019). In conjunction with other screening assessments, a threshold of 800 ms will enrich for a NASH population with fibrosis; this threshold has a sensitivity of 86% and a specificity of 93% for identifying patients with ≥ F1 fibrosis (Banerjee 2014). Stratification for values > 900 ms will ensure a balance between higher vs moderate baseline values between treatment groups.

An MRI cT1 may proceed on the basis of the initial screening ALT and AST values, given all other eligibility criteria are met, but randomization should not occur prior to confirmation of ALT and AST stability as necessary, per Section 5.

An MRI cT1 should be performed at ET if the patient has had at least 4 weeks of dosing.

The images will be analyzed by a central reader.

MRI-PDFF quantifies the relative amount of water vs fat in a tissue bases on signals from proton groups that vary depending on tissue cell type (Caussy 2018). PDFF is expressed as a percentage (range from 0-100%) representing the ratio of density of mobile protons from triglycerides relative to total triglyceride and water mobile proton density (although there are also triglyceride elements that are not visible by magnetic resonance and do not contribute to PDFF determination). In the liver, PDFF correlates with histological assessment of hepatic steatosis, and PDFF has been advanced as a measure of liver fat content to assess treatment response in NASH studies (Caussy 2018). PDFF values correlate with NAS score on liver histology, with a strong correlation with steatosis ($rs = 0.68$, $p < 0.001$) (Dennis 2021). A PDFF threshold of ≥ 5% generally reflects abnormal steatosis as seen in NAFLD or NASH (Szczepaniak 2005; Tang 2013). PDFF and cT1 values have been shown to be strongly correlated with each other in NASH patients ($rs = 0.66$, $p < 0.001$) (Dennis 2021), but it is not yet established how values with these modalities may change in response to anti-inflammatory therapies such as TERN-201. MRI-PDFF data will be collected along with MRI cT1.

8.2. Pharmacokinetics

Plasma samples will be collected for measurement of plasma concentrations of study drug and metabolites as specified in the Schedule of Activities and Appendix 2.

Urine samples will be collected for measurement of urine concentrations of study drug and metabolites as specified in the Schedule of Activities and Appendix 2.

Patients in the PK/PD sub-study will undergo intensive and trough PK sample collection as specified in the Schedule of Activities and Appendix 2.

Patients who are not participating in the PK/PD sub-study will undergo trough PK sampling only, as specified in the Schedule of Activities and Appendix 2.

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

Samples will be used to evaluate the PK of study drug and its metabolites. Samples collected for analyses of parent drug and metabolite concentration may also be used to evaluate safety or efficacy aspects related to concerns arising during or after the study.

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

In addition, any remaining (leftover) samples may be stored and used for optional exploratory future research on biomarker variants thought to play a role in NASH or to develop methods or assays related to the disease process or mechanism of action of the study drug. Patients must provide informed consent for optional exploratory future research as specified in Section 10.1.2.

8.3. Pharmacodynamics

Plasma samples will be collected for measurement of VAP-1/SSAO activity and methylamine levels as specified in the Schedule of Activities and Appendix 2.

Patients in the PK/PD sub-study will undergo intensive PD sample collection as specified in the Schedule of Activities and Appendix 2.

Patients who are not participating in the PK/PD sub-study will undergo trough PD sampling only as specified in the Schedule of Activities and Appendix 2.

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

Samples will be used to evaluate the pharmacodynamics of study drug. Samples collected for analyses of study drug pharmacodynamics may also be used to evaluate safety or efficacy aspects related to concerns arising during or after the study.

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

In addition, any remaining (leftover) samples may be stored and used for optional exploratory future research on biomarker variants thought to play a role in NASH or to develop methods or assays related to the disease process or mechanism of action of the study drug. Patients must provide informed consent for optional exploratory future research as specified in Section 10.1.2.

8.4. Biomarkers

Collection of samples for biomarkers related to NASH and inflammation are also part of this study. The following samples will be collected from all patients in this study as specified in the Schedule of Activities:

- Blood collection for the following NASH/fibrosis biomarkers: CK-18 (M30 and M65), PIIINP, TIMP-1, HA, PRO-C3, and C3M
- Blood collection for the following inflammation biomarkers: hs-CRP, IL-6, ICAM-1, and VCAM-1

The following exploratory fibrosis scores may also be calculated: FIB-4, enhanced liver fibrosis (ELF), and NAFLD. The PRO-C3/C3M ratio may be calculated.

In addition, any remaining (leftover) samples may be stored and used for optional exploratory future research on biomarker variants thought to play a role in NASH or to develop methods or assays related to the disease process or mechanism of action of the study drug. Patients must provide informed consent for optional exploratory future research as specified in Section 10.1.2.

8.5. Adverse Events and Serious Adverse Events

An AE is any untoward medical occurrence in a patient or clinical study patient, temporally associated with the use of study drug, whether or not considered related to the study drug.

An SAE is defined as any untoward medical occurrence that, at any dose, results in the following: death; is life threatening; requires in-patient hospitalization; results in persistent disability or incapacity; is a congenital anomaly or birth defect; or is a medically important event or reaction that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require medical or surgical intervention to prevent one of the other outcomes in the definition.

Events meeting the definition of an AE or SAE are defined in Appendix 6, including details on recording, reporting, and follow-up of AEs and SAEs, assessment of severity, and assessment of causality. AEs will be reported by the patient (or, when appropriate, by a caregiver, surrogate, or the patient's legally authorized representative) at every study visit.

The Investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following up AEs that are serious, considered related to the study drug or study procedures, or that caused the patient to discontinue the study drug (see Section 7).

8.5.1. Time Period and Frequency for Collecting AE and SAE Information

After informed consent but prior to initiation of study drug, the following types of events should be reported: all AEs and SAEs related to protocol-mandated procedures.

Medical occurrences (events considered not related to protocol-mandated procedures) that begin before the start of study drug but after obtaining informed consent will be recorded on the Medical History/Current Medical Conditions section of the eCRF, not the AE section.

All AEs and SAEs, regardless of cause or relationship, will be collected from the start of study drug through the Follow-Up Period, at every study visit, as specified in the Schedule of Activities (Section 1.3).

All SAEs will be recorded and reported to the Sponsor or designee immediately and under no circumstance should this exceed 24 hours, as indicated in Appendix 6. The Investigator will submit any updated SAE data to the Sponsor within 24 hours of it being available.

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

8.5.2. Method of Detecting AEs and SAEs

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Appendix 6.

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

8.5.3. Follow-up of AEs and SAEs

After the initial AE and/or SAE report, the Investigator is required to proactively follow each patient at subsequent visits/contacts. All SAEs will be followed until resolution, stabilization, the event is otherwise explained, or the patient is lost to follow-up (as defined in Section 7.3). Further information on follow-up procedures is provided in Appendix 6.

8.5.4. Regulatory Reporting Requirements for SAEs

Prompt notification by the Investigator to the Sponsor of a SAE is essential so that legal obligations and ethical responsibilities towards the safety of patients and the safety of a study drug under clinical investigation can be met.

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

Investigator safety reports must be prepared for SUSARs according to local regulatory requirements and sponsor policy and forwarded to Investigators as necessary.

An Investigator who receives an investigator safety report describing a SAE or other specific safety information (e.g., summary or listing of SAEs) from the sponsor will review and then file

it along with the Investigator's Brochure and will notify the IRB/IEC, if appropriate according to local requirements.

8.5.5. Pregnancy

Details of all pregnancies in female patients and female partners of male patients will be collected after the start of study drug until 30 days following the last dose of the study drug.

If a pregnancy is reported, the Investigator should inform the Sponsor within 24 hours of learning of the pregnancy and should follow the procedures outlined in Appendix 6 and Appendix 7.

Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs.

8.6. Treatment of Overdose

Overdose with this product has not been reported. Neither the effect of overdose nor antidote are known. The maximum amount of TERN-201 that can be safely administered in a single dose has not been determined. The highest single dose of TERN-201 capsules in clinical studies was 10 mg. Patients who receive higher than the protocol-defined dose should be carefully monitored for adverse events, and the quantity of the excess dose and duration of excess dose should be documented in the eCRF; the Medical Monitor should be notified immediately. Refer to Appendix 6 for additional information on AE reporting.

In an instance in which a patient receives higher than the protocol-defined dose, decisions regarding any future dosing of study drug will be made by the Investigator in consultation with the Sponsor based on the clinical evaluation of the patient.

9. Statistical Considerations

9.1. Statistical Hypotheses

The primary objective of the study is to evaluate the safety and tolerability of orally administered TERN-201. No statistical hypothesis testing will be applied.

9.2. Sample Size Determination

The sample size is based on clinical feasibility and adequate size to characterize safety in the study population, without consideration for statistical power.

Patients who are randomized but do not receive study drug for any reason may be replaced. Patients who discontinue treatment early for reasons other than safety (e.g., withdrawal of consent, lost to follow-up, patient relocated) may also be replaced. Replacement patients will receive the same treatment assignment as the patient that discontinued treatment early.

9.3. Analysis Sets

The following analysis sets are defined:

Analysis Sets	Description
Randomized	All patients who are randomized into any one of the treatment groups
PK	All randomized patients who received at least 1 dose of TERN-201 and have evaluable PK data
PD	All randomized patients who received at least 1 dose of study drug (TERN-201 or placebo) and have evaluable PD data
Safety	All patients who received at least 1 dose of study drug. Patients will be analyzed according to the intervention they actually received.
Efficacy Analysis Set	All randomized patients who received at least 1 dose of study drug. Patients will be analyzed according to the intervention they are planned to receive.
Per Protocol Analysis Set (PP)	All randomized patients who have completed the study without any major protocol deviations. The major protocol deviations will be defined in the Statistical Analysis Plan (SAP) and finalized prior to database lock (DBL). A separate completer analysis set may also be defined in the SAP.

A patient is considered to have completed the study if he/she has completed all phases of the study including the last scheduled assessment in the Follow-Up Period.

9.4. Statistical Analyses

This section presents a summary of the planned statistical analyses. The SAP will provide the details and will be finalized prior to clinical database lock.

9.4.1. General Considerations

For continuous data, summary statistics will include the arithmetic mean, arithmetic standard deviation, median, minimum, maximum, and number of patients with non-missing assessments.

For log-normal data (e.g., the PK parameters: AUCs and maximum observed concentration [C_{max}]), the geometric mean and coefficient of variation (CV%) will also be presented. For categorical data, frequency counts and percentages will be presented.

9.4.2. Primary Endpoint(s)

The primary safety parameters will include TEAEs and treatment emergent clinical safety laboratory parameters.

Reported AEs will be coded using the latest version of Medical Dictionary for Regulatory Activities (MedDRA) and graded for severity according to NCI CTCAE, Version 5.0.

All TEAEs will be listed and incidence summarized by MedDRA Preferred Term and System Organ Class, as well as by maximum severity and study drug causality. Summaries of treatment emergent SAEs, TEAEs related to study drug, TEAEs resulting in study drug discontinuations, and deaths will also be produced.

Changes and percent changes from baseline of quantitative measurements will be summarized by treatment group and timepoints. Laboratory abnormalities will be graded according to NCI CTCAE Version 5.0, where applicable. Shifts in CTCAE grade from baseline will be summarized by treatment group.

Further details on the analysis of additional safety parameters will be provided in the SAP.

9.4.3. Secondary Endpoints

9.4.3.1. Pharmacokinetic Endpoints

Noncompartmental PK analysis will be performed on individual plasma and urine concentration data.

Individual plasma concentrations of TERN-201 and its metabolites, if applicable, will be listed by timepoint and summarized by treatment group. Individual and mean concentration-time profiles will be presented graphically in linear and semi-log scales.

PK parameters of TERN-201 and its metabolites (exploratory endpoint) will be listed individually and summarized with descriptive statistics, including arithmetic and geometric mean, median, standard deviation, arithmetic and geometric CV%, minimum and maximum. The C_{max} and AUC will be plotted.

9.4.3.2. Change from Baseline in Plasma VAP-1/SSAO Activity

A secondary efficacy endpoint is change from baseline in plasma VAP-1/SSAO activity with 12 weeks of treatment in patients treated with either TERN-201 or matching placebo. The change and percent change from baseline in plasma VAP-1/SSAO amine oxidase activity in each TERN-201 group will be compared with placebo separately at each post baseline visit, without controlling for any family-wise error rate (overall type I error), using MMRM (mixed model repeated measures) model with treatment group, visit, and treatment group by visit interaction as factors and baseline value as covariate.

Change and percent change from baseline plasma VAP-1/SSAO amine oxidase activity will be listed and summarized with descriptive statistics including arithmetic and geometric mean, median, standard deviation, arithmetic and geometric CV, minimum, and maximum. Exposure-response and dose-response relationships of orally administered TERN-201 will also be assessed as applicable (exploratory endpoints).

Exposure-response and dose-response analysis may be produced if Part 2 of the study is enrolled, as applicable. The change and percent change from baseline in plasma VAP-1/SSAO activity will be compared between the different TERN-201 dose groups and placebo using an analysis of covariance (ANCOVA) model with the treatment group as a factor and baseline values as a covariate. Corresponding least square mean treatment differences with 2 sided 95% confidence limits will be computed for each pairwise comparison.

Further details on the analysis models will be provided in the SAP.

9.4.4. Exploratory Endpoints

Descriptive statistics for the values, change from baseline, and percent change from baseline will be summarized by treatment group over time.

The following exploratory endpoints will be analyzed at each visit using an MMRM model similar to the model described in Section 9.4.3.1. Exposure-response and dose-response analysis may be produced if Part 2 of the study is enrolled, as applicable.

- Change from baseline in cT1 by MRI
- Change from baseline in liver fat content by MRI-PDFF
- Change from baseline in stiffness by transient elastography
- Change from baseline in ALT
- Change from baseline in GGT
- Change from baseline in AST
- Change from baseline in NASH and fibrosis biomarkers
- Change from baseline in inflammatory biomarkers
- Change from baseline in eGFR, urine protein, UPCR, and UACR
- Change from baseline in plasma methylamine levels (PD marker of VAP-1/SSAO inhibition)

9.4.4.1. PD Endpoints

In addition to analyses described above, pharmacodynamic parameters (plasma VAP-1/SSAO activity and plasma methylamine levels) will be listed, summarized, and described by plotting the concentration-time curve or time-effect curve. The correlation of PK and PD parameters will also be explored.

9.5. Interim Analysis

An interim analysis will be performed after all patients in Part 1 have completed Week 6 assessments. Interim PD data will be assessed as described in Section 9.4.4.1. If robust VAP-1/SSAO activity suppression is observed and available PK suggests that a lower dose may also possibly lead to robust VAP-1/SSAO activity suppression, enrollment in Part 2 with 4 mg TERN-201 may be initiated. Additionally, if safety data indicates 10 mg TERN-201 is overall safe and well-tolerated and anticipated exposures with a higher dose remain below the exposure limit (see Section 4.3), enrollment in Part 2 to assess a dose up to 20 mg TERN-201 in Part 2 may be initiated.

Additionally, an administrative interim analysis may be conducted after the completion of Part 1 of the study and will be detailed in the SAP.

10. Regulatory, Ethical, and Study Oversight Considerations

10.1. Regulatory and Ethical Considerations

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

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

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

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

The Investigator will be responsible for the following:

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

10.1.1. Financial Disclosure

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

10.1.2. Informed Consent Process

The Investigator or his/her representative will explain the nature of the study to the patient or his/her legally authorized representative and answer all questions regarding the study.

Patients must be informed that their participation is voluntary. Patients or their legally authorized representative will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study center.

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

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

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

The ICF will contain a separate section that addresses the use of remaining mandatory samples for optional exploratory research for up to 15 years after the end of the study. The Investigator or authorized designee will explain to each patient the objectives of the exploratory research. Patients will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the storage period. A separate signature will be required to document a patient's agreement to allow any remaining specimens to be used for exploratory research. Patients who decline to participate in this optional research will not provide this separate signature.

Written informed consent may be obtained via telephone with appropriate documentation of how the informed consent form was transmitted to the patient, (such as via email, fax, or mail) and how signature was obtained. Screening may be initiated via telephone to avoid a visit to the site if the patient is disqualified based on medical history.

10.1.3. Data Protection

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

The patient must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to

the patient who will be required to give consent for their data to be used as described in the informed consent.

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

10.1.4. Dissemination of Clinical Study Data

A clinical study report (CSR) will be prepared and provided to the regulatory agency(ies) by Terns, as appropriate. Terns will ensure that the report meets the standards set out in the ICH Guideline for Structure and Content of Clinical Study Reports (ICH E3). Note that an abbreviated report may be prepared in certain cases. Public disclosure of study results will be in accordance with all applicable laws and ICH guidelines. The posting of company-sponsored study information and tabular study results may be presented on the US National Institutes of Health's website www.ClinicalTrials.gov and other publicly accessible sites.

10.1.5. Data Quality Assurance

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

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

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

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

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

The sponsor assumes accountability for actions delegated to other individuals (e.g., Contract Research Organizations).

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

Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the Investigator until at least 2 years after the last approval of a marketing application in an ICH region (i.e., United States, Europe, or Japan) and until there are no pending or contemplated marketing applications in an ICH region (i.e., United States, Europe, or Japan) or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period however if required by the applicable regulatory requirement(s) or if needed by the sponsor. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

10.1.6. Protocol Deviations

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted. In the event of a significant deviation related to gross non-compliance from the protocol, or events that impose significant risk to patient safety, the Investigator or designee must notify the Sponsor or designee immediately. Deviations must be documented in accordance with the Sponsor's procedures, and in accordance with any site procedures or processes.

10.1.7. Source Documents

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

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

The required source data should include notes containing at least the following information for each patient:

- Patient identification (name, date of birth, gender)
- Documentation that the patient meets eligibility criteria

- Documentation of the reason(s) a consented patient is not enrolled
- Participation in study (including study number)
- Study discussed and date of informed consent
- Dates of all visits
- Documentation that protocol specific procedures were performed
- Results of efficacy parameters, as required by the protocol
- Start and end date (including dose regimen) of study drug administration, including dates of dispensation and return as applicable
- Record of all adverse events and other safety parameters (start and end date, and including causality and severity)
- Concomitant medication (including start and end date, dose if relevant; dose changes)
- Date of study completion and reason for early discontinuation, if applicable

10.1.8. Study and Site Start and Closure

The first patient screened is considered the first act of recruitment and will be the study start date.

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

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

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

- Failure of the Investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the sponsor's procedures, or GCP guidelines
- Inadequate recruitment of patients by the Investigator
- Discontinuation of further study drug development

If the study is prematurely terminated or suspended, the sponsor shall promptly inform the Investigators, the IECs/IRBs, the regulatory authorities, and any contract research

organization(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The Investigator shall promptly inform the patient and should assure appropriate follow-up care as warranted by the protocol or as medically necessary.

Appendix 1: Clinical Laboratory Tests

The tests detailed in Table 2 will be performed by the central laboratory. Local laboratory testing should only be used in the event that central laboratory results would not available in time for necessary clinical decision making. If a local sample is required, it is important that a sample for central analysis is obtained at the same time. Additionally, if the local laboratory results are used to make either a study drug decision or response evaluation, the results must be entered into the eCRF.

Protocol-specific requirements for inclusion or exclusion of patients are detailed in Section 5. Additional tests may be performed at any time during the study as determined necessary by the Investigator or required by local regulations.

Table 2 Protocol-Required Clinical Laboratory Assessments

Laboratory Assessments	Parameters	
Hematology	Hematocrit Hemoglobin Hemoglobin A1c[1] Platelet Count RBC Count RBC Indices: • MCV • MCH • MCHC • % Reticulocytes	WBC count with Differential: • Neutrophils • Lymphocytes • Monocytes • Eosinophils • Basophils
Clinical Chemistry[2]	Bicarbonate BUN Calcium Chloride CPK Creatinine eGFR[3] Glucose Phosphorus Potassium Sodium	Liver Function Tests: • ALT • Albumin • AST • ALP • GGT • Total and Direct Bilirubin[4]

Laboratory Assessments	Parameters
	Total Protein
Coagulation[5]	aPTT[1] PT/INR
Fasting Lipid Profile	HDL LDL Total Cholesterol Triglycerides VLDL
Urinalysis	• Specific gravity • pH, glucose, protein, albumin, creatinine, blood, ketones, bilirubin, urobilinogen, nitrite, leukocyte esterase by dipstick, UPCR, and UACR • Microscopic examination (if blood or protein is abnormal)
Pregnancy	Highly sensitive serum β-hCG (WOCBP only)
Other Tests	• FSH (to confirm post-menopausal status)[1] • Blood alcohol test[1] • Urine drug screen including amphetamines, barbiturates, cocaine, opiates, cannabinoids and benzodiazepines • Serology[1]: HIV antibody, HBsAg, and HCV antibody[6] • COVID-19: SARS-CoV-2 test for active infection (e.g., molecular test such as PCR or viral antigen serology), and SARS-CoV-2 Ab test (IgG and IgM)

NOTES:
[1] Only collected at Screening.
[2] Details of liver chemistry increased monitoring criteria are given in Appendix 3.
[3] eGFR to be calculated by central lab; refer to Appendix 5 for the formula.
[4] If total bilirubin is increased above the upper limit of normal there should be a reflex to direct and indirect bilirubin, as outlined in Appendix 3.
[5] At Screening, Week 0, and if significant abnormal liver function is observed, as outlined in Appendix 3.
[6] If HCV antibody positive, conduct HCV RNA test.

Abbreviations: ALP = alkaline phosphatase; ALT = alanine transaminase; AST = aspartate transaminase; aPTT = activated partial thromboplastin time; β-hCG = β-human chorionic gonadotropin; BUN = blood urea nitrogen; CPK = creatine phosphokinase; eGFR = estimated glomerular filtration rate; FSH = Follicle-stimulating hormone GGT = gamma-glutamyl transpeptidase; HbA1c = hemoglobin A1c; HBsAg = hepatitis B surface antigen; HCG = human chorionic gonadotropin; HCV = hepatitis C virus; HDL = high-density lipoprotein; HIV = human immunodeficiency virus; IgG = immunoglobulin G; IgM = immunoglobulin M; INR = international normalized ratio; LDL = low-density lipoprotein; MCH = mean corpuscular hemoglobin; MCHC = mean corpuscular hemoglobin concentration; MCV = mean corpuscular volume; PCR = polymerase chain reaction; PT =

prothrombin time; RBC = red blood cell; RNA = ribonucleic acid; SARS-CoV-2 = Severe Acute Respiratory Syndrome Coronavirus 2; UACR = urine albumin:creatinine ratio; UPCR = urine protein:creatinine ratio; VLDL = very low-density lipoprotein; WBC = white blood cell; WOCBP = women of childbearing potential

Investigators must document their review of each laboratory safety report. Clinically significant laboratory shifts, or any clinically significant abnormalities considered possibly related to study drug in the opinion of the Investigator, should be repeated within 48-72 hours and followed to resolution or until stable.

Appendix 2: Sample Collection for Pharmacokinetics and Pharmacodynamics

Table 3 presents a description of PK/PD sample requirements at each study visit and timepoint.

Table 3 PK/PD Sampling Timepoints

Week	Day	Timepoint
0[1]	1	• Pre-dose (All Patients) • Post dose at the following timepoints (PK/PD sub-study only): o 30 ± 2 minutes o 1 hour ± 5 minutes o 2 hours ± 5 minutes o 4 hours ± 15 minutes o 6 hours ± 15 minutes o 8 hours ± 30 minutes • Total urine collection from 0-8 hours post dose (PK/PD sub-study only)
0	2	• Post Day 1 dose at the following timepoint (PK/PD sub-study only): o 24 hours ± 1 hour
2	15 ± 3	• Pre-dose (All Patients)
4	29 ± 3	• Pre-dose (All Patients)
6	43 ± 3	• Pre-dose (All Patients) • Post dose at the following timepoints (PK/PD sub-study only): o 30 ± 2 minutes o 1 hour ± 5 minutes o 2 hours ± 5 minutes o 4 hours ± 15 minutes o 6 hours ± 15 minutes o 8 hours ± 30 minutes • Total urine collection from 0-8 hours post dose (PK/PD sub-study only)
6	44	• Post Week 6 dose at the following timepoint (PK/PD sub-study only): o 24 hours ± 1 hour
8	57 ± 3	• Pre-dose (All Patients)

Week	Day	Timepoint
12	85 ± 3	• Pre-dose (All Patients) • Post dose at the following timepoints (PK/PD sub-study only): o 30 ± 2 minutes o 1 hour ± 5 minutes o 2 hours ± 5 minutes o 4 hours ± 15 minutes o 6 hours ± 15 minutes o 8 hours ± 30 minutes
12	86	• Post Week 12 dose at the following timepoint (PK/PD sub-study only): o 24 hours ± 1 hour
12	87	• Post Week 12 dose at the following timepoint (PK/PD sub-study only): o 48 hours ± 2 hours
12	88	• Post Week 12 dose at the following timepoint (PK/PD sub-study only): o 72 hours ± 4 hours
ET	ET	• At the ET Visit, for all patients discontinuing the study at any time for any reason prior to Week 12
NOTES: [1] sVAP-1 will be collected along with PD sampling at Week 0/Day 1 pre-dose.		

Abbreviations: ET = early termination; PD = pharmacodynamics; PK = pharmacokinetics; sVAP-1 = soluble vascular adhesion protein-1

Appendix 3: Liver Chemistry Increased Monitoring Criteria

Table 4 summarizes requirements for follow-up of liver function test abnormalities.

Table 4 Liver Chemistry Increased Monitoring Criterion and Follow-Up

Criterion	Actions
Elevated ALT and/or AST above 2 × Baseline or above 5 × ULN for < 1 week	• Patient can continue study drug at the discretion of the Investigator • Repeat measurement of LFTs (including ALT, AST, ALP, and total bilirubin) will be performed within 48-72 hours to confirm the abnormalities and to determine if they are increasing or decreasing. If total bilirubin is increased there should be a reflex to direct and indirect bilirubin. • PT/INR and albumin will be tested when significantly abnormal liver function is observed, and repeated with repeat measurement of LFTs. • Upon confirmation of elevated LFTs, close observation by repeating LFTs every 24 to 72 hours will be initiated immediately. • Frequency of monitoring can be decreased as LFTs decrease at the Investigator's discretion. • The Investigator will collect detailed history information on concomitant symptoms, new medications, drug or alcohol exposure, etc., to identify possible cause of abnormal LFTs. • Close observation on abnormal LFTs will last until the parameters return to baseline, or to a stable level judged by the Investigator.
Note: If one of the following situations occurs and is considered related to the study drug without alternative etiology, study drug may be discontinued at the discretion of the Investigator and the Medical Monitor should be informed (with repeat test performed within 48-72 hours once initial abnormality is detected): • ALT or AST > 8 × ULN • ALT or AST > 5 × ULN for more than 1 week • ALT or AST > 2× Baseline with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (> 5%) • ALT or AST > 2 × Baseline and total bilirubin > 2 × ULN or INR >1.5 for more than 1 week, confirmed with a repeat assessment	

Abbreviations: ALP = alkaline phosphatase; ALT = alanine transaminase; AST = aspartate transaminase; INR = international normalized ratio; LFT = liver function test; PT = prothrombin time; ULN = upper limit of normal

Appendix 4: Fridericia's Formula

A single 12-lead ECG will be obtained as outlined in the Schedule of Activities (see Section 1.3) using an ECG machine that automatically calculates the heart rate and measures PR, QRS, and QT intervals. QTc will be calculated using Fridericia's Formula as outlined below.

The Investigator will review the ECGs for any clinically significant abnormalities.

Fridericia's Formula:

QTcF = QT/(RR^0.33)

http://www.thecalculator.co/health/QTc-Calculator-385.html

Appendix 5: Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) Formula to Estimate Glomerular Filtration Rate

$$GFR = 141 \times \min(S_{cr}/\kappa, 1)^{\alpha} \times \max(S_{cr}/\kappa, 1)^{-1.209} \times 0.993^{Age} \times 1.018 \text{ [if female]} \times 1.159 \text{ [if black]}$$

Abbreviations / Units:
SCr (standardized serum creatinine) = mg/dL
κ = 0.7 (females) or 0.9 (males)
α = -0.329 (females) or -0.411 (males)
min = indicates the minimum of SCr/κ or 1
max = indicates the maximum of SCr/κ or 1
age = years

Appendix 6: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

AE Definition

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

Events Meeting the AE Definition

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

Events NOT Meeting the AE Definition
• Abnormal laboratory findings or other abnormal safety assessments that are associated with an underlying disease present at baseline without worsening, unless judged by the Investigator to be more severe than expected for the patient's condition. • An abnormal laboratory test that is not accompanied with other signs or symptoms. • The disease/disorder being studied or signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the patient's condition. • Medical or surgical procedure (e.g., endoscopy, appendectomy): the condition that leads to the procedure is the AE. • Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital). • Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

Definition of SAE

An SAE is an AE that meets the following criteria:

An SAE is defined as any untoward medical occurrence that, at any dose:
a. Results in death
b. Is life-threatening The term 'life-threatening' in the definition of 'serious' refers to an event in which the patient was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
c. Requires inpatient hospitalization or prolongation of existing hospitalization • In general, hospitalization signifies that the patient has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious. • Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.
d. Results in persistent disability/incapacity

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

e. Is a congenital anomaly/birth defect

f. Other situations:

- Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.
- Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

If an event does not meet the AE definition, then it cannot be an SAE even if serious conditions are met (e.g., hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

Recording and Follow-Up of an AE and/or SAE

AE and SAE Recording

- When an AE and/or SAE occurs, it is the responsibility of the Investigator to review all documentation (e.g., hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The Investigator will then record all relevant AE and/or SAE information in the eCRF.
- It is **not** acceptable for the Investigator to send photocopies of the patient's medical records to the Sponsor or designee in lieu of completion of the AE or SAE eCRF.
- There may be instances when copies of medical records for certain cases are requested by the Sponsor or designee. In this case, all patient identifiers, with the exception of the patient number, will be redacted on the copies of the medical records before submission to the Sponsor or designee.

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

Assessment of Severity

The Investigator will be asked to provide an assessment of the severity of the AE using NCI CTCAE v5.0 categories as follows:

- Grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
- Grade 2: Moderate; minimal, local, or noninvasive intervention indicated; limiting age appropriate instrumental ADL.
- Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL.
- Grade 4: Life-threatening consequences; urgent intervention indicated.
- Grade 5: Death related to AE.

For detailed organ system AE severity grading, please refer to NCI CTCAE v5.0:

https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5x11.pdf

Assessment of Causality

- The Investigator is obligated to assess the relationship between study drug and each occurrence of each AE and/or SAE.
- The Investigator (or designee) will make a determination of the relationship of the AE to the study drug using a 4-category system according to the following guidelines:
    - **Not Related:** The AE is definitely caused by the subject's clinical state or the study procedure/conditions.
    - **Unlikely Related:** The temporal association between the AE and the drug is such that the drug is not likely to have any reasonable association with the AE.
    - **Possibly Related:** The AE follows a reasonable temporal sequence from the time of drug administration but could have been produced by the subject's clinical state or the study procedures/conditions.
    - **Related:** The AE follows a reasonable temporal sequence from administration of the drug, abates upon discontinuation of the drug, follows a known or hypothesized cause effect relationship, and (if appropriate) reappears when the drug is reintroduced.
- For each AE and/or SAE, the Investigator **must** document in the medical notes that he/she has reviewed the AE and/or SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the Investigator has minimal information to include in the initial report to the Sponsor or designee. However, it is very important that the Investigator always make an assessment of

causality for every event before the initial transmission of the SAE data to the Sponsor or designee.
- The Investigator may change his/her opinion of causality in light of follow-up information and send a SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AEs and SAEs

- The Investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the Sponsor or designee to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- If a patient dies during participation in the study or during a recognized follow-up period, the Investigator will provide the Sponsor or designee with a copy of any post-mortem findings including histopathology.
- New or updated information will be recorded in the originally completed CRF.
- The Investigator will submit any updated SAE data to the Sponsor or designee within 24 hours of receipt of the information.

Reporting of SAEs

SAE Reporting to Sponsor or designee via Paper CRF

- Email transmission of the SAE paper Report Form is the preferred method to transmit this information to the CATO Safety Group (Terns-PhV@cato-sms.com).
- Notification by facsimile transmission to the CATO Safety Group is also acceptable (919-361-2536)
- Initial notification via telephone or email does not replace the need for the Investigator to complete, sign, and return the SAE report form within the designated reporting time frames.
- Contacts and additional instructions for SAE reporting can be found in in the Study Procedures Manual provided.

Appendix 7: Contraceptive Guidance and Collection of Pregnancy Information

Definitions:

Woman of Childbearing Potential (WOCBP)

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

Women in the following categories are not considered WOCBP

1. Premenopausal female with surgical sterility defined as 1 of the following:
   - Documented hysterectomy
   - Documented bilateral salpingectomy
   - Documented bilateral oophorectomy

2. Postmenopausal female
   - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
     - A high follicle stimulating hormone (FSH) level in the postmenopausal range should be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT).
   - Females on HRT and whose menopausal status is in doubt will be required to follow the protocol-mandated contraception guidance if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

For individuals with permanent infertility due to an alternate medical cause not listed above, (e.g., mullerian agenesis, androgen insensitivity), Investigator discretion should be applied to determining study entry.

Note: Documentation can come from the site personnel's: review of the patient's medical records, medical examination, or medical history interview.

Contraception Guidance:

Male patients who are sexually active with a female partner of childbearing potential must be either surgically sterile (confirmed by documented azoospermia > 90 days after the procedure) or follow the guidance per Table 5, during the study and until 30 days following the last dose of study drug. Male patients must not donate sperm from the first dose of study drug until 30 days following the last dose of the study drug.

Female patients of childbearing potential must have negative serum pregnancy test at screening and randomization, not be breastfeeding, and not plan to become pregnant during study or within 30 days after dosing of study drug. Female patients of childbearing potential must either be surgically sterile (documented hysterectomy, bilateral salpingectomy, bilateral oophorectomy) or follow the guidance per Table 5, during the study and until 30 days following the last dose of the study drug.

Table 5 Contraceptive Methods

CONTRACEPTIVE METHODS ALLOWED DURING THE STUDY INCLUDE:
A. Highly Effective Methods That Have Low User Dependency and May be Used Alone *Failure rate of <1% per year when used consistently and correctly.*
• Documented bilateral tubal occlusion
• Vasectomized partner Vasectomized partner is a highly effective contraceptive method provided that the partner is the sole sexual partner of the woman of childbearing potential and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. Spermatogenesis cycle is approximately 90 days.
B. Highly Effective Methods That Must be Used in Combination with a Barrier Method *Failure rate of <1% per year when used consistently and correctly.*
Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation – oral – intravaginal – transdermal – injectable Male condoms must be used in addition to hormonal contraception. Hormonal contraception must be at a stable dose for ≥ 3 months prior to randomization.
Progestogen-only hormone contraception associated with inhibition of ovulation – oral – injectable Male condoms must be used in addition to hormonal contraception. Hormonal contraception must be at a stable dose for ≥ 3 months prior to randomization.
Implantable progestogen-only hormone contraception associated with inhibition of ovulation
Intrauterine device (IUD)
Intrauterine hormone-releasing system (IUS)
C. Barrier Methods That Must be Used in Combination with a Highly Effective Method (B, above)
Male condom with or without spermicide (single barrier).
D. Double Barrier Methods That May be Used Alone
A combination of male condom with either cervical cap, diaphragm, or sponge with spermicide (double-barrier).
E. SEXUAL ABSTINENCE Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the patient.
UNACCEPTABLE CONTRACEPTIVE METHODS Periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhoea method (LAM) are not acceptable methods of contraception.

Collection of Pregnancy Information:

Male Patients with Partners Who Become Pregnant

The Investigator will attempt to collect pregnancy information on any male patient's female partner who becomes pregnant while the male patient is in this study, or if they become pregnant

within 30 days following the last dose of the study drug. This applies only to male patients who receive study drug.

After obtaining the necessary signed informed consent from the pregnant female partner directly, the Investigator will record pregnancy information on the appropriate form and submit it to the sponsor within 24 hours of learning of the partner's pregnancy. The female partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to the sponsor. Generally, the follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any termination of the pregnancy will be reported regardless of fetal status (presence or absence of anomalies) or indication for the procedure.

Female Patients Who Become Pregnant

Any female patient who becomes pregnant while participating in the study will discontinue study drug.

The Investigator will collect pregnancy information on any female patient who becomes pregnant while participating in this study, or if they become pregnant 30 days following the last dose of study drug. The initial information will be recorded on the appropriate form and submitted to the sponsor within 24 hours of learning of a patient's pregnancy.

The patient will be followed to determine the outcome of the pregnancy. The Investigator will collect follow-up information on the patient and the neonate and the information will be forwarded to the sponsor. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date. Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for the procedure.

While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE.

A spontaneous abortion (occurring at < 22 weeks gestational age) or still birth (occurring at > 22 weeks gestational age) is always considered to be an SAE and will be reported as such.

Any post-study pregnancy related SAE considered reasonably related to the study drug by the Investigator will be reported to the sponsor as described in Section 8.5.5. While the Investigator is not obligated to actively seek this information in former study patients, he or she may learn of an SAE through spontaneous reporting.

Appendix 8: COVID-19 Assessments

At Screening:

- SARS-CoV-2 testing to assess for active infection (e.g., molecular test such as polymerase chain reaction [PCR] or viral antigen serology) and past infection (Immunoglobulin G [IgG] and Immunoglobulin M [IgM] antibodies)
- Testing at Screening may be omitted for patients who have completed a COVID-19 vaccination series, with adequate documentation, at the Investigator's discretion

At Week 0, 6, and 12:

- Testing for past infection via antibody testing (IgG and IgM) if prior IgG was negative
- If Week 0 occurs within 2 weeks of Screening, site may omit repeat SARS-CoV-2 testing at Investigator's discretion
- If IgM antibody test is positive, may reflex to test for SARS-CoV-2 active infection at Investigator's discretion
- Testing at these timepoints may be omitted for patients who have completed a COVID-19 vaccination series, with adequate documentation, at the Investigator's discretion

Ad-hoc:

- In the event of symptoms suggestive of COVID-19, ad hoc testing (including molecular test such as PCR or viral antigen serology, and/or antibody testing), may be completed at Investigator's discretion

Sites may use local laboratory testing for COVID-19 assessments instead of central laboratory, per site preference. If a local laboratory is used, the results must be entered into the eCRF. Results from previous testing may be used if completed within 2 weeks of a scheduled Screening or on-study visit.

Any positive tests reflecting active or recent infection (e.g., molecular test such as PCR or viral antigen serology, or IgM antibody) require management per local public health guidelines, at the direction of the Investigator.

If technological changes result in changes to the assays implemented to assess for SARS-CoV-2, available central lab assays and testing mechanisms may change.

The testing approach and schedule may be modified based on the evolving landscape of the pandemic or in response to local public health requirements. In that event, regulatory requirements, IRB requirements, and local institutional guidelines will be followed, as necessary.

Appendix 9: Abbreviations

Abbreviation or special term	Explanation
AAT	Alpha-1 antitrypsin
AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
anti-HCV	HCV antibody
AST	Aspartate transaminase
AUC	Area under the plasma concentration-time curve
β-hCG	Human chorionic gonadotropin
BMI	Body mass index
BUN	Biliary urea nitrogen
C3M	Type III collagen
CAP	Controlled attenuation parameter
CBD	Cannabidiol
CCl_4	Carbon tetrachloride
CDHFD	Choline deficient high fat diet
CFR	Code of Federal Regulations
CIOMS	Council for International Organizations of Medical Sciences
CK-18	Cytokeratin-18
C_{max}	Maximum observed plasma concentration
CNS	Central nervous system
CPK	Creatinine phosphokinase
CONSORT	Consolidated Standards of Reporting Trials
COVID-19	Coronavirus disease 2019
CRF	Case report form
CSR	Clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
cT1	Corrected T1
CV	Coefficient of variation
CYP	Cytochrome P450
DBL	Database lock
eCRF	Electronic case report form
eGFR	Estimated glomerular filtration rate
ECG	Electrocardiogram
EEG	Electroencephalogram

Abbreviation or special term	Explanation
ELF	Enhanced liver fibrosis
ET	Early termination
FAD	Flavin adenine dinucleotide
FAS	Full Analysis Set
FDA	Food and Drug Administration
FIB-4	Fibrosis-4 index
FIH	First-in-human
FSH	Follicle stimulating hormone
GCP	Good clinical practice
GFR	Glomerular filtration rate
GGT	Gamma-glutamyl transpeptidase
GLP	Good Laboratory Practice
GPCR	G-protein coupled receptors
HA	Hyaluronic acid
HbA1c	Hemoglobin A1c
HBsAg	Hepatitis B virus surface antigen
HCV	Hepatitis C virus
HDL	High-density lipoprotein
HDPE	High-density polyethylene
HIV	Human immunodeficiency virus
HIPAA	Health Insurance Portability and Accountability Act
HRT	Hormone replacement therapy
HSC	Hepatic stellate cell
hs-CRP	High sensitivity C-reactive protein
IC_{50}	Half maximal inhibitory concentration
ICAM-1	Intercellular adhesion molecule-1
ICF	Informed consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IgG	immunoglobulin G
IgM	Immunoglobulin
IL-6	Interleukin-6
IMP	Investigational medicinal product
IND	Investigational new drug
INR	International normalized ratio
IRB	Institutional Review Board

Abbreviation or special term	Explanation
IUD	Intrauterine device
IUS	Intrauterine hormone-releasing system
IWRS	Interactive web response system
LAM	Lactational amenorrhoea method
LFT	Liver function test
LDL	Low-density lipoprotein
MAD	Multiple ascending dose
MCH	Mean corpuscular hemoglobin
MCHC	Mean corpuscular hemoglobin concentration
MCV	Mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed model for repeated measures
MRI	Magnetic Resonance Imaging
MRI-PDFF	Magnetic Resonance Imaging Proton Density Fat Fraction
mRNA	Messenger RNA
MTD	Maximum tolerated dose
NAFLD	Nonalcoholic fatty liver disease
NASH	Nonalcoholic Steatohepatitis
NCI	National Cancer Institute
NFS	NAFLD fibrosis score
NIMP	Noninvestigational medicinal product
NOAEL	No observed adverse effect level
PCR	Polymerase chain reaction
PD	Pharmacodynamic(s)
PIIINP	Procollagen III N-terminal propeptide
PK	Pharmacokinetic(s)
po	*Per os* (oral)
PP	Per protocol
PPV	Positive predictive value
PRO-C3	Pro-peptide of type III collagen
PT	Prothrombin time
PTZ	Pentylenetetrazole
QD	Once daily
RBC	Red blood cell
RNA	Ribonucleic acid
SAD	Single ascending dose
SAE	Serious adverse event

Abbreviation or special term	Explanation
SAP	Statistical analysis plan
SARS-COV-2	Severe Acute Respiratory Syndrome Coronavirus 2
SCr	Standardized serum creatinine
SSAO	Semicarbazide-sensitive amine oxidase
SUSAR	Suspected unexpected serious adverse reactions
TEAE	Treatment emergent adverse event
TERN-201	An investigational selective VAP-1/SSAO inhibitor; a.k.a., LSN3415221 (LSN3379274·TsOH), LSN3394258 (LSN3379274·2HCl) and LSN3379274 (free base))
THC	Tetrahydrocannibinol
TIMP-1	Tissue inhibitor of metalloproteinases-1
TRN-001021	O-demethylation metabolite of TERN-201
TRN-001744	O-dealkylation metabolite of TERN-201
UACR	Urine albumin:creatinine
ULN	Upper limit of normal
UPCR	Urine protein: creatinine
US	United States
VAP-1	Vascular Adhesion Protein-1
VCAM-1	Vascular cell adhesion molecule-1
VLDL	Very low-density lipoprotein
WBC	White blood cell
WOCBP	Women of childbearing potential

Appendix 10: Investigator Signature Page

A Multi-Center, Randomized, Double-Blind, Dose-Ranging, Placebo-Controlled, Proof of Concept, Adaptive, Phase 1b Clinical Study to Evaluate the Safety, Pharmacokinetics, Pharmacodynamics, and Efficacy of Orally Administered TERN-201 in Patients with Presumed Non-Cirrhotic Non-Alcoholic Steatohepatitis (NASH)

Protocol Number: TERN201-1007

Protocol Version/Date: Amendment 3; 17 August 2021

I confirm that I have read the above-mentioned protocol and its attachments. I agree to conduct the described study in compliance with all stipulations of the protocol, regulations and ICH E6 Guideline for Good Clinical Practice (GCP). I will provide all study personnel under my supervision copies of the protocol and access to all information provided by Terns, Inc. I will discuss this material with them to ensure that they are fully informed about the study drug and the study.

Principal Investigator Name (Printed)	Signature
Date	

Appendix 11: Protocol Amendment History

This document (dated 17 August 2021) is Amendment 3. The document history is below. The Summary of Changes for each amendment listed below will be provided separately.

DOCUMENT HISTORY	
Document	**Date**
Amendment 3	17 August 2021
Amendment 2	21 June 2021
Amendment 1	20 April 2021
Original	18 December 2020

Appendix 12: References

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