CLINICAL STUDY PROTOCOL

Protocol Title:	A Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Phase 2a Clinical Trial to Evaluate the Safety, Tolerability, Efficacy, and Pharmacokinetics of Orally Administered TERN-101 Tablets in Adult Patients with Presumed Non-Cirrhotic Non-Alcoholic Steatohepatitis (NASH)
Protocol Number:	TERN101-2001
Protocol Version:	Amendment 1
Version Date:	22 May 2020
Supersedes:	Original; 26 February 2020
Compound:	TERN-101
Study Phase:	2a
Sponsor Name:	Terns, Inc.
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Regulatory Agency Identifier Number(s)	
US FDA IND:	[redacted]

CONFIDENTIAL

Sponsor Signatory:

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Signing Reason: I approve this document
Signing Time: 22-May-2020 | 1:11:04 PM PDT
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22-May-2020

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Chief Medical Officer
Terns, Inc.

Date

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1. Protocol Summary

1.1. Synopsis

Protocol Title:

A Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Phase 2a Clinical Trial to Evaluate the Safety, Tolerability, Efficacy, and Pharmacokinetics of Orally Administered TERN-101 Tablets in Adult Patients with Presumed Non-Cirrhotic Non-Alcoholic Steatohepatitis (NASH)

[redacted]

[redacted]

Objectives:

Primary Objective:

- To evaluate safety and tolerability of 3 doses of orally administered TERN-101 versus placebo for 12 weeks in non-cirrhotic presumed NASH patients, with clinical or histological NASH diagnosis

Secondary Objectives:

- To evaluate the change in alanine aminotransferase (ALT) with 3 doses of TERN-101 for 12 weeks versus placebo in non-cirrhotic presumed NASH patients

- To evaluate the pharmacokinetics (PK) of 3 doses of TERN-101 in non-cirrhotic presumed NASH patients

Exploratory Objectives:

- To assess the effect of 3 doses of TERN-101 on liver fat content (LFC) and additional indicators of NASH disease activity
- To evaluate FXR target engagement of 3 doses of TERN-101 in non-cirrhotic presumed NASH patients
- To evaluate the effect of 3 doses of TERN-101 on biomarkers of liver fibrosis

Endpoints:

Primary Endpoint:

- Overall safety assessed by adverse events (AEs) including treatment emergent AEs (TEAEs), and proportion of patients with treatment-emergent clinical safety laboratory abnormalities

Secondary Endpoints:

- Percent change from baseline in ALT levels at 12 weeks
- Plasma PK for [redacted] TERN-101 [redacted]

Exploratory Endpoints:

- Change from baseline in LFC by magnetic resonance imaging-proton density fat fraction (MRI-PDFF)
- Change from baseline in gamma-glutamyl transpeptidase (GGT)
- Change from baseline in aspartate aminotransferase (AST)
- Change from baseline in FGF-19
- Change from baseline in 7-α-C4
- Change from baseline in NASH/fibrosis blood biomarkers
- [redacted]

Overall Design:

This study is a multicenter, randomized, double-blind, placebo-controlled, parallel-group study.

Approximately 96 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 1:1:1:1 into 4 groups receiving 5 mg (n = 24), 10 mg (n = 24), 15 mg (n = 24) TERN-101 tablets, or matching placebo (n = 24) orally once daily.

Of the 96 patients randomized, 24 patients will take part in an intensive PK and pharmacodynamic (PD) collection after the first dose and after the last dose of study drug. This includes 6 patients at each TERN-101 dose level, and 6 patients in the placebo group. 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 24 weeks, consisting of an 8-week Screening Period, a 12-week Treatment Period and a 4-week Follow-up Period.

Disclosure Statement:

This is a parallel-group treatment study.

Number of Patients:

Approximately 96 patients will be randomly assigned to treatment with TERN-101 tablet or matching placebo.

Patients who are randomized but do not receive study drug for any reason may be replaced.

Study Centers Planned:

Approximately 40 centers in the United States.

Intervention Groups and Duration:

The total study duration will be approximately 24 weeks, consisting of an 8-week Screening Period, a 12-week Treatment Period and a 4-week Follow-up Period.

Screening Period

The 8-week Screening Period initiates upon signing an Informed Consent, at which point eligibility criteria will be reviewed. Each eligible patient will be scheduled for Week 0/Day 1.

Treatment Period

The 12-week double-blind, randomized Treatment Period will initiate at Week 0/Day 1 after confirming eligibility. The blinded study drug (TERN-101 tablet or placebo) will be orally administered once daily in the morning, without regard to food.

Patients will return to the site at Weeks 2, 4, 6, 8, and 12 for safety and laboratory assessments. Study drug will be dispensed at Week 0/Day 1, Week 4, and Week 8. Week 12 is the last day of treatment.

Intensive PK/PD sampling will be performed in 24 patients participating in the PK/PD sub-study after the first dose (Week 0/Day 1) and after the last dose of study drug (Week 12).

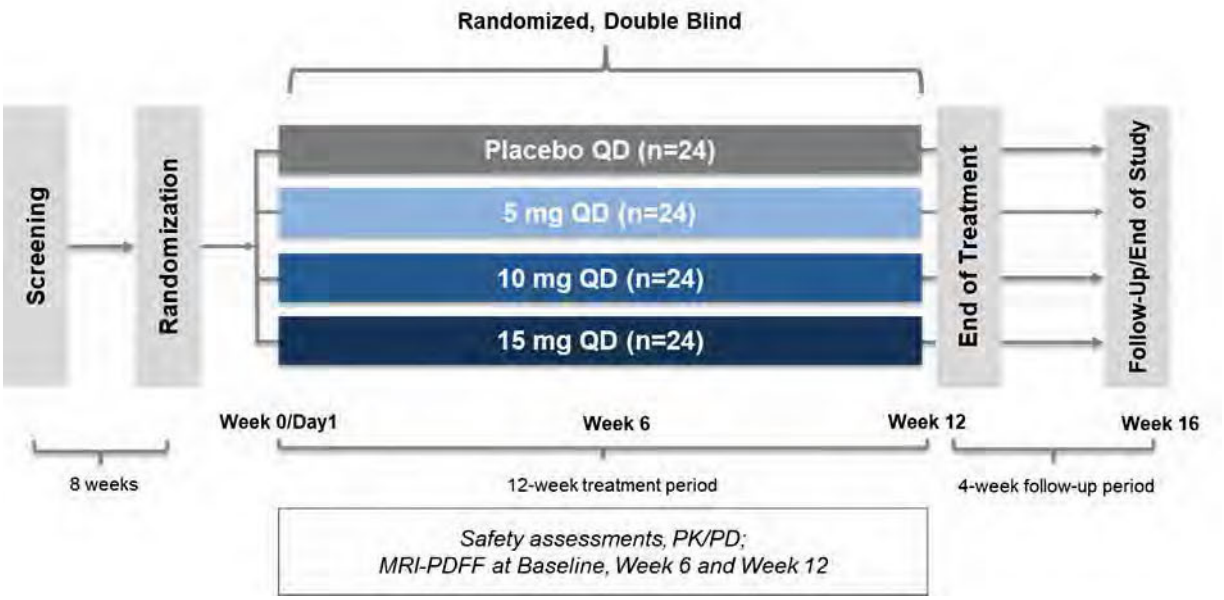
Imaging (MRI-PDFF) will be completed at Week 0, Week 6, and Week 12. An MRI is performed at early termination (ET) only if not done within the prior 4 weeks, and the patient has had at least 4 weeks of dosing.

Follow-up Period

All patients will return to site for follow up safety assessments at Week 16.

If study drug is permanently discontinued for any reason outlined in Section 7, the patient will be encouraged to 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.

1.2. Schema



Abbreviations: MRI-PDFF = magnetic resonance imaging proton density fat fraction; PK/PD = pharmacokinetics/pharmacodynamics; QD = once a day

1.3. Schedule of Activities (SoA)

	Screening	Treatment Period[e]						Follow-Up[b]	ET[a]	Notes
Visit	**Screening**	**Week 0**	**Week 2**	**Week 4**	**Week 6**	**Week 8**	**Week 12**	**Week 16**		
Study Day	**-56 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 /+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 to avoid a visit to the site, if the patient is disqualified based on medical history.
Patient Fasting	X	X		X		X	X	X	X	Patients must be in fasted state for at least 8 hours prior to blood collection and treatment 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	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 Week 0, 4, 6, 8, 12, 16, and ET.
Medical history	X									Includes details of illnesses and allergies, date(s) of onset, whether condition(s) is currently ongoing, and medication history, including alcohol use.
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.

	Screening	Treatment Period[e]						Follow-Up[b]	ET[a]	Notes
Visit	**Screening**	**Week 0**	**Week 2**	**Week 4**	**Week 6**	**Week 8**	**Week 12**	**Week 16**		
Study Day	**-56 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 /+2 days from the specified study day.
Vital Signs	X	X	X	X	X	X	X	X	X	Includes temperature, pulse rate, respiratory rate, and blood pressure.
Chemistry[c]	X	X	X	X	X	X	X	X	X	Specific analytes are listed in Appendix 1. ALT/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[c]	X	X	X	X	X	X	X	X	X	Specific analytes are listed in Appendix 1.
Coagulation[c]	X	X								Specific analytes are listed in Appendix 1. PT/INR will be tested at Screening, Week 0, and if significant abnormal liver function is observed.
Fasting Lipid Profile[c]	X	X		X		X	X	X	X	Specific analytes are listed in Appendix 1.
Serology	X									Includes HBsAg, anti-HCV and anti-HIV.
COVID-19 Assessment[c,f]	X	X			X		X			Screening and on study COVID-19 assessments should be conducted in accordance with Appendix 9.
[redacted]	[redacted]	[redacted]		[redacted]		[redacted]	[redacted]		[redacted]	[redacted]
[redacted]	[redacted]									[redacted]
Blood Alcohol Test	X									

	Screening	Treatment Period[e]						Follow-Up[b]	ET[a]	Notes
Visit	**Screening**	**Week 0**	**Week 2**	**Week 4**	**Week 6**	**Week 8**	**Week 12**	**Week 16**		
Study Day	**-56 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 /+2 days from the specified study day.
Urinalysis[c]	X				X			X	X	Specific analytes are listed in Appendix 1. Microscopic examination is required if blood or protein is abnormal.
Urine Drug Screen[c]	X	X		X		X	X	X	X	Randomization may proceed at Week 0 provided exclusion criteria 21 and 22 are not met.
Intensive PK Sampling *(PK/PD Sub-Study only)*		X					X			Intensive PK sampling will be performed pre-dose and 0.5, 1, 3, 6, and 24 hours post the first dose of study drug on Week 0/Day 1, and at pre-dose and 0.5, 1, 3, 6, 24, 48 and 72 hours post last dose of study drug at Week 12. Refer to Appendix 2 for additional detail.
Intensive PD Sampling for FGF19 and 7-α-C4 *(PK/PD Sub-Study Only)*		X					X			At matching timepoints to Intensive PK sampling. Refer to Appendix 2 for additional detail.
Trough PK Sampling[c]		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.
Trough PD Sampling for 7-α-C4 [redacted]		X	X	X	X	X	X		X	Only one sample will be collected at each visit prior to drug administration on the visit day [redacted] 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.
NASH/Fibrosis Biomarkers[c]		X			X		X		X	Includes CK-18 (M30 and M65), PIIINP, TIMP-1, HA, Pro-C3, and hs-CRP.

	Screening	Treatment Period[e]						Follow-Up[b]	ET[a]	Notes
Visit	**Screening**	**Week 0**	**Week 2**	**Week 4**	**Week 6**	**Week 8**	**Week 12**	**Week 16**		
Study Day	**-56 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 /+2 days from the specified study day.
[redacted]										[redacted]
Transient Elastography	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-PDFF[d]	X				X		X		X	A Screening MRI-PDFF may proceed on the basis of the initial ALT/AST level at Screening, given all other eligibility criteria are met, but randomization should not occur prior to confirmation of ALT/AST stability as necessary. An MRI-PDFF should be performed at ET only if not done within the prior 4 weeks, and the patient has had at least 4 weeks of dosing
[redacted]										[redacted]
Drug Accountability			X	X	X	X	X		X	
[redacted]										[redacted]

	Screening	Treatment Period[e]						Follow-Up[b]	ET[a]	Notes
Visit	**Screening**	**Week 0**	**Week 2**	**Week 4**	**Week 6**	**Week 8**	**Week 12**	**Week 16**		
Study Day	**-56 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 /+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.
Pruritus Assessment		←═══════════════════→						X	X	Reported AEs consistent with pruritus will be assessed using a numeric scaling tool (Appendix 8).
Concomitant Medications Review		←═══════════════════→						X	X	
[redacted]										[redacted]

a Patients discontinuing the study at any time for any reason (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.
b 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 (Early Termination).
c Samples collected during the treatment period should be collected pre-dose
[redacted]
e 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, in accordance with Section 6.8.1 home health care visits may be made available 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.

f 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, once available via the central laboratory), may be completed at Investigator's discretion.
g 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 (ie, curbside pickup, etc.).

Abbreviations: AE = adverse event; ALT = alanine transaminase; AST = aspartate transaminase; BMI = body mass index; CK18 = cytokeratin-18; COVID-19 = coronavirus disease 2019; CTCAE = common terminology criteria for adverse events; 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; INR = international normalized ratio; IWRS = interactive web response system; MRI = magnetic resonance imaging; NCI = National Cancer Institute; PCR = polymerase chain reaction; PD = pharmacodynamics; PIIINP = Procollagen III N-Terminal Propeptide; PK = pharmacokinetics; Pro-C3 = released N-terminal pro-peptide of type III collagen; SAE = serious adverse event; TIMP-1 = tissue inhibitor of metalloproteinases-1; ULN = upper limit of normal; WOCBP = women of childbearing potential.

2. Introduction

2.1. Overview of Nonalcoholic Steatohepatitis (NASH) and Unmet Need

This study is a randomized, double-blind, placebo-controlled, parallel-group, Phase 2a study to evaluate the safety, tolerability, efficacy, and PK of various doses of TERN-101 in non-cirrhotic presumed NASH patients. TERN-101 is a highly selective and potent small molecule agonist of FXR in development for the treatment of patients with NASH.

[redacted]

2.2. Background

2.2.1. TERN-101 and FXR Agonists for Treatment of NASH

[redacted]

[redacted]

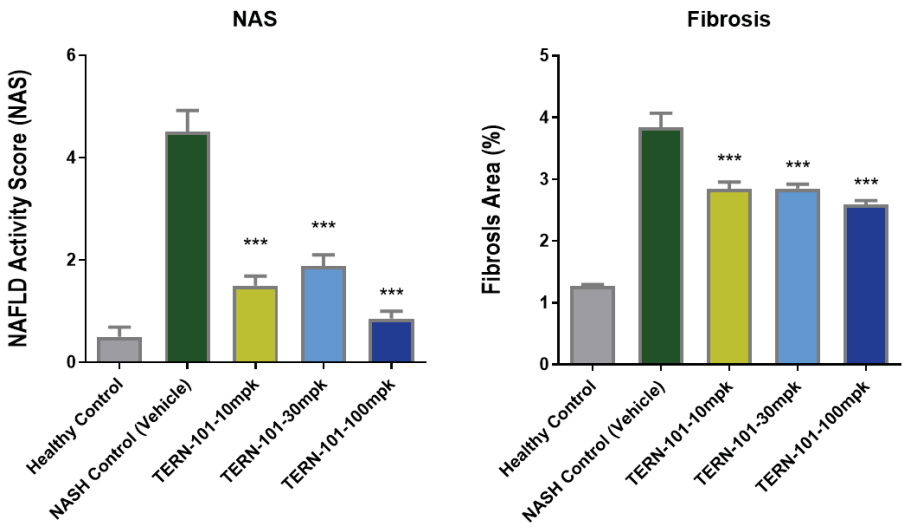
TERN-101 is a non-steroidal, synthetic small molecule [redacted] and is formulated for oral administration in capsule or tablet form. TERN-101 is a potent FXR agonist. As a selective and potent nonsteroidal, non-bile acid FXR agonist, TERN-101 may offer a unique safety and efficacy profile to benefit the NASH patient population. As summarized

below, nonclinical studies and Phase 1 clinical studies of TERN-101 support its potential utility as a disease-modifying treatment for NASH.

2.2.2. Summary of Nonclinical Studies

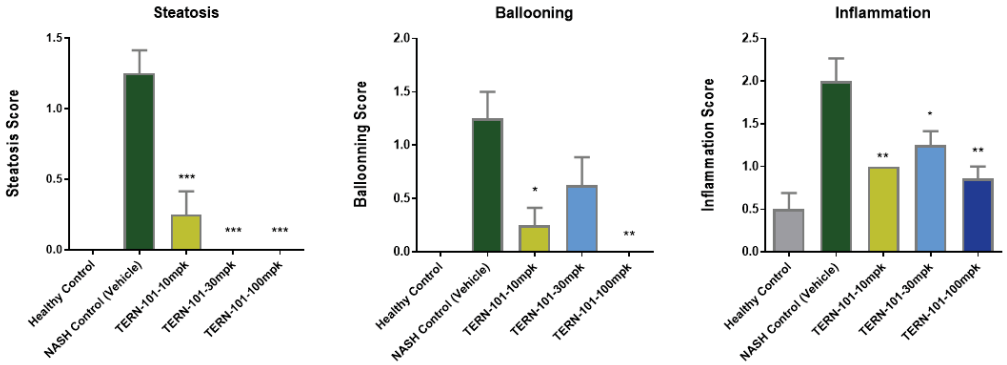
In mouse NASH models, TERN-101 inhibited 7-α–C4 and significantly reduced NAFLD activity score (NAS) and liver fibrosis area. NAS was markedly reduced by all doses of TERN-101 tested (Figure 1, left panel) with an 80% reduction from baseline at 100 mg/kg (mpk). Steatosis was reduced to healthy control (lean mice) levels at 30 mpk (Figure 2, left), and hepatocellular ballooning was reduced to healthy control levels at 100 mpk (Figure 2, middle). Hepatic inflammation was also reduced in TERN-101 treated mice (Figure 2, right). The improvement in liver histology correlated with a reduction in liver triglycerides, serum lipids and the liver-related enzymes ALT and AST. These results indicate potent FXR agonist activity and support that TERN-101 has the potential for use in the treatment of NASH.

Figure 1. TERN-101 Reduces NAS and Liver Fibrosis in a NASH Mouse Model



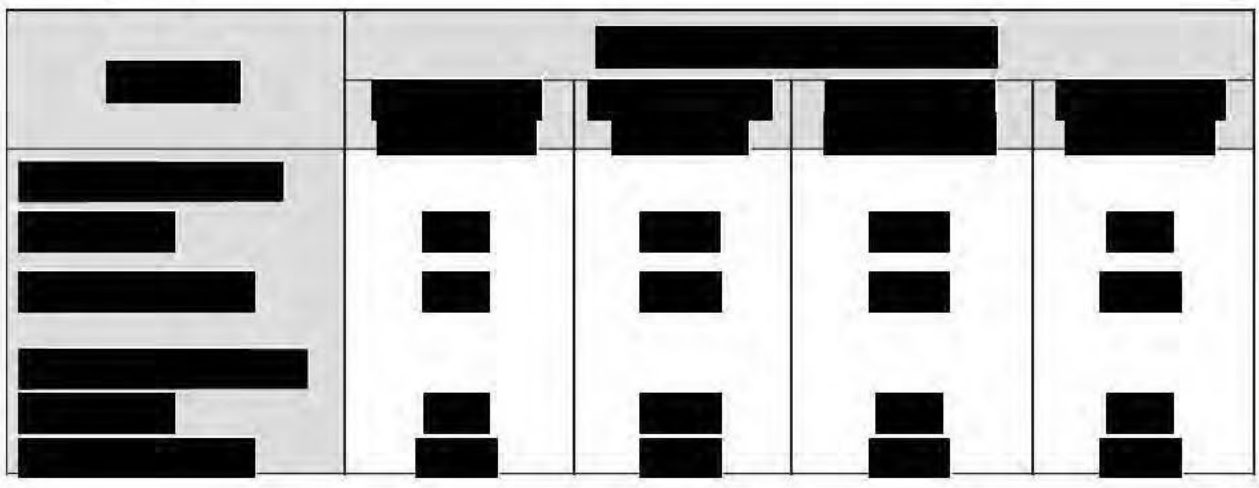
Obese mice fed a high-fat diet and chronically treated with CCl_4 were dosed with varying amounts of TERN-101 for 28 days. Liver tissue was isolated at end of study and analyzed by histopathology for NAFLD Activity Score (NAS, combination of liver steatosis, ballooning and inflammation determined by hematoxylin and eosin staining) (left) or liver fibrosis area (sirius red staining) (right). Data are presented as Mean ± SEM (n=7 for TERN-101/100 mpk, n=8 for all other groups; ***p< 0.001, **p<0.01, *p<0.05 vs NASH Control (Vehicle); statistics determined by one-way ANOVA followed by Tukey).

Figure 2. TERN-101 Reduces Liver Steatosis, Ballooning, and Inflammation in a NASH Mouse Model



Obese mice fed a high-fat diet and chronically treated with CCl_4 were dosed with varying amounts of TERN-101 for 28 days. Liver tissue was isolated at end of study and analyzed by histopathology for liver steatosis (left), ballooning (middle) and inflammation (right) using H&E staining. Data are presented as Mean ± SEM (n=7 for TERN-101/100 mpk, n=8 for all other groups; ***p<0.001, **p<0.01, *p<0.05 vs NASH Control (Vehicle); statistics determined by one-way ANOVA followed by Tukey).

[redacted]



[redacted]

2.2.3. Clinical Trials of TERN-101

TERN-101 has been administered to healthy human subjects in 4 completed Phase 1 clinical studies as described below. As of 14 January 2020, a total of 119 human subjects have received at least 1 dose of TERN-101 in these 4 studies combined (Table 2).

Table 2 List of Completed TERN-101 Clinical Studies

Study Number and Number of Subjects	Study Title
[redacted]	[redacted]
[redacted]	
TERN101-US-A101 (N = 36)	A Single Center, Randomized, Double-blind, Placebo-controlled, Parallel-group, Multiple Dose, Phase I Clinical Trial to Evaluate the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of Orally-Administered TERN-101 in Healthy Subjects
TERN101-US-A104 (N = 34)	An Adaptive, Multi-Part Phase 1 Study in Healthy Subjects to Compare the Pharmacokinetics of Tern-101 Tablets and Capsules, and to Investigate the Effects of Food and Co-administered Medications on the Pharmacokinetics of Orally Administered TERN-101 Tablets

[redacted]

In the fourth study, TERN101-US-A104 (N = 34), TERN-101 25 mg capsule was administered as a single oral dose, and TERN-101 tablets were administered as single oral doses of 5 and 25 mg. TERN-101 tablet PK was dose linear in the range of 5 mg to 25 mg for the tablet formulation. Following single doses of TERN-101 tablets administered in the fasted state, area under the concentration-time curve $(AUC)_{0\text{-}inf}$ was 453 (31.3) ng*hr/mL, 2720 (25.2) ng*hr/mL, and 689 (45.0) ng*hr/mL for TERN-101 5-mg tablet, 25-mg tablet, and 25-mg capsule, respectively. Maximal plasma concentrations on average were reached at 0.75 hours postdose for

TERN-101 5-mg tablet and at 1.52 hours for TERN-101 25-mg tablet. Transient increases in FGF-19 concentrations and dose-dependent decreases in 7-α-C4 concentrations were observed after single doses of TERN-101 tablets. Administration of TERN-101 (5 mg) tablet with food delayed the time of maximal plasma concentrations (from ~1 hour fasted to ~4 hours fed) but did not result in significant differences in exposure as assessed by AUC. [redacted]

Safety findings from the 4 clinical studies showed that TERN-101 was well-tolerated overall. AEs were predominantly mild and transient. The predefined maximum tolerated dose was not reached in any study. The overall AE incidence was generally balanced between dose groups. Following multiple doses of TERN-101 capsules of up to 400 mg, no TEAEs were attributable to TERN-101 on the basis of frequency, dose-relationship, or expected pharmacology. Pruritus was not reported by any of the 119 human subjects who have received TERN-101 to date. [redacted] No transaminase elevations > 1.5 times upper limit of normal were observed in the subsequent completed repeat dose study (TERN101-US-A101) [redacted] or Study TERN101-US-A104). In the 2 completed repeat dose Phase 1 TERN-101 studies, no consistent trends in changes from baseline in LDL cholesterol were observed with TERN-101. In the recently completed Phase 1 study TERN101-US-A104, there was no consistent pattern of LDL change on-study; several subjects had elevated levels prior to dosing, and LDL remained at overall similar levels on-study.

Additional information on available TERN-101 clinical study results, including clinical pharmacology and dose-selection considerations, is provided in the Investigator's Brochure.

2.3. Benefit/Risk Assessment

[redacted]

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, and lipid levels will be obtained and monitored for abnormalities in a blinded fashion.

Overall, based on past experience of clinical studies of TERN-101 in healthy volunteers, the benefit/risk assessment is considered to be positive for patients to be enrolled in this study. More detailed information about the known and expected benefits and risks and reasonably expected adverse events of TERN-101 may be found in the Investigator's Brochure.

3. Objectives and Endpoints

Objectives:

Primary Objective:

- To evaluate safety and tolerability of 3 doses of orally administered TERN-101 versus placebo for 12 weeks in non-cirrhotic presumed NASH patients, with clinical or histological NASH diagnosis

Secondary Objectives:

- To evaluate the change in ALT with 3 doses of TERN-101 for 12 weeks versus placebo in non-cirrhotic presumed NASH patients
- To evaluate the PK of 3 doses of TERN-101 in non-cirrhotic presumed NASH patients

Exploratory Objectives:

- To assess the effect of 3 doses of TERN-101 on LFC and additional indicators of NASH disease activity
- To evaluate FXR target engagement of 3 doses of TERN-101 in non-cirrhotic presumed NASH patients
- To evaluate the effect of 3 doses of TERN-101 on biomarkers of liver fibrosis

Endpoints:

Primary Endpoint:

- Overall safety assessed by AEs including TEAEs, and proportion of patients with treatment-emergent clinical safety laboratory abnormalities

Secondary Endpoints:

- Percent change from baseline in ALT levels at 12 weeks
- Plasma PK for [redacted] TERN-101 [redacted]

Exploratory Endpoints:

- Change from baseline in LFC by MRI-PDFF
- Change from baseline in GGT

- Change from baseline in AST
- Change from baseline in FGF-19
- Change from baseline in 7-α-C4
- Change from baseline in NASH/fibrosis blood biomarkers
- [redacted]

4. Study Design

4.1. Overall Design

This study is a multicenter, randomized, double-blind, placebo-controlled, parallel-group study.

Approximately 96 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 1:1:1:1 into 4 groups receiving 5 mg (n = 24), 10 mg (n = 24), 15 mg (n = 24) TERN-101 tablet or matching placebo (n = 24) orally once daily.

Of the 96 patients randomized, 24 patients will take part in an intensive PK and PD collection after the first dose and after the last dose of study drug. This includes 6 patients at each TERN-101 dose level, and 6 patients in the placebo group. Patients who are not participating in the PK/PD sub-study will have trough PK/PD sampling only.

The total study duration will be approximately 24 weeks, consisting of an 8-week Screening Period, a 12-week Treatment Period and a 4-week Follow-up Period.

4.2. Scientific Rationale for Study Design

The study will enroll male and female patients with non-cirrhotic presumed NASH in order to obtain evidence of safety, preliminary efficacy, PK, and PD of 3 dose levels of TERN-101. The multiple-dose design of this study is randomized and double-blinded to minimize bias and to enable efficient evaluation of different dose levels. The placebo control is included to facilitate identification of effects related to administration of TERN-101 rather than the study procedures, disease, or situation. The study duration will allow characterization of the safety and tolerability of TERN-101 with 12 weeks of dosing as well as initial assessment of effect of TERN-101 on efficacy parameters in a NASH population.

4.3. Justification for Dose

Based on PK results from TERN101-US-A104 Phase 1 study in healthy subjects, the tablet formulation of TERN-101 was dose linear in the range of 5 mg to 25 mg, with AUC_{0-t} of 475 (±161) ng*hr/mL and 2890 (±720) ng*hr/mL for 5 and 25 mg tablets, respectively. [redacted] Evidence of FXR target engagement was seen for doses ranged from 5 mg to 25 mg tablets of TERN-101 (see Section 2.2.3). The doses selected for this study of 5 mg, 10 mg, and 15 mg TERN-101 tablets are expected to achieve FXR target engagement and will allow for characterization of the safety and efficacy of TERN-101 across these dose levels.

There was no significant impact of food intake on TERN-101 PK based on results from Study TERN101-US-A104, thus TERN-101 can be dosed without regard to food intake.

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:

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

[redacted]

3. Overweight or obese with a body mass index (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 7.6 - 21 kPa and controlled attenuation parameter (CAP) > 300 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-PDFF and must have liver fat content ≥ 10% 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 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-PDFF and must have liver fat content ≥ 10% for randomization.
5. All patients must have:
    - ALT ≥ 43 IU/L for men and ≥ 28 IU/L for women
    - MRI PDFF liver fat content ≥ 10 %

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:

Medical Conditions

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

    - Active hepatitis B defined as positive Hep B surface antigen at screening
    - Active hepatitis C defined as positive Hep C virus (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
    - Gilbert's syndrome if direct bilirubin is above 0.3 mg/dL or evidence of active hemolysis
    - Hemochromatosis or other iron overload
    - Alpha-1-antitrypsin deficiency
    - 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. Total bilirubin > 1.2 mg/dL. Note patients with Gilbert syndrome may be enrolled if total bilirubin < 2 mg/dL and direct bilirubin ≤ 0.3 mg/dL.

5. Albumin < 3.5 g/dL

6. INR > 1.1

7. ALT or AST > 5 × ULN

8. Unstable elevated ALT or AST. Patients with ALT or AST > 60 IU/L must have evidence of a stable ALT/AST over at least a 2-week time period prior to randomization [redacted]

9. ALP > 156 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 HbA1c > 9.5%. [redacted]

15. Unstable cardiovascular (CV) disease defined as myocardial infarction, unstable angina, percutaneous intervention, coronary artery bypass graft, or stroke within 6 months prior to randomization

16. Uncontrolled hyperlipidemia defined as fasting LDL ≥ 150 mg/dL despite treatment or total triglycerides > 300 mg/dL

17. QTc > 450 ms for males, > 470 ms for females

18. Known allergy to study drug

[redacted]

20. 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.

21. Illicit substance/chemical abuse in the 12 months prior to Screening

22. Cannabis use (tetrahydrocannabinol [THC] and cannabidiol [CBD]) within 14 days of randomization

23. Unwilling to abstain from excessive alcohol use (defined in #20 above), cannabis use, and illicit substance use during study participation

24. Contraindications or inability to complete MRI scanning (ie, weight restrictions, presence of permanent pacemaker, implanted cardiac devices, etc.)

25. Positive for human immunodeficiency virus (HIV) infection

26. Laboratory or clinical evidence of current infection with Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), i.e. COVID-19

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

Prior or Anticipated Therapy

28. Treatment with OCA, other investigational FXR agonists, pioglitazone or other PPARγ agonists, or high-dose vitamin E (> 400 IU/day) within 3 months prior to Screening. Patients treated with vitamin E ≤ 400 IU/day must have been on stable dose for at least 3 months prior to Screening and should remain on the same dose during study. Patients treated with GLP-1 analogues, DPP-4 inhibitors, and SGLT2 inhibitors must have been on a stable dose for at least 3 months prior to Screening and should remain on the same dose during study.

29. Use of medications potentially impacting steatohepatitis within 3 months of randomization, including but not limited to systemic corticosteroids (prednisone equivalent of > 10 mg/day for > 2 weeks), amiodarone, tamoxifen and methotrexate)

30. Initiation of the following medications within 3 months of randomization; or dose adjustment expected during study participation:

    - Statins or PCSK9 inhibitors
    - Metformin and other antidiabetic drugs (must have been on stable dose for at least 2 months before randomization). Note: GLP-1 analogues, DPP-4 inhibitors, and SGLT2 inhibitors addressed above.
    - Hormonal contraceptives

[redacted]

Prior Clinical Study Experience

32. Participation in another clinical trial within 3 months prior to randomization. [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

5.3.2. Meals and Dietary Restrictions

Patients should arrive at the clinic fasting for assessments and dosing 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.

Patients participating in the PK/PD Sub-Study at (Week 0/Day 1) 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-dose.

[redacted]

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).

Any 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)

[redacted]

6.4. Measures to Minimize Bias: Randomization and Blinding

Patients will be randomized to TERN-101 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 96 patients will be randomized at an overall ratio of 1:1:1:1 into 4 groups receiving 5 mg (n = 24), 10 mg (n = 24), 15 mg (n = 24) TERN-101 tablet, or matching placebo (n = 24). Randomization will ensure 6 patients at each TERN-101 dose level and 6 patients in the placebo group are assigned to the PK/PD sub-study.

Investigators, patients, all study personnel, and the Sponsor will remain blinded to each patient's assigned dose group throughout the course of the study. 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.

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 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. Compliance will be assessed [redacted]

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

[redacted]

Medications prohibited for use within 3 months of randomization and through the end of the study:

- Medications with potential impact on NASH outcome, including OCA, other investigational FXR agonists, pioglitazone or other PPARγ agonists, or high-dose vitamin E (> 400 IU/day).
    - Patients treated with vitamin E ≤ 400 IU/day must have been on stable dose for at least 3 months prior to screening and should remain on the same dose during study.
    - Patients treated with GLP-1 analogues, DPP-4 inhibitors, and SGLT2 inhibitors must have been on a stable dose for at least 3 months prior to screening and should remain on the same dose during 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.

[redacted]

Medications allowed with steady use *if initiated* at least 3 months before randomization, with expectation of no dose adjustment during study participation:

- Statins or PCSK9 inhibitors
- Metformin and other diabetic drugs (must have been on stable dose for at least 2 months before randomization). Note: GLP-1 analogues, DPP-4 inhibitors, and SGLT2 inhibitors addressed above.
- Hormonal contraceptives

The Medical Monitor should be contacted if there are any questions regarding concomitant therapy. Any dose adjustments that may be required during study participation should be discussed with the Medical Monitor.

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, without regard to food. [redacted]

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 made available 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 or Withdrawal

7.1. Discontinuation of Study Drug

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.

[redacted]

7.3. Lost to Follow up

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

[redacted]

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 550 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, in accordance with Section 6.8.1, home health care visits may be made available 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 for eligibility. Waist circumference is also measured at Screening. Only weight is collected at Weeks 0, 4, 6, 8, 12, 16, and ET.

8.1.3. Medical History

Medical 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 and throat), lymph nodes, thyroid, and musculoskeletal systems.

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

[redacted]

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 (eg, television, cell phones).

8.1.6. Electrocardiograms

Single 12-lead electrocardiograms (ECGs) 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 the formula outlined in Appendix 4.

[redacted]

8.1.7. Clinical Laboratory Assessments

See Appendix 1 for the list of clinical laboratory tests to be performed and to 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.

Shifts of clinically significant Grade 3 or Grade 4 laboratory abnormalities or any clinically significant laboratory 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 his study, patients must have an ALT ≥ 43 IU/L for men and ≥ 28 IU/L for women. ALT/AST stability may be evaluated prior to randomization per Section 5.

During the course of the study, 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

Liver stiffness will be assessed by transient elastography 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.

[redacted]

8.1.9. MRI-PDFF

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

Degree of liver steatosis will be measured by MRI-PDFF at Screening. An MRI-PDFF may proceed on the basis of the initial screening ALT/AST level, given all other eligibility criteria are met, but randomization should not occur prior to confirmation of ALT/AST stability as necessary, per Section 5.

An MRI-PDFF should be performed at ET only if not done within the prior 4 weeks, and the patient has had at least 4 weeks of dosing.

The images will be analyzed by a central reader. MRI-cT1 will be collected along with MRI-PDFF at sites with this capability,[redacted]

8.2. Pharmacokinetics

Plasma samples will be collected for measurement of plasma concentrations of study drug 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. [redacted]

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

[redacted]

8.3. Pharmacodynamics

Plasma samples will be collected for measurement of FGF19, 7-α-C4, [redacted] as specified in the Schedule of Activities and Appendix 2. [redacted]

Patients in the PK/PD sub-study will undergo intensive PD sample collection for FGF19 and 7-α-C4, and trough PD sample collection for 7-α-C4 [redacted] 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 for 7-α-C4 [redacted] 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. [redacted]

[redacted]

8.4. Biomarkers

Collection of samples for biomarkers related to NASH is 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 biomarkers: CK-18 (M30 and M65), PIIINP, TIMP-1, HA, Pro-C3, [redacted]

[redacted]

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 intensity, 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 (eg, 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

[redacted]

8.5.6. Assessment of Pruritus

For patients who report AEs consistent with pruritus, photographs of the affected area(s) will be taken at the discretion of the Investigator (eg, if there are visible skin lesions; photos that would identify the patient, ie, of the entire face, will be avoided), and a qualified staff member will administer the Pruritus Numerical Rating Scale (Appendix 8) at each study visit where pruritus is reported or noted to be ongoing. If pruritus is reported, the clinical site will provide details on these events in the eCRF.

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

- Grade 1: Mild or localized; topical intervention indicated.

- Grade 2: Widespread and intermittent; skin changes from scratching (eg, edema, papulation, excoriations, lichenification, oozing/crusts); oral intervention indicated; limiting instrumental activities of daily living (ADL).
- Grade 3: Widespread and constant; limiting self-care, ADL, or sleep; systemic corticosteroid or immunosuppressive therapy indicated.

For Grade 3 cases, follow up by telephone contact or in person visit should occur within 3 days or at the discretion of the Investigator. Additional follow up may take place until symptoms improve. Refer to Section 7 for additional information on study drug discontinuation.

[redacted]

9. Statistical Considerations

9.1. Statistical Hypotheses

The primary objective of the study is to evaluate the safety and tolerability of orally administered TERN-101. No statistical hypothesis is 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 (Table 4).

The mean percent change from baseline in ALT in each TERN-101 group will be compared with placebo separately without any family-wise error rate (overall type I error) control approach, since it is a non-confirmatory study.

Patients who are randomized but do not receive study drug for any reason may be replaced.

9.3. Analysis Sets

The following analysis sets are defined:

Analysis Sets	Description
Enrolled	All patients who sign the ICF
Randomized	All patients who meet all eligibility criteria and are randomized into any one of treatment groups.
[redacted]	[redacted]
Pharmacodynamic (PD)	All randomized patients who received at least 1 dose of study drug (TERN-101 or placebo) and for whom PD markers can be evaluated.
Safety	All randomized patients who received at least 1 dose of study drug and have post dose safety data. Patients will be analyzed according to the intervention they actually received.
Efficacy (Full analysis Set [FAS])	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.
[redacted]	[redacted]

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 statistical analysis plan (SAP) will provide the details and will be finalized prior to clinical DBL.

9.4.1. General Considerations

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

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

The baseline value is defined to be the latest assessment value prior to the first dose of study drug, unless specified in the SAP for some particular tests.

Missing values will not be imputed.

Data analysis will be performed using SAS® Version 9.4 or higher.

SDTM (Study Data Tabulation Model) and Analysis Data Model (ADaM) datasets will be prepared using Clinical Data Interchange Standards Consortium (CDISC) SDTM IG Version 3.2, ADaM Version 2.1, and CDISC ADaM Implementation Guide Version 1.1.

9.4.2. Primary Endpoints

Safety parameters will be listed and summarized using descriptive statistics. The safety parameters will include AEs, and treatment emergent clinical laboratory parameters. No formal statistical testing is planned.

Reported AEs will be coded using the latest version of Medical Dictionary for Regulatory Activities (MedDRA Version 22.1, or most recent) and graded for severity according to NCI CTCAE, Version 5.0.

All TEAEs will be listed and summarized by MedDRA Preferred Term and System Organ Class, as well as by maximum intensity and study drug causality, in frequency and percentage. Summaries of treatment-emergent SAEs, TEAEs related to study drug, TEAEs resulting in study drug discontinuations and death will be produced.

Grade shifts in laboratory tests will be summarized in addition to AEs. Absolute or relative changes from baseline of quantitative measurements will be analyzed by treatment group and timepoints and presented in shift tables, if applicable. Laboratory abnormalities will be graded according to NCI CTCAE Version 5.0.

The number and percentage of subjects experiencing treatment-emergent graded lab toxicities will be summarized by treatment group and severity grade.

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

9.4.3. Secondary Endpoints

9.4.3.1. Change from Baseline in ALT Levels at 12 Weeks

The secondary efficacy variable is the percent change from Baseline in the ALT after 12 weeks of treatment in patients treated with either TERN-101 or matching placebo. The mean percent change from baseline in ALT in each TERN-101 group will be compared with placebo separately without controlling for any family-wise error rate (overall type I error) by using analysis of covariance (ANCOVA) methods. The percent change from baseline in ALT will also

be compared between the three dose groups and placebo using a mixed-model repeated-measures (MMRM) analysis. Corresponding least square mean (LSMEAN) treatment differences with 2 sided 95% confidence limits will be computed for each overall treatment vs placebo comparisons. Pairwise contrasts between active treatments and placebo and a dose-response trend will be produced.

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

[redacted]

9.4.4. Exploratory Endpoints

All exploratory analyses will be performed on efficacy analysis set (FAS). Descriptive statistics for the values, absolute change from baseline, and percent change from baseline will be presented for efficacy continuous variables at various study time points. Categorical variables will be summarized using frequencies and percentages at various study time points.

The following exploratory variables will be analyzed using a mixed-effects model for repeated-measures similar to the MMRM model described in Section 9.4.3.1.

- Change from baseline in LFC by MRI-PDFF at 6 weeks
- Change from baseline in LFC by MRI-PDFF at 12 weeks
- Change from baseline in GGT at 12 weeks
- Change from baseline in AST at 12 weeks

The following exploratory variables will be analyzed using a mixed-effects model for repeated-measures similar to the MMRM model described in Section 9.4.3.1 for the trough PD sampling.

- Change from baseline in FGF-19 and 7-α-C4
- Change from baseline in NASH/fibrosis biomarkers

For the Intensive PD sampling sub-study an ANOVA model will be fit with change from baseline as response variable, and baseline value and treatment as fixed effects.

- Change from baseline in FGF-19 and 7-α-C4
- Change from baseline in NASH/fibrosis biomarkers

[redacted]

MRI-cT1 [redacted] will be addressed in the SAP.

9.4.4.1. PD Endpoints

[redacted] No formal statistical analysis of PD data is planned, however, data may be used for statistical analysis or modeling to evaluate correlation of PK and PD parameters, if applicable. These analyses will be defined in the SAP.

[redacted]

[redacted]

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 on Harmonisation (ICH) Good Clinical Practice (GCP) Guidelines
- Applicable laws and regulations

The protocol, protocol amendments, ICF, Investigator Brochure, and other relevant documents (eg., 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, Inc, as appropriate. Terns, Inc. 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 on the US National Institutes of Health's website www.ClinTrials.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 (eg, 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 (eg, 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 (eg, 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 (ie, United States, Europe, or Japan) and until there are no pending or contemplated marketing applications in an ICH region (ie, 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 subject 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 5 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 5 Protocol-Required Clinical Laboratory Assessments

Laboratory Assessments	Parameters	
Hematology	Hematocrit Hemoglobin Hemoglobin A1c[1] Platelet Count RBC Count RBC Indices: • MCV • MCH • % Reticulocytes	WBC count with Differential: • Neutrophils • Lymphocytes • Monocytes • Eosinophils • Basophils
Clinical Chemistry[2]	Bicarbonate BUN Chloride CPK Creatinine eGFR[3] Glucose Potassium Sodium Total Protein	Liver Function Tests: • ALT • Albumin • AST • ALP • GGT [redacted]
Coagulation[5]	Prothrombin Time (PT)/International Normalized Ratio (INR)	
Fasting Lipid Profile	HDL LDL	

	Total Cholesterol Triglycerides VLDL
Urinalysis	• Specific gravity • pH, glucose, protein, blood, ketones, bilirubin, urobilinogen, nitrite, leukocyte esterase by dipstick • Microscopic examination (if blood or protein is abnormal)
[redacted]	[redacted]
Other Tests	• [redacted] • 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: β-hCG = β-human chorionic gonadotropin; ALP = alkaline phosphatase; ALT = alanine transaminase; AST = aspartate transaminase; 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; LDL = low-density lipoprotein; MCH = mean corpuscular hemoglobin; MCV = mean corpuscular volume; PCR = polymerase chain reaction; RBC = red blood cell; RNA = ribonucleic acid; SARS-CoV-2 = Severe Acute Respiratory Syndrome Coronavirus 2; VLDL = very low-density lipoprotein; WBC = white blood cell; WOCBP = women of childbearing potential

Investigators must document their review of each laboratory safety report. Shifts of clinically significant Grade 3 or Grade 4 laboratory abnormalities or any clinically significant laboratory 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.

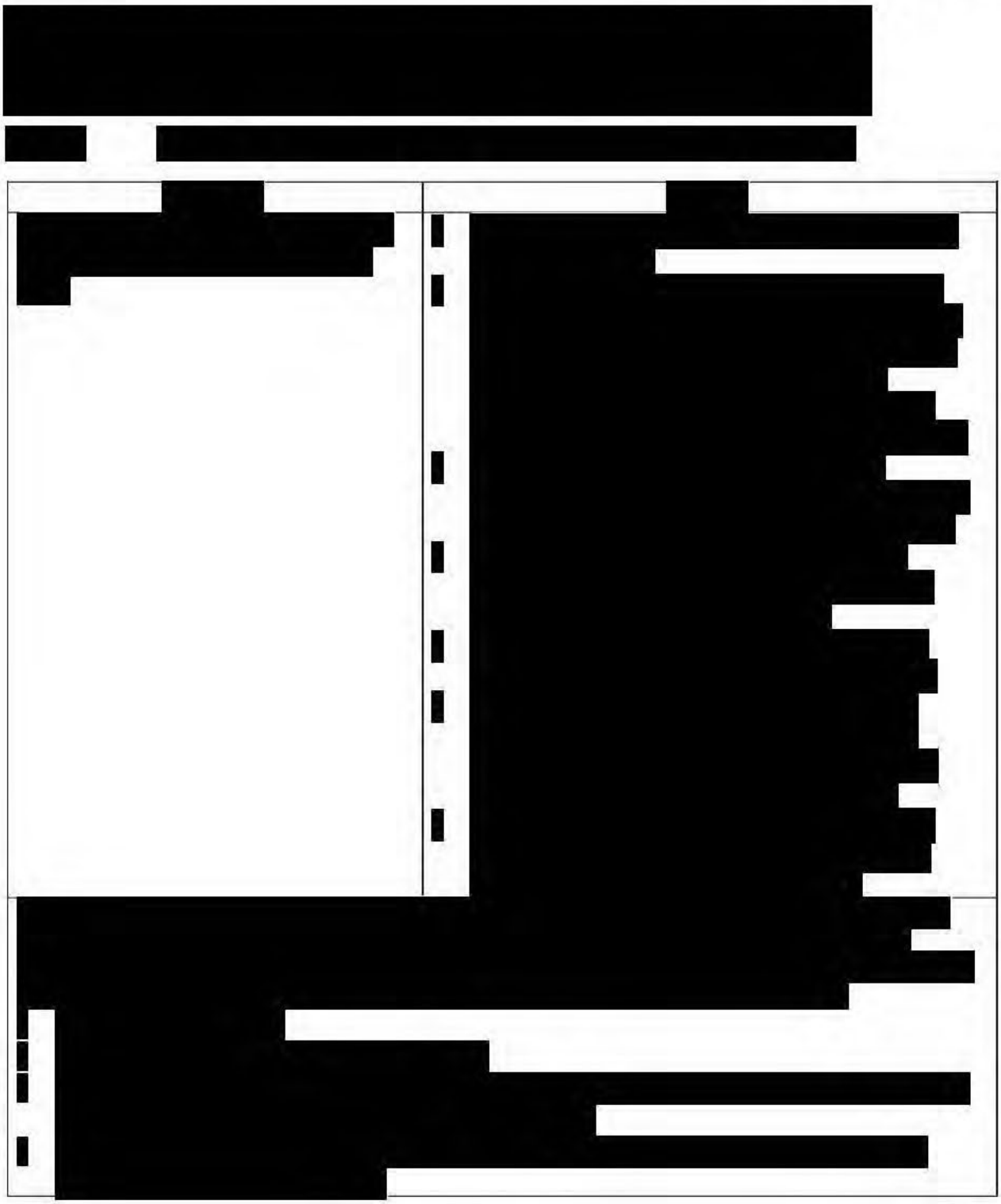
Laboratory/analyte results that could unblind the study will not be reported to investigative sites or other blinded personnel until the study has been unblinded.

Appendix 2: Sample Collection for Pharmacokinetics and Pharmacodynamics

Table 6 presents a description of PK/PD sample requirements at each study visit and timepoint.

Table 6 PK/PD Sampling Timepoints

Week	Day	Timepoint
0	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 3 hours ± 15 minutes o 6 hours ± 15 minutes
0	2	• Post Day 1 dose at the following timepoint (PK/PD sub-study only): o 24 hours ± 1 hour prior to dosing on Day 2
2	15 ± 3	• Pre-dose (All Patients)
4	29 ± 3	• Pre-dose (All Patients)
6	43 ± 3	• Pre-dose (All Patients)
8	57 ± 3	• Pre-dose (All Patients)
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 3 hours ± 15 minutes o 6 hours ± 15 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
[redacted]	[redacted]	[redacted]



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 Fredericia's Formula as outlined below.

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

Fridericia's Formula:

QTc = 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
$\kappa = 0.7$ (females) or 0.9 (males)
$\alpha = -0.329$ (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 (eg, ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (ie, 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 intensity 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 (eg, 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 (eg, 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 (eg, 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 (eg, 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 Intensity

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.

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.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.

[redacted]

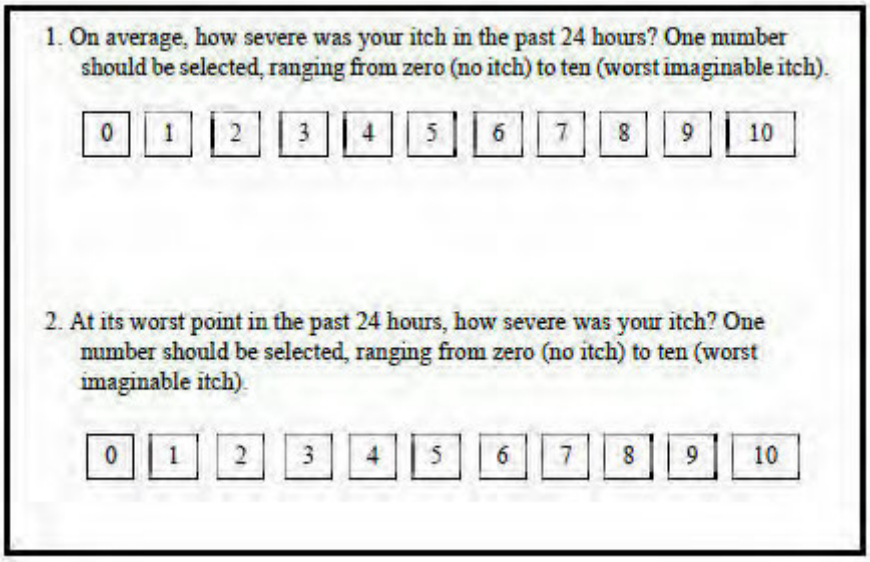
[redacted]

[redacted]

[redacted]

Appendix 8: Pruritus Numerical Rating Scale

This Numerical Rating Scale was adapted from IFSI SIG/EADV Task Force Pruritus assessments available at http://www.pruritussymposium.de/numericalratingscale.html.


1. On average, how severe was your itch in the past 24 hours? One number should be selected, ranging from zero (no itch) to ten (worst imaginable itch).

0	1	2	3	4	5	6	7	8	9	10

2. At its worst point in the past 24 hours, how severe was your itch? One number should be selected, ranging from zero (no itch) to ten (worst imaginable itch).

0	1	2	3	4	5	6	7	8	9	10

Appendix 9: 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] antibody required; Immunoglobulin M [IgM] antibody recommended in addition).
- Prior to central laboratory testing availability, antibody testing may be omitted if not available locally.

At Week 0, 6, and 12:

- Testing for past infection via antibody testing (IgG required; IgM recommended in addition) if prior IgG was negative.
- Prior to central laboratory testing availability, testing for active infection (e.g. molecular test such as PCR or viral antigen serology) may replace antibody testing if the latter is not available locally.
- If Week 0 occurs within 2 weeks of Screening, site may omit repeat SARS-CoV-2 testing at PI discretion.
- If IgM antibody test is positive, may reflex to test for SARS-CoV-2 active infection at 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, once available via the central laboratory), 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 10: Abbreviations

Abbreviation or Special Term	Explanation
7-α-C4	7α-hydroxy-4-cholesten-3-one
β-hCG	Human chorionic gonadotropin
ADaM	Analysis Data Model
ADL	Activities of Daily Living
AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine transaminase
ANCOVA	Analysis of covariance
AST	Aspartate transaminase
AUC	Area under the concentration-time curve
BMI	Body mass index
BUN	Biliary urea nitrogen
CAP	Controlled attenuation parameter
CDISC	Clinical Data Interchange Standards Consortium
CFR	Code of Federal Regulations
CIOMS	Council for International Organizations of Medical Sciences
COVID-19	Coronavirus disease 2019
CPK	Creatinine phosphokinase
CONSORT	Consolidated Standards of Reporting Trials
C_{max}	Maximal concentration
CRF	Case report form
CSR	Clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
CYP	Cytochrome P450
CV	Coefficient of variation
DBL	Database lock
eGFR	Estimated glomerular filtration rate
eCRF	Electronic case report form
ECG	Electrocardiographic
ET	Early Termination
FAS	Full Analysis Set
FDA	Food and Drug Administration
FGF	Fibroblast growth factor
FSH	Follicle stimulating hormone

Abbreviation or Special Term	Explanation
FXR	Farnesoid X receptor
GCP	Good clinical practice
GGT	Gamma-glutamyl transpeptidase
HBsAG	Hepatitis B virus surface antigen
HCV	Hepatitis C virus
HDL	High-density lipoprotein
HIV	Human immunodeficiency virus
HIPAA	Health Insurance Portability and Accountability Act
HRT	Hormone replacement therapy
ICF	Informed consent form
ICH	International Council on Harmonisation
IEC	Independent Ethics Committee
IND	Investigational new drug
INR	International normalized ratio
IRB	Institutional Review Board
IUD	Intrauterine device
IUS	Intrauterine hormone-releasing system
IWRS	Interactive web response system
LAM	lactational amenorrhoea method
LDL	Low-density lipoprotein
LDLR	Low-density lipoprotein receptor
LFC	Liver fat content
LFT	Liver function test
MCH	Mean corpuscular hemoglobin
MCV	Mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
MRI-PDFF	Magnetic Resonance Imaging Proton Density Fat Fraction
mpk	mg/kg
NAFLD	Non-alcoholic fatty liver disease
NAS	Non-alcoholic fatty liver disease activity score
NASH	Non-alcoholic Steatohepatitis
NCI	National Cancer Institute
NHP	Nonhuman primate
NOAEL	No observed adverse effect level
OCA	Obeticholic acid
PCR	Polymerase chain reaction

Abbreviation or Special Term	Explanation
PD	Pharmacodynamics
PK	Pharmacokinetics
po	*Per os* (oral)
QD	Once daily
RBC	Red blood cell
RNA	Ribonucleic acid
SAE	Serious adverse event
SAP	Statistical analysis plan
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SCr	Standardized serum creatinine
SD	Sprague Dawley
SoA	Schedule of Activities
SUSAR	Suspected unexpected serious adverse reactions
TEAE	Treatment emergent adverse event
TERN-101	An investigational agonist of Farnesoid X receptor
US	United States
VLDL	Very low-density lipoprotein
WBC	White blood cell
WOCBP	Women of child bearing potential

Appendix 11: Investigator Signature Page

Protocol Title: A Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Phase 2a Clinical Trial to Evaluate the Safety, Tolerability, Efficacy, and Pharmacokinetics of Orally Administered TERN-101 Tablets in Adult Patients with Presumed Non-Cirrhotic Non-Alcoholic Steatohepatitis (NASH)

Protocol Number: TERN101-2001

Protocol Version/Date: Amendment 1; 22 May 2020

I confirm that I have read the above-mentioned protocol and its attachments. I agree to conduct the described trial 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 12: Protocol Amendment History

This document (dated 22 May 2020) is Amendment 1, the document history is below. The Summary of Changes for each amendment listed below will be provided separately.

DOCUMENT HISTORY	
Document	**Date**
Amendment 1	22-May-2020
Original	26-Feb-2020

Appendix 13: References

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