CLINICAL STUDY PROTOCOL

Protocol Title:	A Multicenter, Randomized, Double-Blind, Placebo-Controlled, Phase 2a Clinical Study to Evaluate the Safety, Efficacy, Pharmacokinetics, and Pharmacodynamics of Orally Administered TERN-501 as Monotherapy as well as in Combination with TERN-101 in Noncirrhotic Adults with Presumed Non-Alcoholic Steatohepatitis (NASH)
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CONFIDENTIAL

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Chief Medical Officer
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1. Protocol Summary

1.1. Synopsis

Protocol Title:

A Multicenter, Randomized, Double-Blind, Placebo-Controlled, Phase 2a Clinical Study to Evaluate the Safety, Efficacy, Pharmacokinetics, and Pharmacodynamics of Orally Administered TERN-501 as Monotherapy as well as in Combination with TERN-101 in Noncirrhotic Adults with Presumed Non-Alcoholic Steatohepatitis (NASH)

Rationale:

[redacted]

Due to the multifactorial pathophysiology of NASH, including metabolic dysregulation, increased hepatic oxidative stress and inflammation, and the onset of profibrogenic processes (Magee 2016), a combination approach to treatment with complementary mechanisms may be more efficacious than monotherapy. FXR activation has been shown to improve histological features associated with NASH including hepatic steatosis, inflammation, hepatocyte ballooning, and, in a phase 3 study, fibrosis (Younossi 2019). [redacted]

[redacted]

[redacted]

Objectives and Endpoints:

Primary Objective	Primary Endpoint
• To evaluate the effect of TERN-501 monotherapy on liver fat content as assessed by MRI-PDFF compared to placebo	• Relative change from baseline in MRI-PDFF at Week 12 for TERN-501 compared to placebo
Secondary Objectives	**Secondary Endpoints**
• To evaluate the effect of TERN-501 monotherapy on cT1 relaxation time compared to placebo • To evaluate the effect of TERN-501+TERN-101 on liver fat content as assessed by MRI-PDFF and on cT1 relaxation time compared to placebo • To evaluate safety and tolerability of TERN-501 monotherapy and TERN-501+TERN-101	• Change from baseline in cT1 relaxation time at Week 12 for TERN-501 compared to placebo • Relative change from baseline in MRI-PDFF at Week 12 for TERN-501+TERN-101 compared to placebo • Change from baseline in cT1 relaxation time at Week 12 for TERN-501+TERN-101 compared to placebo • Patient incidence of treatment emergent adverse events
Exploratory Objectives	**Exploratory Endpoints**
• To explore the effect of TERN-501 monotherapy on efficacy and markers of target engagement compared to placebo • To explore the effect of TERN-501+TERN-101 on efficacy and markers of target engagement, compared to placebo and/or each monotherapy	• Change from baseline in the following parameters, as applicable: ○ ALT, AST, and GGT ○ FIB-4, CK-18 (M30 and M65), ELF (PIIINP, TIMP-1, HA), PRO-C3, and FAST score ○ TE and CAP ○ MRI-PDFF (relative change) and cT1 ○ SHBG ○ Lipid panel (for PD as well as safety evaluation) ○ rT3 ○ FGF19, bile acids, and 7αC4 • Proportion of responders on MRI-PDFF and/or cT1 with the following:

	○ ≥ 30% relative reduction in MRI-PDFF ○ ≥ 80 msec reduction in cT1
• To evaluate the pharmacokinetics of TERN-501 and TERN-101 administered alone and in combination	• PK parameters (e.g., AUC, C_{max}, C_{tau})

Abbreviations: 7αC4 = 7α-hydroxy-4-cholesten-3-one; ALT = alanine transaminase; AST = aspartate transaminase; AUC = area under the concentration-time curve, CAP = controlled attenuation parameter; CK-18 = cytokeratin-18; C_{max} = maximum observed concentration; cT1 = corrected T1; C_{tau} = concentration at the end of the dosing interval; ELF = enhanced liver fibrosis; FAST score = FibroScan AST score; FGF19 = fibroblast growth factor-19; FIB-4 = fibrosis-4; GGT = gamma-glutamyl transferase; HA = hyaluronic acid; MRI = magnetic resonance imaging; MRI-PDFF = magnetic resonance imaging proton density fact fraction; PIIINP = procollagen III N-terminal propeptide; PD = pharmacodynamics; PK = pharmacokinetics; PRO-C3 = released N-terminal pro-peptide of type III collagen; rT3 = reverse T3; SHBG = sex hormone binding globulin; TIMP-1 = tissue inhibitor of metalloproteinases-1; TE = transient elastography

Overall Design:

This study is a multicenter, randomized, double-blind, placebo-controlled, parallel-group treatment, phase 2a study.

Approximately 140 noncirrhotic NASH patients with fibrosis identified based on prior liver biopsy and/or imaging and clinical criteria who meet study eligibility criteria will be enrolled and randomized into one of the 7 treatment groups: once daily orally administered TERN-501 1 mg (n=20), TERN-501 3 mg (n=20), TERN-501 6 mg (n=20), TERN-501 3 mg+TERN-101 10 mg (n=20), TERN-501 6 mg+TERN-101 10 mg (n=20), TERN-101 10 mg (n=20), or matching placebo (n=20).

Of the 140 patients randomized, approximately 42 patients (approximately 6 per group) will take part in an intensive PK and pharmacodynamic (PD) collection after the first dose and after the last dose of study drug. Patients who are not participating in the PK/PD sub-study will have sparse PK and trough PD sampling.

Number of Patients:

Approximately 140 patients will be randomly assigned to one of the 7 treatment groups specified above.

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

Study Centers Planned:

Approximately 40 centers in the United States

Intervention Groups and Duration:

The total study duration will be approximately 22 weeks, consisting of up to a 6-week Screening period (42 days), a 12-week Treatment period, and a 4-week Follow-up period.

Screening Period

The ≤ 6-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 drugs (TERN-501, TERN-101, TERN-501+TERN-101, or matching placebo) will be orally administered once daily.

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 approximately 42 patients participating in the PK/PD sub-study on the day of first dose (Week 0/Day 1) and on the day of last dose of study drug (Week 12).

Transient elastography (TE) and controlled attenuation parameter (CAP) by FibroScan® will be completed at Screening or Day 1, and Week 12. MRI-PDFF, and cT1 will be completed at Screening, Week 6, and Week 12. FibroScan® and MRI-PDFF will be 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.

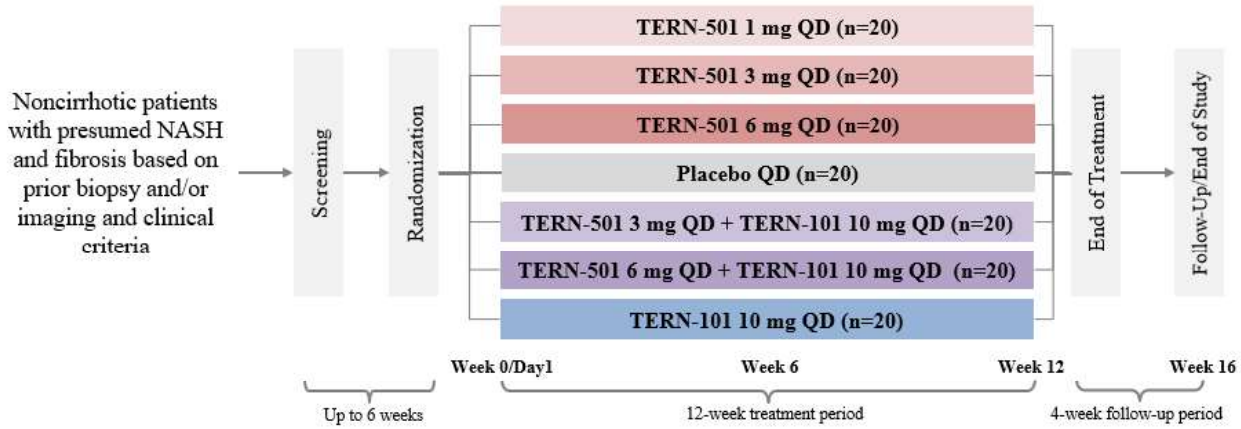
All visits through Week 12 will have a ± 3 days visit window from the specific study day.

Follow-up Period

All patients will return to site for follow up safety assessments at Week 16. Week 16 will have a –7 days /+2 days visit window.

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 at the remaining visits through the Follow-Up visit. 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


Noncirrhotic patients with presumed NASH and fibrosis based on prior biopsy and/or imaging and clinical criteria
Screening
Randomization
TERN-501 1 mg QD (n=20)
TERN-501 3 mg QD (n=20)
TERN-501 6 mg QD (n=20)
Placebo QD (n=20)
TERN-501 3 mg QD + TERN-101 10 mg QD (n=20)
TERN-501 6 mg QD + TERN-101 10 mg QD (n=20)
TERN-101 10 mg QD (n=20)
End of Treatment
Follow-Up/End of Study
Week 0/Day1
Week 6
Week 12
Week 16
Up to 6 weeks
12-week treatment period
4-week follow-up period

1.3. Schedule of Activities (SoA)

	Screening	Treatment Period[f]						Follow-Up[b]	ET[a]	Notes
Visit	**Screening**	**Week 0**	**Week 2**	**Week 4**	**Week 6**	**Week 8**	**Week 12**	**Week 16**		
Study Day		**Day 1**	**15**	**29**	**43**	**57**	**85**	**113**		
Schedule Window (days)	**-42 days**		**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**-7 /+2**		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 visit 4 weeks (-7 days /+2 days) after the last dose of study drug.
Clinical Procedures/Assessments										
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.
Demographics	X									Includes age (year of birth), sex, race, and ethnicity.
Weight	X	X			X		X	X	X	
BMI	X									
Height	X									
Medical history	X									Medical history including details of illnesses, allergies, or procedures including liver biopsy, date(s) of onset, whether condition(s) is currently ongoing, medication history, including alcohol use
Complete Physical Examination	X							X	X	

	Screening	Treatment Period[f]						Follow-Up[b]	ET[a]	Notes
Visit	**Screening**	**Week 0**	**Week 2**	**Week 4**	**Week 6**	**Week 8**	**Week 12**	**Week 16**		
Study Day		**Day 1**	**15**	**29**	**43**	**57**	**85**	**113**		
Schedule Window (days)	**-42 days**		**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**-7 /+2**		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 visit 4 weeks (-7 days /+2 days) after the last dose of study drug.
Targeted Physical Examination		X[c]	X	X	X	X	X			A targeted physical examination will be conducted as needed, based on clinical judgement of the Investigator, to evaluate reported current or prior AEs, symptoms reported by the patient, or abnormal laboratory readouts.
Vital Signs	X	X[c]	X	X	X	X	X	X	X	Includes temperature, pulse rate, respiratory rate, and blood pressure. Blood pressure and pulse measurements should be preceded by at least 5 minutes of rest for the patient in a quiet setting without distractions.
12-lead ECG	X	X[c]	X	X	X	X	X	X	X	Participants will lie supine in a quiet setting without distractions for at least 10 minutes prior to 12-lead ECG collection.
Smoking status		X					X		X	
AE Review		←==========						==========→		See Section 8.5 for additional details on AE and SAE reporting.
Pruritus Assessment		←==========						==========→		Reported AEs consistent with pruritus will be assessed using the Pruritus Numerical Rating Scale (Appendix 8). See Section 8.5.6 for additional details.
Concomitant Medications Review		←==========						==========→		

	Screening	Treatment Period[f]						Follow-Up[b]	ET[a]	Notes
Visit	**Screening**	**Week 0**	**Week 2**	**Week 4**	**Week 6**	**Week 8**	**Week 12**	**Week 16**		
Study Day		**Day 1**	**15**	**29**	**43**	**57**	**85**	**113**		
Schedule Window (days)	**-42 days**		**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**-7 /+2**		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 visit 4 weeks (-7 days /+2 days) after the last dose of study drug.
Lifestyle Counseling		←==========	==========	==========	==========	==========	==========→			Guidance should be provided on key elements of a healthy lifestyle at each visit including diet, exercise, weight loss, and avoidance of alcohol per standard of care management for this patient population.
Imaging Assessments										
TE and CAP by FibroScan®	X	X[i]					X		X	If TE and CAP by FibroScan® was performed at Screening, it does not need to be repeated at Day 1. TE and CAP by FibroScan® 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.
MRI-PDFF[e]	X				X		X		X	Screening MRI-PDFF and MRI-cT1 may proceed on the basis of the initial ALT and AST level at Screening, given all other eligibility criteria are met, but randomization should not occur prior to confirmation of ALT and AST stability, as necessary. MRI-PDFF and MRI-cT1 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.
MRI-cT1[e]	X				X		X		X	
PK and PD Procedures/Assessments										
Sparse PK Sampling			X[c]	X[d]	X[c]	X[c]	X[c]		X	Only one sample will be collected at each visit, see footnotes for timing. 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.

	Screening	Treatment Period[f]						Follow -Up[b]	ET[a]	Notes
Visit	**Screening**	**Week 0**	**Week 2**	**Week 4**	**Week 6**	**Week 8**	**Week 12**	**Week 16**		
Study Day		**Day 1**	**15**	**29**	**43**	**57**	**85**	**113**		
Schedule Window (days)	**-42 days**		**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**-7 /+2**		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 visit 4 weeks (-7 days /+2 days) after the last dose of study drug.
Trough PD Sampling[c]		X	X	X	X		X		X	Refer to Appendix 2 for additional detail.
NASH/ Fibrosis Biomarkers[c]		X			X		X		X	Includes CK-18 (M30 and M65), ELF (PIIINP, TIMP-1, HA), and PRO-C3.
Intensive PK Sampling *(PK/PD sub-study only)*		X					X[j]			Intensive PK sampling will be performed pre-dose and 1, 2, 4, 6, and 24 hours post the first dose of study drug on Week 0/Day 1, and at pre-dose and 1, 2, 4, 6, 24, 48, and 72 hours post last dose of study drug at Week 12. Patients should be instructed to hold their dose of study drug until after pre-dose and after 24-hour PK samples are collected. Refer to Appendix 2 for additional detail.
Intensive PD Sampling *(PK/PD sub-study Only)*		X					X[j]			7αC4 and FGF19 will be collected at matching timepoints to Intensive PK sampling (above) except at Week 12 when 7αC4 and FGF19 will not be collected at 48 and 72 hours post dose. Refer to Appendix 2 for additional detail.
Clinical Laboratory Procedures/Assessments										
Patient Fasting	X	X	X	X	X	X	X	X	X	Patients must be in fasted state for at least 8 hours prior to blood collection and treatment administration, where applicable.

	Screening	Treatment Period[f]						Follow-Up[b]	ET[a]	Notes
Visit	**Screening**	**Week 0**	**Week 2**	**Week 4**	**Week 6**	**Week 8**	**Week 12**	**Week 16**		
Study Day		**Day 1**	**15**	**29**	**43**	**57**	**85**	**113**		
Schedule Window (days)	**-42 days**		**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**-7 /+2**		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 visit 4 weeks (-7 days /+2 days) after the last dose of study drug.
Chemistry[c]	X	X	X	X	X	X	X	X	X	Specific analytes are listed in Appendix 1. ALT and AST stability may be evaluated prior to randomization per Section 5. Increased monitoring criteria for elevated ALT and/or AST above 2×Baseline or above 5×ULN, and elevated ALP above 3×ULN are outlined in Appendix 3. A standard lipid test will be collected as part of the clinical chemistry at Screening to confirm eligibility (Appendix 1). During study treatment, lipid parameters for PD assessments listed in Table 9 of Appendix 2 will be collected and results will be blinded. HDL will remain unblinded and will be collected as part of clinical chemistry at all visits. 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.
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 29 and 30 are not met.

	Screening	Treatment Period[f]						Follow-Up[b]	ET[a]	Notes
Visit	**Screening**	**Week 0**	**Week 2**	**Week 4**	**Week 6**	**Week 8**	**Week 12**	**Week 16**		
Study Day		**Day 1**	**15**	**29**	**43**	**57**	**85**	**113**		
Schedule Window (days)	**-42 days**		**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**-7 /+2**		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 visit 4 weeks (-7 days /+2 days) after the last dose of study drug.
Thyroid Axis Testing[c]	X	X	X		X		X	X	X	All thyroid axis samples (including any repeat tests) should be collected in the morning at approximately the same time on each visit day. Specific analytes are listed in Appendix 1. Post-dose T4 and rT3 results will remain blinded as outlined in Section 8.1.9.1. Refer to Section 8.1.8 for additional detail on thyroid axis safety monitoring. TBG and rT3 will be analyzed only at Week 0/Day 1 and Week 12 or ET.
Bone turnover markers[c]		X					X	X	X	Includes sCTX and sPINP.
Sex Hormone Panel[c]		X					X	X	X	Specific analytes are listed in Appendix 1.
Serology	X									Includes HBsAg, anti-HCV and anti-HIV.
COVID-19 Assessment[c,g]	X	X			X		X			Screening and on study COVID-19 assessments should be conducted in accordance with Appendix 9.
Serum pregnancy test[c]	X	X		X		X	X		X	WOCBP only.
Urine pregnancy test[c]		X								WOCBP only. Urine pregnancy test will be completed on Day 1 and negative test result must be confirmed prior to randomization.
Serum FSH	X									Women of non-childbearing potential only. In the absence of 12 months of amenorrhea, confirmation with more than one FSH measurement is required.
Blood Alcohol Test	X									

	Screening	Treatment Period[f]						Follow -Up[b]	ET[a]	Notes
Visit	**Screening**	**Week 0**	**Week 2**	**Week 4**	**Week 6**	**Week 8**	**Week 12**	**Week 16**		
Study Day		**Day 1**	**15**	**29**	**43**	**57**	**85**	**113**		
Schedule Window (days)	**-42 days**		**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**-7 /+2**		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 visit 4 weeks (-7 days /+2 days) after the last dose of study drug.
Study Drug Procedures										
Randomization		X								Confirm Inclusion and Exclusionary criteria before randomization and first dose of study drug.
Take Study Drug		X	X	X	X	X	X			At all study visits, study drug administration will be observed at the study site. Patients should be instructed to hold their dose of study drug on visit days until necessary visit procedures have been completed. On all other days, patients will self-administer the study drug orally once daily at approximately the same time, on an empty stomach (no food or drink besides clear liquids for approximately 2 hours before and 1 hour after study drug administration).
Dispense Study Drug[h]		X		X		X				Study drug will be assigned via the IWRS and provided in a carton containing four bottles: 2 capsules and 2 tablets for 4-week use.
Drug Accountability			X	X	X	X	X		X	

[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 (-7 days /+2 days) after the last dose of study drug.
[b] The Follow-Up may take place at Week 16 (-7 days /+2 days) or 4 weeks (-7 days/+2 days) after the last dose of study drug if patients discontinue the study at any time for any reason (Early Termination).
[c] Assessment should be collected pre-dose, as applicable.
[d] A single PK sample should be collected between 2 and 6 hours postdose.
[e] MRI-cT1 will be collected along with MRI-PDFF.

[f] 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.
[g] In the event of symptoms suggestive of COVID-19, ad hoc testing (including molecular test such as PCR or viral antigen serology, and/or antibody testing) may be completed at Investigator's discretion.
[h] If a patient is required to be quarantined due to active infection of COVID-19 or exposure to COVID-19 or is otherwise unable to visit the site due COVID-19, study drug may be mailed to the patient or made available via another appropriate mechanism (ie, curbside pickup, etc.).
[i] If TE and CAP were collected at Screening, these assessments will not be required on Day 1. See Section 5.1, inclusion criteria #4b for additional details.
[j] For patients participating in the PK/PD sub-study, drug must be self-administered in the morning approximately 24 hours before their Week 12 visit. If not, the Week 12 PK/PD sub-study visit should be re-scheduled for the following day.

Abbreviations: 7αC4 = 7α-hydroxy-4-cholesten-3-one; AE = adverse event; ALT = alanine transaminase; AST = aspartate transaminase; BMI = body mass index; CAP = controlled attenuation parameter; CK18 = cytokeratin-18; COVID-19 = coronavirus disease 2019; CTCAE = common terminology criteria for adverse events; sCTX = serum terminal telopeptide of type 1 collagen; ECG = electrocardiogram; ELF = enhanced liver fibrosis; ET = early termination; eGFR = estimated glomerular filtration rate; FSH = follicle stimulating hormone; HA = hyaluronic acid; FGF19 = fibroblast growth factor-19; 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-cT1 = magnetic resonance imaging corrected T1; MRI-PDFF = magnetic resonance imaging proton density fact fraction; NCI = National Cancer Institute; PCR = polymerase chain reaction; PD = pharmacodynamics; PIIINP = procollagen III N-terminal propeptide; sPINP = serum procollagen type I N-propeptide; PK = pharmacokinetics; PRO-C3 = released N-terminal pro-peptide of type III collagen; rT3 = reverse T3; SAE = serious adverse event; TBG = thyroid binding globulin; TE = transient elastography; TIMP-1 = tissue inhibitor of metalloproteinases-1; ULN = upper limit of normal; WOCBP = women of childbearing potential.

2. Introduction

2.1. Overview of Non-alcoholic Steatohepatitis (NASH) and Unmet Need

This study is a randomized, double-blind, placebo-controlled, parallel-group treatment, phase 2a study to evaluate the safety, efficacy, pharmacokinetics, and pharmacodynamics of orally administered TERN-501 as monotherapy and in combination with TERN-101 in noncirrhotic adult patients with presumed NASH.

NAFLD is characterized by an excessive accumulation of fat deposits in liver tissue, commonly associated with co-morbidities such as obesity, diabetes mellitus, and dyslipidemia, in the absence of secondary causes of liver fat accumulation. NASH, an advanced form of NAFLD, is defined by the presence of hepatic inflammation and hepatocellular ballooning, with or without fibrosis, in the setting of underlying hepatic steatosis. Progression from NAFLD to NASH can be rapid and, with progression, NASH can lead to cirrhosis, decompensated liver disease, and increased risk for hepatic carcinoma and liver-related mortality (Ekstedt 2015). Complications from end-stage liver disease (e.g., jaundice, edema, ascites, portal hypertension, coagulopathy, hepatic encephalopathy) are challenging to manage and may require liver transplantation. NASH was recently identified as the second leading etiologic indication for liver transplantation in the United States (US), and it is projected to become the leading cause of liver transplantation in the coming years (Wong 2015). Patients with NAFLD have a 7-fold increased risk of mortality from hepatocellular carcinoma compared with a matched reference population (Ekstedt 2015).

NAFLD is the most common cause of chronic liver disease in North America (Chalasani 2018), and its prevalence of NAFLD is steadily increasing with the aging population and cardiovascular and endocrine comorbidities associated with obesity, (e.g., atherosclerosis, insulin resistance/diabetes mellitus) (Dietrich 2014, Lonardo 2018, Andronescu 2018). Approximately 30% of patients with NAFLD may progress to NASH. Currently, there are no approved therapies for NASH. Therapeutic options are limited to management of comorbidities such as hyperlipidemia, insulin resistance/diabetes, and obesity, with weight loss through diet and exercise as a key treatment for NASH (Chalasani 2018). However, many patients are unable to comply long-term with the required dietary and lifestyle changes. For advanced fibrosis, cirrhosis, and hepatocellular carcinoma, liver transplantation may be the only treatment option. A therapeutic agent that addresses NASH would offer a significant advancement for this unmet medical need.

2.2. Background

2.2.1. THR-β Agonism and TERN-501 for Treatment of NASH

THR-β is the major form of thyroid hormone receptor in the liver, where it plays an important role in energy metabolism, with stimulation of THR-β leading to liver fat and serum lipids

reduction (Taub 2013; Harrison 2019). Thyroid hormone regulates metabolism by modulating gene expression directly and through crosstalk with other nuclear hormone receptors (Liu 2010).

Thyroid hormone agonism was initially explored for treatment of dyslipidemia using first generation agents such as eprotirome and sobetirome (Zucchi 2020). Eprotirome, a modestly selective THR-β agonist, reduced LDL cholesterol when added to conventional statin therapy, but led to increased liver enzymes in a phase 3 trial (Sjouke 2014). Other earlier agonists with modest THR-β selectivity, led to concerns of bone loss (Ladenson 2010) and cardiac toxicity (Coronary Drug Project 1972). Currently, two synthetic THR-β selective agonists are in clinical development for NASH, resmetirom (MGL-3196, Madrigal Pharmaceuticals) a liver-directed, orally active agonist of THR-β, and VK2809 (MB07811, Viking Therapeutics), a cytochrome P450-activated prodrug. Resmetirom improved lipid parameters, reduced liver fat, and improved histologic measures of NASH on liver biopsy over 36 weeks, with an overall reassuring safety profile (Harrison 2019). VK2809 reduced cholesterol and both serum and hepatic triglycerides at doses that were sparing of cardiac toxicity and did not affect body or heart weight, glycemia, or the thyroid hormone axis in animal models (Erion 2007). Preliminary clinical study data indicates that VK2809 reduced liver fat content and improved lipid profiles over 12 weeks of treatment with no noted safety concerns (Loomba 2019); however, increases in mean ALT in a dose-dependent fashion over 14 days of dosing in healthy volunteers have been reported (Lian 2016).

TERN-501, a novel thyroid hormone analogue, is being developed for NASH. TERN-501 has a 23-fold selectivity for THR-β over THR-α in vitro and shows enhanced liver distribution. In a rat distribution study, TERN-501 concentrations in the liver were 2.5-fold higher than in plasma and kidney, and 16-fold higher than in the heart. With high selectivity for THR-β over THR-α and enhanced liver distribution, TERN-501 may offer NASH patients an important treatment option. In the FIH study (Study TERN501-1009), single doses up to 60 mg and once daily doses up to 10 mg for 14 days were assessed in healthy subjects with mildly elevated LDL cholesterol. TERN-501 was overall safe and well-tolerated with a favorable PK profile and demonstrated significant increases in SHBG, a key marker of hepatic THR-β engagement and significant reductions in LDL cholesterol and other lipid parameters, supporting further investigation of TERN-501 in patients with NASH (See Section 2.2.1.2). Detailed background on thyroid hormone and the potential role of THR-β selective agonism and TERN-501 in NASH are provided in the Investigator's Brochure.

2.2.1.1. Nonclinical Studies of TERN-501

Key findings from nonclinical studies including pharmacology, pharmacokinetics, and toxicology for TERN-501, are summarized below. Additional details are available in the Investigator's Brochure.

2.2.1.1.1. Pharmacology of TERN-501

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2.2.1.1.2. Nonclinical Safety Studies of TERN-501

2.2.1.1.2.1. Toxicology, Toxicokinetics, and Safety Pharmacology

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2.2.1.2. Clinical Study of TERN-501

One clinical study of TERN-501 (Study TERN501-1009) has been conducted to-date. Study TERN501-1009 was a FIH, phase 1 study conducted in healthy human subjects and is

described below. Additional details of the study design and results are available in the Investigator's Brochure.

Study TERN501-1009 had four parts: Parts A and B were double-blinded, randomized, and placebo-controlled and included single- and multiple-ascending dose (SAD and MAD) cohorts, respectively. Single doses of 3 mg, 10 mg, 30 mg, and 60 mg TERN-501 were evaluated in Part A (SAD) and once daily dosing of 1 mg, 3 mg, 6 mg, and 10 mg TERN-501 for 14 days were evaluated in Part B (MAD), with 8 subjects in each dose cohort randomized 3:1 (TERN-501:placebo); Part C consisted of 2 open-label, drug-drug interaction (DDI) cohorts – one cohort evaluated the effect of 10 mg TERN-501 at steady-state on the PK of a single 10-mg dose of rosuvastatin, a probe OATP (organic anion transporting polypeptide)/BCRP (breast cancer resistance protein) substrate. The other DDI cohort in Part C evaluated the effect of 15 mg TERN-101 at steady-state on the PK of a single 3 mg dose of TERN-501, and the results are summarized in Section 2.2.2.4.1; Part D of the study was an open-label, food effect cohort which evaluated the effect of a high-fat meal on the PK of a single 10-mg dose of TERN-501 compared to fasted administration.

Treatments in all cohorts were overall safe and well-tolerated. No deaths, serious AEs, or withdrawals due to AEs were reported in the study. In Part A (SAD) and Part B (MAD), no predefined study or study drug stopping criteria or dose escalation stopping criteria were met. Frequent vital signs and 12-lead ECG collection in the SAD and MAD cohorts revealed no remarkable findings. In Part A (SAD cohorts), all AEs were mild or moderate in severity, and no clinically meaningful changes or trends were seen in clinical laboratory parameters after single-dose administration of TERN-501 up to 60 mg. In Part B (MAD cohorts), all AEs were mild in severity. Thyroid axis test findings appeared consistent with peripheral thyroid hormone modulation with lowering of free T4 without changes in free T3 or TSH, which were highly variable. ALT and AST values were also highly variable, but overall similar across the treatment groups; no subject who received TERN-501 had ALT $\geq$ 2x ULN and no subject with elevated ALT (i.e., $\geq$ 2x baseline) had an associated increase in bilirubin levels. GGT mean values over time were generally similar to placebo for 1 mg, 3 mg, and 6 mg TERN-501 groups, and changes were not significantly different from placebo at Day 15 for these dosing groups. GGT increases for 10 mg TERN-501 were significantly higher than placebo throughout the treatment period, although values remained below the ULN. No apparent changes or trends were seen in ALP or total bilirubin levels over time. Total testosterone increases seen at doses $\geq$ 3 mg TERN-501 appear to be dose-dependent and can be explained by increases seen in SHBG, reflecting THR-β agonist target engagement. Free testosterone and other sex hormones including estradiol, FSH, and LH remained largely unchanged. No clinically meaningful changes were observed in other clinical laboratory and safety assessments including cardiac biomarkers.

TERN-501 PK had low variability and was approximately dose-proportional from 3 mg to 60 mg following single doses and from 1 mg to 10 mg following multiple doses. Single-dose PK was predictive of multiple-dose PK with modest (< 2-fold) accumulation at steady state upon once daily dosing, consistent with the median half-life of approximately 14 to 21 hours following single or multiple doses. Urinary clearance appears to be a minor pathway of elimination of TERN-501, with a mean of < 3% of the dose excreted as unchanged TERN-501 in the urine.

In Part B (MAD cohorts), SHBG increases were significant and dose-dependent (Table 3), with least squares mean (LSM) percent changes from baseline of 17%, 57%, 136%, and 165% on Day 15 in the 1 mg, 3 mg, 6 mg, and 10 mg groups, respectively (-6% in placebo). In general, SHBG levels continued to increase during the 2-week treatment period and were significantly different from placebo at most time points in the 3 mg, 6 mg, and 10 mg cohorts. Significant reductions in LDL cholesterol were observed at most timepoints during the treatment period in the 6 mg and 10 mg cohorts. Although reductions in LDL cholesterol were similar between TERN-501 dose groups at Day 15, the rate of LDL cholesterol decline appeared slower in the 1 mg group during the 14-day treatment period. Dose-dependent reductions in Apo B were observed on Day 15 and were significant in the 3 mg, 6 mg, and 10 mg groups. Total cholesterol was reduced in all TERN-501 groups with statistically significant percent reductions at Day 15 in the 3 mg and 10 mg dose groups compared to placebo. Triglycerides were numerically lower in TERN-501 groups, which reached statistical significance at Day 15 in the TERN-501 10 mg group compared to placebo. Percent change in HDL cholesterol at Day 15 was not significantly different for any TERN-501 group vs placebo. Together these data indicate that administration of TERN-501 led to robust THR-β engagement in the liver and significant decreases in circulating lipid levels including LDL cholesterol, Apo B, total cholesterol, and triglycerides.

Table 3 Pharmacodynamic effects of multiple dose administration of TERN-501 at Day 15

	Placebo	1 mg	3 mg	6 mg	10 mg
SHBG	-5.8% (19.6)	17.4% (20.6)	57.4% (20.8)*	135.5% (20.5)*	165.0% (20.6)*
LDL cholesterol	-3.9% (5.0)	-16.4% (5.2)	-16.7% (5.1)	-18.8% (5.2)	-20.2% (5.1)*
Apo B	-4.8% (3.9)	-14.4% (4.1)	-17.9% (4.0)*	-22.8% (4.0)*	-27.0% (4.0)*
Total cholesterol	-5.5% (3.7)	-14.3% (3.8)	-16.2% (3.8)*	-14.9% (3.8)	-19.7% (3.8)*
Triglycerides	-13.0% (7.1)	-18.3% (7.7)	-21.4% (7.7)	-20.2% (7.7)	-35.8% (7.7)*

Abbreviations: SHBG = sex hormone binding globulin; LDL = low density lipoprotein; Apo B = apolipoprotein B.
Effect of multiple dose administration of TERN-501 on pharmacodynamic (PD) parameters at Day 15. Change in PD parameters expressed as least squares mean (LSM) percent change from baseline (standard error) based on Analysis of Covariance (ANCOVA) model.
*Statistically significant (p-value <0.05) LSM percent change from baseline relative to placebo.

In the TERN-501 10 mg + rosuvastatin 10 mg DDI cohort of Part C where the potential for TERN-501 to affect the exposure of OATP1B1/1B3 and/or BCRP substrates was evaluated, all AEs were mild and determined either not related or unlikely related to TERN-501; an AE of somnolence was considered possibly related to rosuvastatin by the Investigator. The thyroid axis and liver enzyme data were generally consistent with what was observed in the TERN-501 10 mg MAD cohort. In the presence of TERN-501, rosuvastatin AUC_{inf} and C_{max} increased 27% and 41%, respectively, which was not considered clinically significant. As such, TERN-501 is not considered an inhibitor of OATP or BCRP at clinically relevant doses/exposures and OATP

and/or BCRP substrates, including statins, may be co-administered with TERN-501 without dose modification.

The effect of TERN-101 on TERN-501 PK was also evaluated in Part C of the study and the results are reported in Section 2.2.2.4.1.

In Part D (food effect cohort), no AEs were reported and no remarkable findings in safety assessments including vital signs, ECG parameters, and clinical laboratory tests were observed. TERN-501 AUC_{inf} and C_{max} were decreased approximately 38% and 53%, respectively, when administered with a high-fat meal versus fasted administration. The current phase 2a study will require dosing on an empty stomach (no food or drink besides clear liquids for approximately 2 hours before and 1 hour after study drug administration) to minimize PK variability and overlap in exposures between doses.

2.2.2. Combination of TERN-501+TERN-101 for Treatment of NASH

Although the pathogenesis of NASH is not yet fully understood, the mechanisms leading to NASH appear to be multifactorial, involving effects of metabolic dysregulation on hepatocytes with contribution from nonparenchymal liver cells, driving oxidative stress, hepatic cell injury and inflammation, and the onset of fibrosis (Magee 2016). Many therapeutic targets are being pursued for NASH, reflecting the heterogeneous pathways of disease pathogenesis (Romero 2020). Due to the multifactorial pathophysiology of NASH, combination approaches to NASH treatment utilizing agents with complementary mechanisms of action against the multiple pathogenic processes that contribute to the disease may offer the most benefit.

Farnesoid X receptor (FXR), which modulates metabolic pathways including bile acid synthesis, de novo lipogenesis, and glucose metabolism, is the most advanced target currently being pursued for NASH. FXR activation has been shown to improve histological features associated with NASH including hepatic steatosis, inflammation, hepatocyte ballooning, and fibrosis. The anti-fibrotic and pleotropic metabolic benefits of FXR activation may be complementary to the beneficial effects of THR-β agonism. In addition, LDL cholesterol reductions with THR-β agonists such as TERN-501 may provide an advantage in patients when coadministered with an FXR agonist, which can be associated with LDL cholesterol increases.

TERN-101, a highly selective, potent agonist of FXR, was overall safe and well-tolerated at all dose levels evaluated in a 12-week phase 2a, proof-of-concept study in patients with presumed NASH and demonstrated reductions in ALT and liver fat content assessed by MRI-PDFF (Study TERN101-2001; Section 2.2.2.2). In that study, TERN-101 significantly reduced cT1, suggesting a beneficial effect on liver fibroinflammation in NASH. Thus, combining TERN-501, with its anticipated antisteatotic effect in the liver and favorable effects on systemic lipids, and TERN-101, with its potential pleotropic beneficial effects including improvement in fibroinflammation, may provide greater benefit over either agent as monotherapy and warrants further investigation.

Key findings from nonclinical and clinical studies of TERN-101 to-date are summarized below (see Section 2.2.2.1 and Section 2.2.2.2). In addition, nonclinical studies evaluating safety and efficacy of TERN-501+TERN-101 in NASH pharmacology models (see Section 2.2.2.3) and assessments for DDI of TERN-501+TERN-101 (see Section 2.2.2.4.1) are summarized below. Additional details are available in the Investigator's Brochure.

2.2.2.1. Nonclinical Studies of TERN-101

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2.2.2.2. Clinical Studies of TERN-101

TERN-101 was assessed in 4 phase 1 studies of healthy human participants and 1 phase 2a study of patients with noncirrhotic NASH. Overall, 318 subjects have participated in these studies, including 198 who have received at least 1 dose of TERN-101. In addition, 10 healthy study participants received TERN-101 as part of a DDI cohort in TERN-501 first-in-human Study TERN501-1009, as described in Section 2.2.2.4.1.

In the phase 1 studies, single doses of the TERN-101 capsule formulation ranged from 5 mg to 600 mg TERN-101. Multiple doses of the capsule formulation ranged from 5 mg to 400 mg TERN-101, with duration of treatment ranging from 7 to 14 days. TERN-101 was overall safe and well-tolerated in healthy subjects. Relatively limited absorption of the TERN-101 capsule formulation led to development of a tablet formulation. Single doses of the tablet formulation were administered at 5 mg or 25 mg. TERN-101 PK was found to be similar between the 5 mg TERN-101 tablet and the 25 mg TERN-101 capsule and supported switching from capsule to tablet formulation for phase 2 studies (Wang 2021). Additional information on available TERN-101 phase 1 clinical study results, including clinical pharmacology, is provided in the Investigator's Brochure. Results from a phase 2a study in patients with NASH are also briefly described below.

The phase 2a study TERN101-2001 (N = 100 randomized and treated patients) was a randomized (1:1:1:1), double-blind, placebo-controlled, parallel-group study of TERN-101 in adults with noncirrhotic NASH. Study patients received TERN-101 tablets at doses of 5 mg, 10 mg, or 15 mg or matching placebo orally once daily for 12 weeks. In the study, the patient incidence of treatment-emergent AEs was generally similar across treatment groups. Most AEs

were Grade 1 or Grade 2, and there were no treatment related SAEs. No patient discontinued TERN-101 or placebo due to an AE. Pruritus, which was predominantly mild and transient, occurred in 15% of TERN-101 treated patients overall without an apparent dose response, and 11.5% of patients who received the TERN-101 10 mg dose; there were no patients with pruritus events in the placebo group. No patient discontinued or had dose adjustments of TERN-101 due to pruritus. No TERN-101 treated patient had evidence of drug-induced liver injury or a treatment-emergent increase in ALT to > 2x upper limit of normal. TERN-101 doses lower than 15 mg did not result in a clinically meaningful or sustained change from baseline in adverse lipid findings through 12 weeks of treatment. Increases in LDL and decreases in HDL that were significantly different from placebo from Week 4 through Week12 were observed in the TERN-101 15 mg group. Statin therapy was not initiated or changed for any patients during the treatment period.

Efficacy results provide initial evidence of TERN-101 treatment effects in NASH. In the secondary endpoint of percent change from baseline in ALT at Week 12, there were numerical declines in the TERN-101 10 mg and 15 mg groups, of overall similar magnitude, without statistically significant changes relative to placebo. Significant ALT declines relative to placebo were seen at earlier time points (beginning at Week 2) for these dose groups. Significant reduction in GGT with all doses of TERN-101 were seen throughout the dosing period, with overall similar magnitude for the 10 mg and 15 mg groups. Statistically significant decreases in MRI-PDFF were observed at Week 6 in TERN-101-treated patients, indicating early effects of TERN-101 on liver fat content reduction, with numerical reductions at Week 12. Statistically significant reductions were observed in all TERN-101 dose groups relative to placebo in cT1, an imaging biomarker for liver fibroinflammation. The declines were observed at the first assessment time point (Week 6) and were sustained through Week 12. The observation of early and sustained cT1 decreases suggest TERN-101 may primarily act to decrease fibroinflammation in NASH.

TERN-101 exposures in NASH patients were approximately dose proportional and generally as expected based on earlier studies in healthy participants; PD evaluations of 7αC4 and FGF19 confirmed FXR target engagement in the liver and intestines, respectively. Statistically significant declines in trough 7αC4 levels were observed at multiple time points during the study in the TERN-101 10 mg and 15 mg groups indicating sustained hepatic FXR target engagement at these doses, while changes in the 5 mg dose level were not significantly different from placebo. Declines in trough 7αC4 were not statistically different between the TERN-101 10 mg and 15 mg groups at any timepoint. In patients who participated in a PD sub-study (N = 26), maximum induction of FGF19 was observed at 6 hours post-dose, and levels generally returned to baseline levels at 24 hours post-dose, suggestive of transient FXR target engagement in the intestines.

Overall, FXR agonist TERN-101 was generally safe and well-tolerated at all doses studied in NASH patients in Study TERN101-2001. Treatment with TERN-101 resulted in decreases in ALT, cT1, and MRI-PDFF. Significant declines in cT1 as early as Week 6 and through Week 12 suggest TERN-101 may primarily act to decrease fibroinflammation in NASH. Efficacy appeared overall similar for the 10 mg and 15 mg groups.

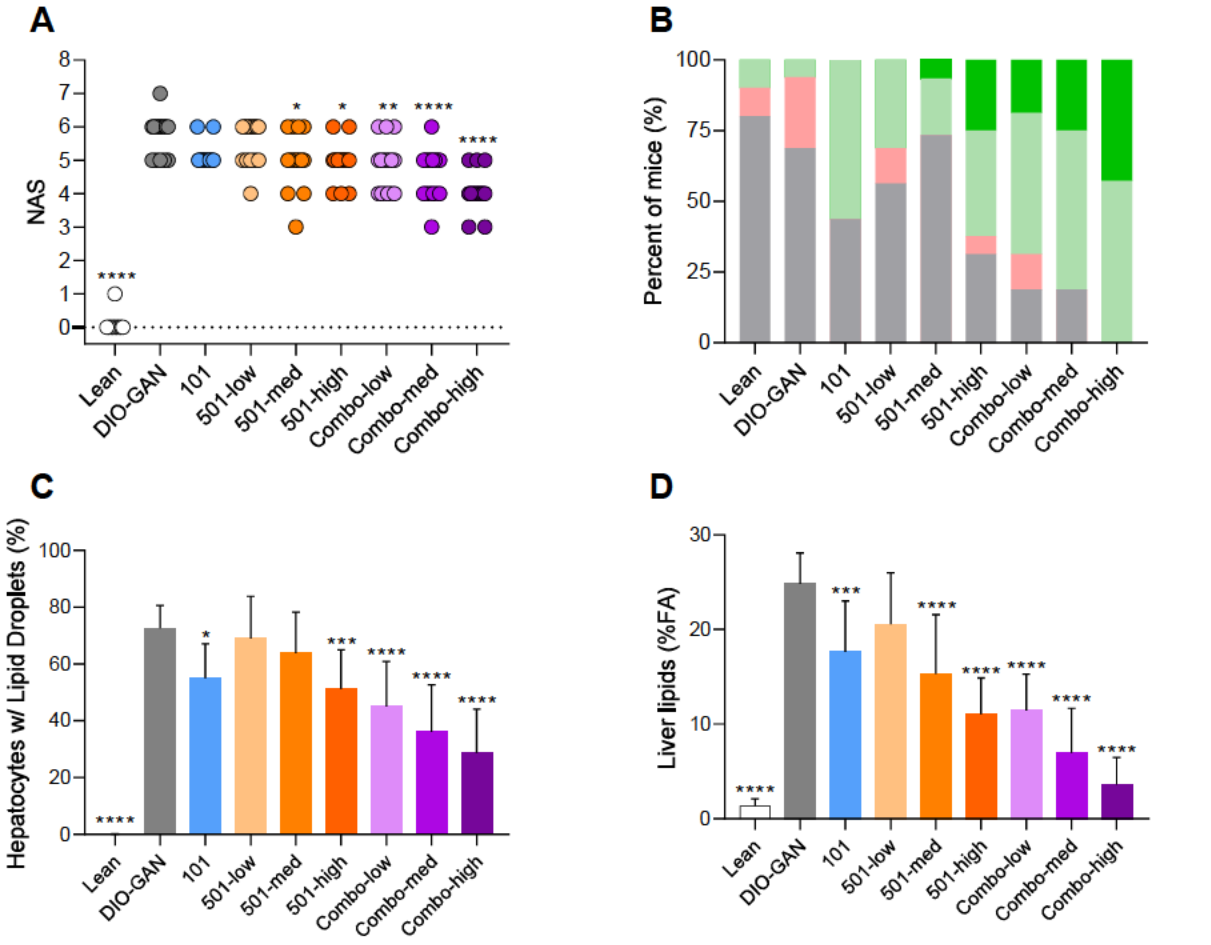
2.2.2.3. Nonclinical Studies of TERN-501+TERN-101

2.2.2.3.1. Evaluation of TERN-501+TERN-101 Combination Efficacy in Pharmacology Models of NASH

To assess the potential therapeutic benefit of combining agonists of THR-β and FXR, the efficacy of TERN-501 and TERN-101 as single agents and in combination was tested in 2 different pharmacology models of NASH. In the first study, DIO mice were administered TERN-501 and TERN-101 for 28 days concomitantly with the hepatoxic agent CCl_4 to induce inflammation and fibrosis. In this model, treatment with TERN-501 and TERN-101 as single agents significantly lowered liver steatosis and serum triglycerides. TERN-501 and the combination of TERN-501+TERN-101 showed significantly greater reductions in steatosis compared to TERN-101 treatment alone. However, since TERN-501 treatment alone reduced steatosis to healthy control levels, potential additive effects of TERN-101 treatment on steatosis were difficult to discern in the combination treatment group. The combination of TERN-501+TERN-101 showed greater reductions in serum total cholesterol compared with either single agent treatment alone. Liver fibrosis in this model was significantly improved by treatment with the combination of TERN-501+TERN-101, but not by treatment with either single agent alone. Gene expression analysis in the liver showed that genes associated with fibrosis and inflammation were significantly reduced by the combination of TERN-501+TERN-101 relative to vehicle control, and the magnitude of change was greater for the combination treatment group compared to treatment with single agents alone.

In a second study, the efficacy of TERN-501 and TERN-101 as single agents and in combination was assessed in a strictly DIO model of NASH developed by Gubra (Hansen 2020). In this model, termed DIO-Gubra Amylin NASH (DIO-GAN), mice were fed a diet high in fat, cholesterol, and fructose for > 35 weeks to induce the histopathological features of NASH and fibrosis. TERN-501 was administered once-daily for 12-weeks as a single agent at doses of 0.3 mg/kg (TERN-501-low), 2 mg/kg (TERN-501-med), 10 mg/kg (TERN-501-high) or at these same dose levels in combination with 10 mg/kg TERN-101 (Combo-low, Combo-med, or Combo-high). 12-week treatment with TERN-501 alone or in combination with TERN-101 significantly reduced hepatomegaly relative to vehicle control, with the greatest effects on liver weight observed in the combination treatment groups. Although all treatment groups reduced plasma and liver total cholesterol, greatest reductions were observed in mice treated with the combination of TERN-501+TERN-101. NAS was used for histological assessment of NASH and determined for each animal at baseline and after 12 weeks of treatment. After a 12-week treatment, NAS was significantly lower in mice treated with the combination of TERN-501+TERN-101 compared with vehicle control (Figure 1A). Moreover, a greater percentage of mice treated with the combination of TERN-101+TERN-101 showed NAS improvement relative to baseline compared to single agent treatments. In the TERN-101 treatment group, 56% of the animals showed a ≥ 1 point NAS improvement, compared to 31%, 27%, and 62% in the TERN-501-low, TERN-501-med, and TERN-501-high single agent treatment groups, respectively. Combination treatment was even more effective, with 69%, 81%, and 100% of mice showing ≥ 1-point NAS improvement in the Combo-low, Combo-med, and Combo-high groups, respectively. In addition, the magnitude of NAS improvement from baseline was greater for the combination treatment groups (Figure 1B).

Figure 1 **Effects of 12 Weeks of TERN-501, TERN-101, or TERN-501+TERN-101 Combination on NALFD Activity Score and Steatosis, in a DIO-GAN Mouse Model of NASH**



Treatment with the combination of TERN-501+TERN-101 resulted in greater improvements in NAS and liver steatosis in a diet-induced mouse model of NASH. NAS, the unweighted sum of ballooning, steatosis, and lobular inflammation histological scores was determined at baseline and after 12-weeks of treatment. (A) NAS after 12-weeks of treatment. (B) Percentage of mice with NAS change from baseline: no change (gray); ≥1 point worsening (red); 1 point improving (light green); ≥2 point improving (dark green). Hepatocellular steatosis including the percentage of hepatocytes with lipid droplets (C) and liver lipid content as a percent fractional area (D) was determined by morphometric analysis of liver histological samples at the end of study. The low, med, and high TERN-501+TERN-101 combination groups are denoted as Combo-low, Combo-med, and Combo-high. Statistical comparison to DIO-GAN vehicle control determined by ANOVA followed by Tukey correction for multiple comparisons. *p <0.05, **p <0.01, ***p <0.001, ****p <0.0001

NAS improvements were largely driven by greater reductions in steatosis, which was supported by quantitative liver histomorphometry, including the percent of hepatocytes with lipid droplets (Figure 1C) and liver lipid fractional area (Figure 1D). These results were consistent with liver transcriptomic analysis by RNAseq, which showed increased modulation of genes associated with energy and lipid metabolism in the combination treatment arms relative to single agent treatments. Improvements in fibrosis ≥ 1-stage were more frequently observed in the combination arms relative to single-agent treatments, although differences did not reach

significance. Body weight loss has been associated with beneficial effects on NASH parameters in both rodent models of NASH and in human studies. However, TERN-101 and the combination of TERN-501+TERN-101 (Combo-low and Combo-med) showed comparable effects on weight loss in this study, suggesting that the greater overall efficacy of the combination treatment was not solely due to reductions in body weight.

Together these data suggest that the combination of TERN-501+TERN-101 resulted in greater overall efficacy compared to treatment with single agents.

2.2.2.3.2. Nonclinical Safety Studies of TERN-501+TERN-101

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2.2.2.4. Clinical Study of TERN-501+TERN-101

2.2.2.4.1. Drug-Drug Interaction of TERN-501+TERN-101 in FIH TERN501-1009 Study

The effect of TERN-101 15 mg at steady state on the PK of TERN-501 was assessed in Part C of the FIH study (Study TERN501-1009; Section 2.2.1.2). The effect of 15 mg TERN-101 once daily for 7 days on the PK of a single 3-mg dose of TERN-501 was evaluated in a fixed -sequence crossover design in 10 healthy subjects. All AEs were mild and considered either not related or unlikely related to study drug by the Investigator. Vital signs and ECGs remained stable, and all other safety assessments including thyroid axis testing, liver biochemistry, and lipid parameters were unremarkable. Preliminary PK data from this cohort indicate there was minimal effect of TERN-101 on TERN-501 PK; AUC_{inf} was decreased approximately 18% and C_{max} was decreased approximately 23%. TERN-101 exposures were as

expected. As such, TERN-101 and TERN-501 can be administered in combination without dose modification of either agent.

2.3. Benefit/Risk Assessment

This study will provide information on the safety and potential efficacy of TERN-501 monotherapy and TERN-501+TERN-101 combination therapy in noncirrhotic NASH patients and support development of TERN-501 monotherapy and/or TERN-501+TERN-101 combination therapy for the treatment of NASH. While the safety and efficacy of TERN-501 monotherapy and TERN-501+TERN-101 combination therapy have not been evaluated in a NASH population, nonclinical and clinical experience with TERN-501 and TERN-101 as individual agents, as well as nonclinical data for the combination of TERN-501+TERN-101 (summarized in Section 2.2), indicate the potential for efficacy and an acceptable safety profile of TERN-501 monotherapy and TERN-501+TERN-101 combination therapy.

Potential anticipated risks for the patients participating in the study are assessed based on understanding of the individual agents (i.e., TERN-501, TERN-101) and their mechanisms of action, including known class effects and theoretical risks of THR-β and FXR agonists, as well as available nonclinical and clinical study data. Anticipated risks for each agent and for the combination are discussed separately below. In addition, patients participating in this study may also have study procedure-related risks, including pain and bruising from blood draws.

Risks Relevant to TERN-501 or THR-β Agonism

Based on nonclinical and clinical experience to date, there are no identified adverse drug reactions associated with TERN-501. Data from the TERN-501 FIH study (TERN501-1009) indicate single doses up to 60 mg and once daily doses up to 10 mg for 14 days in healthy subjects were overall safe and well-tolerated.

For any THR-β agonist, a key safety concern is excess systemic thyroid hormone stimulation, which could include effects on the cardiovascular and skeletal systems such as increased heart rate, cardiac hypertrophy, muscle wasting, and reduced bone density, in addition to the other clinical signs or symptoms that are possible with hyper/hypothyroidism. THR-α is the predominant THR expressed in the heart and bone, and responsible for most of the unwanted cardiovascular and skeletal effects associated with thyroid hormone stimulation (Johansson 1998; Gloss 2001; Sinha 2019; Gorka 2013). As described previously, THR-β agonism in the liver has been implicated in lowering free T4 (prohormone) without changes in T3 (active hormone) or TSH, which may be attributed to peripheral thyroid hormone modulation (Taub 2013; Berry 1990).

Toxicology studies for TERN-501 suggest the possibility of peripheral and central thyroid hormone modulation with TERN-501 based on dose-dependent reduction of TSH in rodents, which was considered a non-adverse finding. In FIH Study TERN501-1009, however, thyroid axis test findings appeared consistent with peripheral thyroid hormone modulation, showing dose-dependent lowering of free T4 without changes in free T3 or TSH. No clinical signs or symptoms of hyper/hypothyroidism were reported as AEs at any dose level evaluated in the study. Extensive cardiovascular monitoring including frequent vital signs, 12-lead

electrocardiograms (ECGs), and cardiac biomarkers showed no clinically significant changes in those parameters. Overall, there was no evidence for central thyroid axis suppression or cardiac toxicity with TERN-501 administered at single doses up to 60 mg and repeat doses of up to 10 mg once daily for up to 14 days in the FIH study. Nonclinical studies for TERN-501 support lack of anticipated adverse cardiovascular effects at clinically relevant doses. Refer to the TERN-501 Investigator's Brochure for additional details.

Increased liver enzymes have been observed with THR-β agonism (Lian 2016; Sjouke 2014). In Study TERN501-1009, there was no evidence of drug-induced liver injury and no subject who received TERN-501 in the SAD or MAD cohorts had ALT ≥ 2x ULN. GGT increases for 10 mg TERN-501 were significantly higher than placebo throughout the 14-day treatment period, although values remained below the ULN. GGT changes were not significantly different from placebo at Day 15 for 1 mg, 3 mg, or 6 mg TERN-501 dosing groups. Alkaline phosphatase and total bilirubin values were largely unchanged across all TERN-501 groups over 14 days of dosing in the study.

While bone loss may occur in the setting of thyroid hormone excess, this is mediated largely through THR-α (Sinha 2019; Gorka 2013). There was no evidence in Study TERN501-1009 to indicate a possible adverse effect on bone with TERN-501 over 14 days of dosing, and no nonclinical data for TERN-501 available to date suggest such an effect. Notably, there were no significant effects on bone mineral density observed in the phase 2 study of resmetirom over 36-weeks of dosing (Harrison 2019).

Reflecting hepatic THR-β target engagement with TERN-501, significant and dose-dependent increases in SHBG were observed in the MAD cohorts of Study TERN501-1009. Increases in total testosterone, which were seen at TERN-501 doses ≥ 3 mg, are likely explained by the increases in SHBG. Free testosterone (active hormone) and other sex hormones including estradiol, FSH, and LH remained largely unchanged. Of note, SHBG increases on their own are not considered a safety risk and may in fact reflect potential for NASH benefit; the subgroup of patients with larger SHBG increases with resmetirom had greater benefit in terms of liver fat content reduction and NASH histologic improvement (Harrison 2019).

Potential adverse effects may be anticipated based on results reported with other THR-β agonists. For example, the most commonly reported AEs with resmetirom, currently being evaluated in phase 3, include diarrhea and nausea (Harrison 2019).

Currently, there are no warnings, precautions, or contraindications with the use of TERN-501. Embryofetal development studies have not yet been conducted, and TERN-501 has not been administered to pregnant or breastfeeding women. The risks of TERN-501 to the fetus or neonate are unknown, and TERN-501 should not be administered to pregnant or lactating women or women of childbearing potential who are not using protocol defined methods of contraception.

Risks Relevant to TERN-101 or FXR Agonism

Based on available nonclinical and clinical data to-date, there are no identified adverse drug reactions associated with TERN-101. TERN-101 has been evaluated in four phase 1 studies in healthy volunteers, and a phase 2a study in NASH patients with 12 weeks of dosing and has been overall safe and well-tolerated.

Liver enzyme elevations, lipid abnormalities (elevation in LDL and reduction in HDL), and pruritus have been reported with FXR agonists (e.g., OCA, cilofexor, tropifexor) (Harrison 2021; Patel 2020; Badman 2019; Younossi 2019; Neuschwander-Tetri 2015; Mudaliar 2013). For TERN-101, in the first study of multiple doses of capsule formulation, 2 subjects receiving 400-mg capsules experienced transient, asymptomatic transaminase elevation without hyperbilirubinemia or increases in ALP; a similar finding was seen in one placebo subject. No similar transaminase changes were observed with repeat doses up to 150 mg of TERN-101 capsules or with single TERN-101 tablet doses up to 25 mg in healthy volunteers.

In a phase 2a, 12-week study of TERN-101 5 mg, 10 mg, 15 mg (tablet formulation), or placebo in NASH patients (Study TERN101-2001), no TERN-101 treated patient had evidence of drug-induced livery injury or a treatment-emergent increase in ALT to >2× the ULN. LDL cholesterol increases and HDL cholesterol decreases were statistically different from placebo for the TERN-101 15 mg group, but not for the 5 mg and 10 mg groups at Week 12, and changes were overall moderate in nature. Pruritus, which was predominantly mild and transient, occurred in 15% of TERN-101 treated patients overall and no placebo patients, with no TERN-101 dose-dependent effect. No patient discontinued or had dose adjustments of TERN-101 due to pruritus.

Currently, there are no warnings, precautions, or contraindications with the use of TERN-101. Embryofetal development studies have not been conducted, and TERN-101 has not been administered to pregnant or breastfeeding women. The risks of TERN-101 to the fetus or neonate are unknown, and TERN-101 should not be administered to pregnant or lactating patients or patients of childbearing potential who are not following protocol-specified contraception requirements.

Risks Relevant to TERN-501+TERN-101 Combination

An overview of clinical risks potentially anticipated for TERN-501 and TERN-101 individually is presented above. Data from the TERN-501+TERN-101 DDI cohort of the FIH Study TERN501-1009 indicate that exposures of TERN-501 and TERN-101 when administered in combination are expected to be comparable to exposures of the individual agent when administered alone. Nonclinical safety studies overall support that dosing of TERN-501 and TERN-101 in combination is unlikely to produce unique risks beyond those of the individual agents.

The combination of TERN-501+TERN-101 is not anticipated to change any potential for central thyroid axis modulation relative to TERN-501 alone or increase the theoretical risks for effects on cardiovascular or skeletal systems due to systemic thyroid hormone stimulation. The combination of TERN-501+TERN-101 is also not anticipated to change any potential for TERN-101 effects on sex hormone levels.

There is the possibility that combining TERN-501 and TERN-101 could potentially offset adverse effects from each individual agent. For example, the anticipated LDL cholesterol lowering effect from THR-β agonism may mitigate risk of LDL cholesterol increase associated with FXR agonism. However, TERN-501 is not expected to change the risk of HDL cholesterol reduction by TERN-101.

Although elevation of liver enzymes has been reported with FXR and THR-β agonists (Mudaliar 2013; Lian 2016; Sjouke 2014), evidence of drug-induced liver injury has not been observed with

TERN-501 or TERN-101 and there is no expectation for liver enzymes to worsen with the combination of TERN-501+TERN-101 compared to either agent administered alone based on available data.

Finally, the administration of TERN-501+TERN-101 is not anticipated to change the potential for pruritus associated with TERN-101.

Taking the anticipated or potential risks described above into consideration, the protocol has been designed to minimize the risk to patients. Safety monitoring outlined for the proposed study TERNCB-2002 is intended to detect potential safety signals. Patients will be monitored for AEs during the study and followed appropriately for AE resolution. Detailed guidance on potential signs and symptoms of thyroid dysfunction are provided in Section 8.1.8. Clinical signs or symptoms of hyper/hypothyroidism should be documented as AEs with appropriate follow-up until resolution. Vital signs and 12-lead ECGs will be collected for cardiovascular monitoring to ensure patient safety, along with clinical assessment for any AEs that are cardiovascular in nature (Section 8.1.7). Laboratory tests including thyroid axis tests, liver function tests, lipid panel, hematology, and clinical chemistry will be monitored, with assessment of sex hormones and bone turnover markers for characterization of any changes in these parameters, as well.

There are currently no approved therapies for NASH. Overall, based on clinical experience of TERN-501 in healthy volunteers and TERN-101 in healthy volunteers and in NASH patients, the benefit/risk assessment is considered to be acceptable for patients participating in this study. More detailed information about the nonclinical and clinical data on TERN-501 and TERN-101 that informs benefit-risk considerations may be found in the Investigator's Brochure.

3. Objectives and Endpoints

Primary Objective	Primary Endpoint
• To evaluate the effect of TERN-501 monotherapy on liver fat content as assessed by MRI-PDFF compared to placebo	• Relative change from baseline in MRI-PDFF at Week 12 for TERN-501 compared to placebo
Secondary Objectives	**Secondary Endpoints**
• To evaluate the effect of TERN-501 monotherapy on cT1 relaxation time compared to placebo • To evaluate the effect of TERN-501+TERN-101 on liver fat content as assessed by MRI-PDFF and on cT1 relaxation time compared to placebo	• Change from baseline in cT1 relaxation time at Week 12 for TERN-501 compared to placebo • Relative change from baseline in MRI-PDFF at Week 12 for TERN-501+TERN-101 compared to placebo • Change from baseline in cT1 relaxation time at Week 12 for TERN-501+TERN-101 compared to placebo
• To evaluate safety and tolerability of TERN-501 monotherapy and TERN-501+TERN-101	• Patient incidence of treatment emergent adverse events
Exploratory Objectives	**Exploratory Endpoints**
• To explore the effect of TERN-501 monotherapy on efficacy and markers of target engagement compared to placebo • To explore the effect of TERN-501+TERN-101 on efficacy and markers of target engagement, compared to placebo and/or each monotherapy	• Change from baseline in the following parameters, as applicable: ○ ALT, AST, and GGT ○ FIB-4, CK-18 (M30 and M65), ELF (PIIINP, TIMP-1, HA), PRO-C3, and FAST score ○ TE and CAP ○ MRI-PDFF (relative change) and cT1 ○ SHBG ○ Lipid panel (for PD as well as safety evaluation) ○ rT3 ○ FGF19, bile acids, and 7αC4 • Proportion of responders on MRI-PDFF and/or cT1 with the following: ○ ≥ 30% relative reduction in MRI-PDFF ○ ≥ 80 msec reduction in cT1
• To evaluate the pharmacokinetics of TERN-501 and TERN-101 administered alone and in combination	• PK parameters (e.g., AUC, C_{max}, C_{tau})

Abbreviations: 7αC4 = 7α-hydroxy-4-cholesten-3-one; ALT = alanine transaminase; AST = aspartate transaminase; AUC = area under the concentration-time curve, CAP = controlled attenuation parameter; CK-18 = cytokeratin-18; C_{max} = maximum observed concentration; cT1 = corrected T1; C_{tau} = concentration at the end of the dosing interval; ELF = enhanced liver fibrosis; FAST score = FibroScan AST score; FGF19 = fibroblast growth factor-19; FIB-4 =

fibrosis-4; GGT = gamma-glutamyl transferase; HA = hyaluronic acid; MRI = magnetic resonance imaging; MRI-PDFF = magnetic resonance imaging proton density fact fraction; PIIINP = procollagen III N-terminal propeptide; PD = pharmacodynamics; PK = pharmacokinetics; PRO-C3 = released N-terminal pro-peptide of type III collagen; rT3 = reverse T3; SHBG = sex hormone binding globulin; TIMP-1 = tissue inhibitor of metalloproteinases-1; TE = transient elastography

4. Study Design

4.1. Overall Design

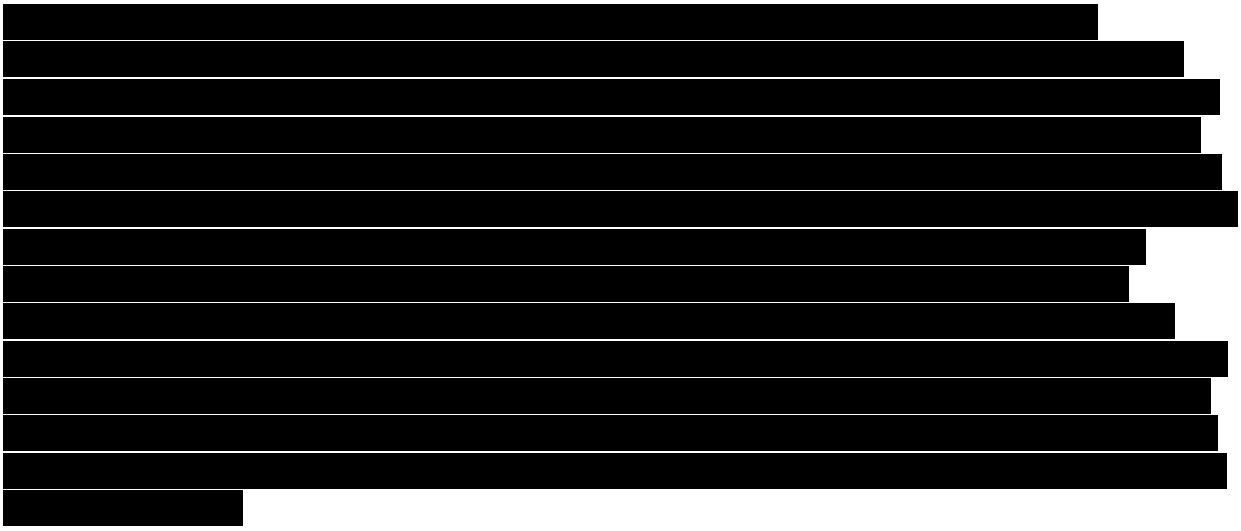
This study is a multicenter, randomized, double-blind, placebo-controlled, parallel-group treatment, phase 2a study.

Approximately 140 noncirrhotic NASH patients with fibrosis identified based on prior liver biopsy and/or imaging and clinical criteria who meet study eligibility criteria will be enrolled and randomized equally into 7 groups: once daily orally administered TERN-501 1 mg (n=20), TERN-501 3 mg (n=20), TERN-501 6 mg (n=20), TERN-501 3 mg+TERN-101 10 mg (n=20), TERN-501 6 mg+TERN-101 10 mg (n=20), TERN-101 10 mg (n=20), or matching placebo (n=20).

Of the 140 patients randomized, approximately 42 patients (approximately 6 per group) will take part in an intensive PK and pharmacodynamic (PD) collection after the first dose and after the last dose of study drug. Patients who are not participating in the PK/PD sub-study will have sparse PK and trough PD sampling only.

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

4.2. Scientific Rationale for Study Design



4.3. Justification for Dose

TERN-501 Dose Rationale as Monotherapy:

Dose levels of 1 mg, 3 mg, and 6 mg TERN-501 administered once daily as monotherapy were chosen based on collective assessments of safety, PK, and PD data from the TERN-501 FIH study (Study TERN501-1009). TERN-501 will be dosed on an empty stomach to minimize variability and overlap in exposures between dose groups. Single doses of TERN-501 up to 60 mg and once daily administration of 1 mg, 3 mg, 6 mg, and 10 mg doses for 14 days were overall safe and well-tolerated in healthy volunteers (Section 2.2.1.2). In the multiple dose

cohorts, all AEs were mild (Grade 1), and most were considered unrelated to study drug. Dose-dependent declines in free T4 were observed without clear changes in TSH or T3, consistent with peripheral thyroid hormone modulation; there were no clinical signs or symptoms of hyper/hypothyroidism reported. GGT changes for 1 mg, 3 mg, and 6 mg TERN-501 were similar to placebo on Day 15. Total testosterone increases seen at doses ≥ 3 mg TERN-501 appeared to be dose-dependent and can be explained by the increases in SHBG observed in the study.

Dose-dependent increases from baseline in SHBG, a highly sensitive PD marker of hepatic THR-β agonism, were seen throughout the TERN-501 treatment period, with mean increases at Day 15 ranging from 17% to 165% in the 1 mg through 10 mg dose cohorts, which were significant in the 3 mg, 6 mg, and 10 mg groups. The mean SHBG increases at 3 mg (57%) and 6 mg (136%) were comparable to or greater than the mean SHBG increases seen after 14-day treatment with 80 mg and 100 mg of resmetirom (Taub 2013), the most advanced THR-β agonist in development for NASH, with both doses currently being evaluated in a registrational phase 3 trial (Harrison 2019). Importantly, high SHBG response (defined as a ≥75% increase in SHBG level from baseline at Week 12) was correlated with the greatest reductions in the MRI-PDFF at Week 12 and histological improvement of NASH at Week 36 (Harrison 2019). The less than dose-proportional increase in SHBG between 6 mg and 10 mg and partially overlapping PK, indicate a potential plateau in effect of TERN-501 at doses higher than 6 mg. LDL cholesterol, another important PD marker of THR-β agonism, was significantly reduced at most timepoints during the treatment period in the 6 mg TERN-501 group, with similar magnitude of decline for the 1 mg, 3 mg, and 6 mg groups at Day 15 (-16.4%, -16.7%, and -18.8% for 1, 3, and 6 mg, respectively). The significant increases in SHBG together with LDL cholesterol decreases seen in the 3 mg and 6 mg TERN-501 groups indicate robust THR-β target engagement and the potential for efficacy, including reductions in liver fat content, in NASH patients. Additionally, the TERN-501 PK exposures observed in the 3 mg and 6 mg groups were at or above the TERN-501 efficacious exposures seen in a NASH mouse model (Kirschberg 2020). While the SHBG increase on Day 15 in the 1 mg group was not statistically significant compared to placebo, the LDL cholesterol decrease in the 1 mg group was comparable to decreases observed in the 3 mg and 6 mg groups, indicating THR-β target engagement and the potential for efficacy, and warranting further investigation of 1 mg as the lower end of the TERN-501 monotherapy dose range in NASH patients.

With the linear, dose-proportional PK demonstrated in the FIH study, dose levels of 1 mg, 3 mg, and 6 mg are expected to provide 2- to 3-fold differences in exposures with minimal overlap. Based on the available safety data from the FIH study and a ≥ 6-fold margin relative to the NOAEL in dogs, the more sensitive toxicology species, all doses selected are expected to have an acceptable safety margin in NASH patients in this 12-week study (see Section 2.2.2.1.2.1). As such, the safety, PK, and PD data support the selection of 1 mg, 3 mg, and 6 mg doses of TERN-501 for the monotherapy arms of this study.

TERN-101 Dose Rationale:

A dose level of 10 mg TERN-101 once daily was selected to be administered in combination with TERN-501, and as a monotherapy control, based on efficacy, safety, PK, and PD data. TERN-101 has been evaluated at doses of 5 mg, 10 mg, and 15 mg once daily in NASH patients for 12 weeks in a phase 2a study (Study TERN101-2001). Overall, TERN-101 was generally

safe and well-tolerated at all dose levels studied. Pruritus was observed in 11.5% of patients who received 10 mg TERN-101 in the study; all pruritus AEs were mild or moderate and did not result in study or treatment discontinuation. LDL cholesterol changes with 10 mg TERN-101 were not statistically different from placebo during the 12 weeks of treatment. Transient reductions in HDL cholesterol were seen in the 10 mg group at Week 4 through Week 8, but percent change from baseline for 10 mg TERN-101 was not statistically different from placebo at Week 12. TERN-101 10 mg reduced ALT, GGT, MRI-PDFF, and cT1. The effects of TERN-101 on 7αC4, a marker of FXR target engagement, appeared to plateau at the 10 mg dose, suggesting maximal or near maximal target engagement was achieved at 10 mg. Additionally, safety, pharmacology, and toxicology studies support the continued study of TERN-101 at 10 mg (see Section 2.2.2.1.2.1). Thus, balancing the potential for efficacy with the overall safety profile, 10 mg TERN-101 was selected as the optimal dose to combine with TERN-501 and as a monotherapy comparator arm.

TERN-501 Dose Rationale in Combination with TERN-101 10 mg:

This study will assess 2 dose levels of TERN-501, 3 mg and 6 mg, in combination with a single dose level of TERN-101 (10 mg), administered once daily. Doses of 3 mg and 6 mg TERN-501 were selected to be evaluated in combination with 10 mg TERN-101 based on a collective consideration of preclinical and clinical safety, PK, and PD data, with the aim to assess dose levels expected to be efficacious as monotherapy. Evaluating the two highest doses of TERN-501 selected for monotherapy dose-ranging to be administered in combination with TERN-101 allows for safety characterization of the combination at the upper end of TERN-501 dose levels and exploration of additive efficacy when the two drugs are combined in comparison to monotherapy doses expected to be efficacious.

Based on the mechanisms of action and available data, TERN-501 and TERN-101 in combination is not expected to worsen the safety profile seen with either agent in monotherapy, with the potential for beneficial effect on certain aspects of safety when administered in combination. TERN-501 is not expected to cause pruritus or increase the incidence or severity of pruritus that may occur with TERN-101 treatment. Additionally, TERN-501 may have a beneficial effect on the safety profile of TERN-101 with respect to LDL cholesterol, as TERN-501 is expected to decrease LDL cholesterol, as seen in Study TERN501-1009. Based on this and the lack of PK interaction between the compounds, evaluation of the monotherapy dose levels of each agent in combination is considered appropriate to maximize potential therapeutic benefit while minimizing risks.

No clinically meaningful difference in PK was observed in Study TERN501-1009 when TERN-501 and TERN-101 were coadministered in healthy subjects that would warrant dose modification. The lowest safety margin for each agent when dosed in combination in nonclinical studies is approximately 16-fold for TERN-501 and approximately 2-fold for TERN-101 relative to anticipated exposures from human doses of 6 mg TERN-501 and 10 mg TERN-101, respectively (see Section 2.2.2.3.2). The lack of a clinically significant PK interaction between TERN-501 and TERN-101 and the preclinical and clinical safety, PK, and PD data available to date provide appropriate evidence for selecting 3 mg and 6 mg doses of TERN-501 to be administered in combination with 10 mg TERN-101 in this study.

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 are met:

1. Must be 18 to 75 years of age inclusive, at the time of signing the informed consent
2. Male or female, willing to follow contraception requirements defined by study protocol (Appendix 7); female patients of childbearing potential must also have negative serum pregnancy test at screening, not be breastfeeding, and not plan to become pregnant during the study or within 30 days after dosing of study drug
3. Overweight or obese with a body mass index (BMI) ≥ 25 kg/m^2
4. NASH diagnosed by prior biopsy and/or imaging criteria as follows:
    a. For diagnosis based on prior biopsy:
        i. Step 1: Noncirrhotic NASH with fibrosis (F1, F2, or F3 based on NASH Clinical Research Network scoring system) diagnosed by historical biopsy within 1 year 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 and must have liver fat content by PDFF ≥ 10% and cT1 ≥ 800 msec for randomization.
    b. For diagnosis based on imaging:
        i. Step 1: Liver stiffness measured by TE of 7.6 - 21 kPa and CAP > 300 dB/m by FibroScan® within 3 months prior to Screening. (If results are available within this timeframe, assessment does not need to be performed at Screening but will be collected on Day 1. If TE and CAP were performed at Screening, these do not need to be repeated on Day 1.)
        ii. Step 2: Patients meeting these and all other eligibility criteria will undergo MRI and must have liver fat content by PDFF ≥ 10% and cT1 ≥ 800 msec for randomization.

5. All patients must have MRI-PDFF ≥ 10% and cT1 ≥ 800 msec
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, including ability to consistently take study drug once daily on an empty stomach

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:
    a. Active hepatitis B defined as positive Hep B surface antigen at screening
    b. 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.
    c. Autoimmune liver disease
    d. Primary biliary cirrhosis
    e. Primary sclerosing cholangitis
    f. Wilson's disease
    g. Gilbert's syndrome if direct bilirubin is above 0.3 mg/dL or evidence of active hemolysis
    h. Hemochromatosis or other iron overload
    i. Alpha-1-antitrypsin deficiency
    j. Alcoholic liver disease
    k. Prior known drug-induced hepatotoxicity
    l. Known bile duct obstruction
    m. Suspected or proven liver cancer
2. History or known clinical evidence of cirrhosis, esophageal varices, 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. Current or prior thyroid cancer, thyrotoxicosis, or pituitary disorders, or with known multiple endocrine neoplasia (MEN) type 2 syndrome
5. Abnormal thyroid examination including but not limited to enlarged thyroid gland (i.e., goiter) or thyroid nodules

6. Current diagnosis or history of thyroid disease, except for patients with primary hypothyroidism who have been on stable dose of thyroid hormone replacement therapy with levothyroxine for at least 6 months prior to Screening through randomization; patients must have normal TSH and free T4, per exclusion criteria #7 and be clinically euthyroid at Screening.
7. Clinical evidence of thyroid disease indicated by TSH or free T4 levels outside the normal range at Screening.

   Note: In patients in whom there is no known history of thyroid disease and who are not on thyroid hormone replacement medication, if TSH is up to 1.5 x ULN at Screening with normal free T4, 1 repeat test is allowed to confirm the elevation in TSH. If TSH and free T4 are normal upon repeat testing and there is no clinical suspicion of thyroid disease or history of elevated TSH, the patient may be included. All thyroid axis testing should be performed in the morning, approximately at the same time.
8. Total bilirubin > 1.2 mg/dL
9. Albumin < 3.5 g/dL
10. INR > 1.2 in patients who are not on anticoagulant therapy
11. ALT or AST > 5 × ULN
12. Unstable elevated ALT or AST: Patients with ALT or AST > 60 IU/L must have evidence of a stable value over at least a 2-week time period prior to randomization as evidenced by one of the following:

    a. Comparison to a historical value, if available, obtained within 2 to 12 weeks prior to the Screening visit: Screening value must be ≤ 30% higher than a documented historical value (Note: the historical value must be ≤ 5 × ULN)

       OR

    b. Repeat value at least 2 weeks after the Screening value: Repeat value should be ≤ 30% higher than the value from the Screening visit, and the repeat value must be ≤ 5 × ULN (Note: repeat only the analyte(s) that is/are > 60 IU/L at Screening)

    Note: If the Investigator has clinical suspicion for acute liver injury in a patient for other reasons, the patient should be excluded after discussion with the Medical Monitor.

    Note: The MRI-PDFF and cT1 may proceed on the basis of the initial ALT value at Screening, given all other eligibility criteria are met, but randomization should not occur prior to confirmation of ALT and/or AST stability as specified above.
13. ALP > 1.5 x ULN
14. Platelet count < 150,000 /mm^3
15. eGFR < 60 mL/min/1.73m^2 (Refer to Appendix 5 for the eGFR formula)
16. Weight loss of > 5% total body weight within 3 months prior to Screening
17. 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

18. Prior or planned (during the study period) bariatric surgery (e.g., gastroplasty, roux-en-Y gastric bypass)
19. Type 1 diabetes
20. Uncontrolled diabetes with HbA1c > 9.5%. Note: Patients with or without Type 2 diabetes may be enrolled provided all eligibility criteria are met
21. Unstable cardiovascular (CV) disease defined as myocardial infarction, unstable angina, percutaneous intervention, coronary artery bypass graft, or stroke within 6 months prior to randomization
22. Uncontrolled hyperlipidemia defined as fasting LDL cholesterol ≥ 150 mg/dL despite treatment or triglycerides > 500 mg/dL
23. LDL cholesterol < 40 mg/dL in patients who are not taking LDL cholesterol lowering therapy
24. Clinically significant abnormalities in 12-lead ECG at Screening, or known history of such abnormalities including but not limited to:

    a. II/III-degree atrioventricular block or bundle branch block (right and left)

    b. Arrhythmia (except occasional supraventricular premature beat)

    c. QT-interval corrected for heart rate using Fridericia's method (QTc) > 450 msec for males or > 470 msec for females

    d. Personal or family history of prolonged QT syndrome

    Note: An ECG can be repeated in instances of lead placement error, incomplete or uninterpretable tracings, or suspicion of machine error at Screening
25. Known hypersensitivities to the study drugs (TERN-501 or TERN-101) or to any formulation excipients
26. Clinically significant multiple or severe drug allergies, intolerance to topical corticosteroids, or severe post-treatment hypersensitivity reactions
27. Known allergy, intolerance, or contraindication to beta blockers
28. Alcohol consumption of > 2 standard drinks per day for males and > one standard drink per day 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 (5% alcohol), 1.5 oz (45 ml) 80 proof liquor (40% alcohol), or 5 oz (150 ml) wine (12% alcohol)
29. Illicit substance/chemical abuse in the 12 months prior to Screening

30. Cannabis use (tetrahydrocannabinol [THC] and cannabidiol [CBD]) within 14 days of randomization
31. Unwilling to abstain from excessive alcohol use (defined in exclusion criterion #28 above), cannabis use, and illicit substance use during study participation
32. Contraindications or inability to complete MRI scanning (ie, weight restrictions, presence of permanent pacemaker, implanted cardiac devices, etc.)
33. Positive for human immunodeficiency virus (HIV) infection
34. Laboratory or clinical evidence of current infection with Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), i.e., COVID-19
35. Presence of any condition that could, in the opinion of the Investigator, compromise the patient's ability to participate in the study

Prior Therapy

36. Historical or current use of drugs or therapies that may interfere with thyroid function (except for thyroid hormone replacement therapy with levothyroxine per exclusion criteria #6 and #37), including but not limited to methimazole, propylthiouracil, tyrosine kinase inhibitors, lithium, iodide, and propranolol; these therapies are also prohibited through end of study follow-up per Section 6.6
37. Initiation, discontinuation, or dose adjustment of thyroid hormone replacement therapy within 6 months prior to Screening through Randomization (Note: patients must be clinically euthyroid per exclusion criteria #6, with normal TSH and T4 per exclusion criteria #7)
38. Use of medications specifically for weight loss within 12 months prior to Randomization; these therapies are also prohibited through end of study follow-up per Section 6.6
39. Use within 3 months prior to Screening through Randomization: resmetirom or other investigational THR-β agonists, OCA or other investigational FXR agonists, pioglitazone or other PPARγ agonists, or high-dose vitamin E (> 400 IU/day); these therapies are also prohibited through end of study follow-up per Section 6.6
40. Initiation, discontinuation, or dose adjustment within 3 months prior to Screening (i.e., must be on stable dose for 3 months prior to Screening) through Randomization; or dose adjustment expected during study participation:
    a. GLP-1 analogues, DPP-4 inhibitors, and SGLT2 inhibitors
    b. Insulin with > 30% dose adjustment (Note: ≤ 30% dose adjustment is allowed)
    c. Statins, PCSK9 inhibitors or other lipid modifying medications
    d. Vitamin E ≤ 400 IU/day
    e. Hormonal contraceptives
41. Use within 3 months prior to Randomization:

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

42. Initiation, discontinuation, or dose titration within 2 months prior to Randomization (i.e. must be on stable dose for 2 months prior to Randomization); or dose adjustment expected during study participation:
    a. Metformin and other antidiabetic drugs not described above
43. Use within 2 weeks prior to Randomization:
    a. Vaccination for influenza, COVID-19, or other routine vaccinations
    b. Strong cytochrome P450 3A (CYP3A), P-glycoprotein (P-gp), or breast cancer resistant protein (BCRP) inducers or inhibitors, or anticipated to require treatment with strong CYP3A, P-gp, or BCRP inducers or inhibitors during study participation (See Section 6.6 for details.)

Prior Clinical Study Experience

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

5.3. Lifestyle Considerations

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

5.3.1. Lifestyle Counseling

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

5.3.2. Meals and Dietary Restrictions

Patients should arrive at the clinic fasting for assessments and dosing as defined in the Schedule of Activities (Section 1.1). 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 Week 12: 48- or 72-hours post-dose.

Patients should refrain from consumption of grapefruit or grapefruit juice 2 weeks before Randomization and through the end of treatment (Section 6.6).

5.3.3. Alcohol, Cannabis, and Illicit Drug Use

Patients must agree to not consume > 14 standard drinks per week for males and > 7 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)

Intervention Name	TERN-501 capsules	TERN-501 Placebo to match (identical in shape, size, appearance, and color to TERN-501 capsules)	TERN-101 tablets	TERN-101 Placebo to match (identical in shape, size, appearance, and color to TERN-101 tablets)
Type	Drug	Drug	Drug	Drug
Dose Formulation	Capsule	Capsule	Tablet	Tablet
Unit Dose Strength(s)	1 mg or 3 mg per capsule	N/A	5 mg per tablet	N/A
Route of Administration	Oral	Oral	Oral	Oral
Use	Experimental	Placebo	Experimental	Placebo
IMP and NIMP	IMP	IMP	IMP	IMP
Sourcing	Provided centrally by the Sponsor	Provided centrally by the Sponsor	Provided centrally by the Sponsor	Provided centrally by the Sponsor
Packaging and Labeling	Study drug will be provided in a labelled carton containing one/two bottles of capsules for 4-week use. Each bottle and carton will be labeled as required per country requirements.	Study drug will be provided in a labelled carton containing one/two bottles of capsules for 4-week use. Each bottle and carton will be labeled as required per country requirements.	Study drug will be provided in a labelled carton containing one/two bottles of tablets for 4-week use. Each bottle and carton will be labeled as required per country requirements.	Study drug will be provided in a labelled carton containing one/two bottles of tablets for 4-week use. Each bottle and carton will be labeled as required per country requirements.

6.2. Study Drug Administration

Patients will be instructed to take one capsule/tablet from each bottle by mouth daily, at approximately the same time each day, on an empty stomach (no food or drink besides clear liquids for approximately 2 hours before and 1 hour after study drug administration), for a total of 2 capsules and 2 tablets each day as shown in Table 6.

For subjects participating in the PK/PD sub-study, study drug should be administered approximately 24 hours prior to their Week 12 visit.

Table 6 Study Drug by Dose Group

Dose Group	TERN-501 Capsules	TERN-501 Placebo to Match	TERN-101 Tablets	TERN-101 Placebo to Match
Placebo QD	Not applicable	Two placebo capsules	Not applicable	Two placebo tablets
TERN-501 1 mg QD	One 1 mg capsule	One placebo capsule	Not applicable	Two placebo tablets
TERN-501 3 mg QD	One 3 mg capsule	One placebo capsule	Not applicable	Two placebo tablets
TERN-501 6 mg QD	Two 3 mg capsules	Not applicable	Not applicable	Two placebo tablets
TERN-501 3 mg QD + TERN-101 10 mg QD	One 3 mg capsule	One placebo capsule	Two 5 mg tablets	Not applicable
TERN-501 6 mg QD + TERN-101 10 mg QD	Two 3 mg capsules	Not applicable	Two 5 mg tablets	Not applicable
TERN-101 10 mg QD	Not applicable	Two placebo capsules	Two 5 mg tablets	Not applicable

Abbreviations: QD = once a day

6.3. Preparation/Handling/Storage/Dispensing/Accountability

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

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

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

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

6.4. Measures to Minimize Bias: Randomization and Blinding

Patients will be randomized to 1 of 3 dose levels TERN-501 monotherapy, 1 of 2 dose levels TERN-501+TERN-101, 10mg TERN-101 monotherapy, 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 140 patients will be randomized equally into one of the 7 treatment groups to receive once daily orally administered TERN-501 1 mg (n=20), TERN-501 3 mg (n=20), TERN-501 6 mg (n=20), TERN-501 3 mg+TERN-101 10 mg (n=20), TERN-501 6 mg+TERN-101 10 mg (n=20), TERN-101 10 mg (n=20), or matching placebo (n=20).

All personnel directly involved in the conduct of the study (i.e., Investigators, patients, all study personnel, Medical Monitor, and the Sponsor) will remain blinded to each patient's assigned dose group throughout the course of the study. Individuals in IP packaging and labeling who have Unblinded Inventory Manager role in the IXRS system for study drug inventory management will remain unblinded. Individuals at the PK bioanalytical laboratory will remain unblinded to facilitate sample processing, as placebo samples will not be analyzed for PK. 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 Medical Monitor/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 (CRF), 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 by direct questioning and counting returned capsules/tablets during the study visits and documented in the source documents and/or electronic case report form (eCRF). Deviation(s) from the prescribed dosage regimen should be recorded in the eCRF.

If a patient is required to be quarantined due to active infection of Coronavirus Disease 2019 (COVID-19) or exposure to COVID-19 or is otherwise unable to visit the site due to COVID-19, study drug may be mailed to the patient or made available via another appropriate mechanism (ie, curbside pickup, etc.).

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

6.6. Concomitant Therapy

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

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

Thyroid hormone replacement therapy during the study treatment:

- If determined necessary by Investigator, in consultation with the Medical Monitor, dose adjustment (dose increase or decrease, or discontinuation) of thyroid hormone replacement therapy with levothyroxine is allowed once after at least 6 weeks of study drug administration. See Section 8.1.8 for more information on thyroid axis safety monitoring

Medications prohibited for use through the end of study:

- Medications or therapies that may interfere with thyroid function (except in patients who were on a stable dose of thyroid hormone replacement therapy with levothyroxine for primary hypothyroidism prior to study entry), including but not limited to initiation of thyroid hormone replacement therapy, methimazole, propylthiouracil, tyrosine kinase inhibitors, lithium, iodide, and propranolol; patients who require such medications or therapies must discontinue study drug (See Section 7.1.2.)
- Medications specifically used for weight loss
- Medications with potential impact on NASH outcome, including resmetirom or other investigational THR-β agonists, obeticholic acid or other investigational FXR agonists, pioglitazone or other PPARγ agonists, or high-dose vitamin E (> 400 IU/day)

- 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 through the end of the study is allowed

Medications discouraged for initiation, discontinuation, or dose adjustment through the end of study, but allowed if deemed necessary for clinical management at Investigator's discretion:

- Vitamin E ≤ 400 IU/day
- Metformin, GLP-1 analogues, DPP-4 inhibitors, SGLT2 inhibitors, and other diabetic drugs
- Insulin with > 30% dose adjustment (Note: ≤ 30% dose adjustment is allowed)
- Statins, PCSK9 inhibitors, or other lipid modifying medications
- Hormonal contraceptives

Medications prohibited for use through the last dose of treatment:

There is potential for TERN-501 absorption to be increased or decreased by co-administered drugs that are intestinal P-gp and BCRP inhibitors or inducers, respectively, based on in vitro data. As such, strong P-gp and/or BCRP inhibitors or inducers are prohibited from this study.

There is potential for CYP3A4 inhibitors or inducers to increase or decrease the exposure of TERN-101, respectively. As such, strong CYP3A4 inhibitors or inducers are prohibited from this study.

A noncomprehensive list of known strong CYP3A inducers and inhibitors, P-gp inhibitors and inducers, and BCRP inhibitors is provided below:

- Potent CYP3A inhibitors prohibited on study include but are not limited to: boceprevir, cobicistat, ritonavir, grapefruit juice, itraconazole, ketoconazole, osaconazole, telaprevir, telithromycin, troleandomycin, voriconazole, clarithromycin, idelalisib, nefazodone, and nelfinavir
- P-gp inhibitors prohibited on study include but are not limited to: amiodarone, carvedilol, clarithromycin, cyclosporine, dronedarone, itraconazole, lapatinib, propafenone, quinidine, ranolazine, ritonavir, and verapamil
- BCRP inhibitors prohibited on study include but are not limited to: curcumin, cyclosporine, eltrombopag
- Potent CYP3A and/or P-gp inducers prohibited on study include but are not limited to: apalutamide, carbamazepine, enzalutamide, fosphenytoin, mitotane, phenytoin, rifampin, and St. John's wort

Patients who require initiation of strong CYP3A and/or P-gp inducers or strong CYP3A, P-gp, and/or BCRP inhibitors during the study should discontinue study drug (Section 7.1.2.). For patients who subsequently discontinue prohibited medications, study drug administration may not be resumed unless agreed by the Medical Monitor. Patients who do not resume study drug will continue in the study to be evaluated at the remaining visits through the Follow-Up visit.

Medications discouraged for use through the last dose of treatment:

Moderate CYP3A inhibitor use is discouraged during study participation. Management of patients who initiate moderate CYP3A4 inhibitors during the course of study treatment should be discussed with the Medical Monitor.

A noncomprehensive list for known moderate CYP3A4 inhibitors is provided below:

- Moderate CYP3A4 inhibitors discouraged on study include but are not limited to: aprepitant, ciprofloxacin, conivaptan, crizotinib, cyclosporine, diltiazem, dronedarone, erythromycin, fluconazole, fluvoxamine, imatinib, and verapamil

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. If a patient forgets to self-administer study drug at their usual time on a given day, the dose can be taken on the same day when the patient remembers, with the exception below:

- For patients participating in the PK/PD sub-study, drug must be self-administered in the morning approximately 24 hours before their Week 12 visit. If not, the Week 12 PK/PD sub-study visit should be re-scheduled for the following day.

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

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

6.8.1. Dose Interruptions due to COVID-19

If a patient requires home quarantine due to SARS-CoV-2 infection or exposure, or due to COVID-19 symptoms, the patient may continue study drug provided that appropriate safety follow-up is possible and that hospitalization is not required. Home health care visits may be 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. For additional details for study drug dispensation, please see Section 6.5.

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 at the remaining visits through the Follow-Up visit.

6.9. Intervention after the End of the Study

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

7. Discontinuation of Study, Study Drug and Patient Discontinuation or Withdrawal

7.1. Study and Study Drug Stopping Criteria

7.1.1. Study Stopping Criteria

Blinded safety review including, but not limited to, laboratory values, vital signs, ECGs, and AEs will be conducted regularly throughout the study and will assess whether any of the following criteria are met:

- One patient experiences a Grade V CTCAE considered related to study medication by the Investigator, or
- Two patients experience the same Grade IV CTCAE considered related to study medication by the Investigator, or
- Three patients experience the same Grade III CTCAE considered related to study medication by the Investigator

Note: Causality of AEs will be determined by the Investigator based on the 4-category system specified in Appendix 6.

In the event that study enrollment and/or dosing is stopped due to one or more of the criteria specified above, the causality of these adverse events will be further investigated by an Independent Medical Monitor (IMM); if adverse events are deemed to be unrelated to study drug (i.e., TERN-501, TERN-101, or TERN-501+TERN-101) by the IMM, then enrollment and/or dosing may resume.

The Sponsor may temporarily or permanently stop the study at any time for safety concerns.

7.1.2. Discontinuation of Study Drug

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

- If an AE of Grade 3 or above based on National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) 5.0 occurs and is considered related to study drug as judged by the Investigator per the guidance in Appendix 6.
- Development of TSH level outside the normal range (confirmed by repeat testing) that is determined to be clinically significant or warrants initiation of new medications or therapies to treat thyroid dysfunction of signs of hyper/hypothyroidism. (Note: Dose adjustment of thyroid hormone replacement therapy with levothyroxine without discontinuing study drug may be allowed once after at least 6 weeks of study drug administration at Investigator's discretion upon consultation with Medical Monitor as referenced in Section 6.6).
- Necessary use of nonpermitted concomitant drug (ie. CYP3A4/P-gp/BCRP strong inhibitor/inducer) as referenced in Section 6.6.

- Symptoms of COVID-19 requiring hospitalization.
- Change in status that, in the judgement of the Investigator compromises the patient's ability to continue treatment or is not considered to be in the patient's best interest.
- Patient request to discontinue study drug for any reason.
- Pregnancy during the study (refer to Appendix 7).
- Sponsor discretion.
- Discontinuation of the study at the request of the Sponsor, a regulatory agency, or Institutional Review Board (IRB)/Independent Ethics Committee (IEC).

Study drug may be discontinued upon confirmation by repeat testing for an individual patient in the following instances at the discretion of the Investigator, and the Medical Monitor should be informed if any of the following occurs:

- If one of the following laboratory abnormalities is confirmed by repeat testing, considered related to the study drug and does not have alternative etiology (repeat test should be performed within 48-72 hours once initial abnormality is detected):
    - ALT or AST > 8 × ULN
    - ALT or AST > 5 × ULN for more than 1 week during study drug administration
    - ALT or AST > 2× Baseline with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (> 5%)
    - ALT or AST > 2 × Baseline and total bilirubin > 2 × ULN or INR > 1.5 for more than 1 week, confirmed with a repeat assessment
    - ALP > 5 x ULN
    - ALP > 3 x ULN and total bilirubin > 2x ULN

Study drug administration may not be resumed unless discussed and agreed with the Medical Monitor.

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

If study drug is permanently discontinued, the patient should remain in the study to be evaluated at the remaining visits through the Follow-Up visit; scheduled assessments may be performed at Investigator's discretion in consultation with Medical Monitor/Sponsor; PK samples will not be collected at subsequent visits after study drug discontinuation. See the Schedule of Activities for data to be collected at the time of discontinuation of study drug and follow-up and for any further evaluations that need to be completed.

7.2. Patient Discontinuation/Withdrawal from the Study

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

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

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

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

7.3. Lost to Follow up

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

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

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

Discontinuation of specific sites or of the study as a whole are addressed in Section 10.1.8 and Section 7.1.1.

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.

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 (Section 1.3).

8.1.1. Demographics

Demographic data includes age (year of birth), sex, race, and ethnicity.

8.1.2. Height and Weight

Height and weight are collected at Screening and will be used to calculate BMI for eligibility. Only weight is collected at Weeks 0, 6, 12, 16, and ET.

8.1.3. Medical History

Medical history including details of illnesses, allergies, or procedures including liver biopsy, date(s) of onset, whether condition(s) is currently ongoing, medication history, including alcohol use, will be collected for all patients at Screening and prior to Randomization.

8.1.4. Physical Examinations

A complete physical examination be performed at Screening, Week 16, and ET and 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 at all other study visits as needed, based on clinical judgement of the Investigator, to evaluate reported current or prior AEs, symptoms reported by the patient, or abnormal laboratory readouts.

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

8.1.5. Vital Signs

Temperature, pulse rate, respiratory rate, and blood pressure will be assessed at all study visits as outlined in the Schedule of Activities (Section 1.3) 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 ECGs will be obtained at all study visits as outlined in the Schedule of Activities (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.

In the instance of patient-reported symptoms considered potentially cardiac in nature such as chest pain/pressure, palpitations, dizziness, shortness of breath, or report of patient recently seeking medical care for such symptoms (e.g., emergency room visit), perform an an-hoc ECG, and, per the clinical judgement of the Investigator, obtain cardiology consult as needed.

Participants will be instructed to lie supine for at least 10 minutes prior to 12-lead ECG collection. During ECG collection, participants should be in a quiet setting, without distractions, and refrain from talking or moving their arms or legs.

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

8.1.7. Cardiovascular Safety Monitoring

Cardiovascular safety will be monitored via vital signs (see Section 8.1.5) and 12-lead ECGs (see Section 8.1.6) along with clinical assessment of adverse events that may represent signs or symptoms of cardiac toxicity.

Signs and symptoms that may reflect cardiovascular toxicity include the following, with clinical significance to be determined by the Investigator:

- Vital signs changes including hypertension, hypotension, tachycardia, or bradycardia
- 12-lead ECG findings including tachycardia, bradycardia, atrial fibrillation or flutter, ventricular arrythmia, or QTc prolongation
- Clinical symptoms suggestive of cardiac ischemia or other cardiac dysfunction such as chest pain/pressure, palpitations, shortness of breath, or edema

Potential signs or symptoms consistent with cardiovascular toxicity should be carefully evaluated, with repeat of assessments (e.g., vital signs, ECG, laboratory values) to confirm findings and follow-up until resolution.

Signs or symptoms should be designated as AEs with CTCAE v5.0 severity determined per Appendix 6. Participant discontinuation of study drug criteria are outlined in Section 7.1.2.

8.1.8. Thyroid Axis Safety Monitoring

Clinical signs and symptoms of hyper/hypothyroidism are variable and should be considered when assessing participants for AEs throughout the course of the study.

Major signs and symptoms of hyperthyroidism are:

- Overt hyperthyroidism is characterized by a constellation of symptoms including anxiety, emotional lability, restlessness, irritability, psychosis, agitation, depression, insomnia, weakness, tremor, palpitations, heat intolerance, increased perspiration, or weight loss (although weight gain may also be seen due to appetite stimulation). Signs may include hyperactivity, rapid speech, eye lid lag, warm and moist skin, tachycardia, systolic hypertension, proximal muscle weakness, or hyperreflexia
- Other symptoms may include hyperdefecation, urinary frequency, atrial fibrillation, heart failure, premature atrial contractions, shortness of breath, myopathy, hypercalcemia, or osteoporosis (with prolonged thyroid hormone excess)

Major signs and symptoms of hypothyroidism are:

- Effects of slowing of metabolic processes such as slow movement and speech, delayed relaxation of tendon reflexes, bradycardia, fatigue and weakness, cold intolerance, dyspnea on exertion, weight gain, cognitive dysfunction, or constipation
- Effects of accumulation of matrix substances such as coarse skin, puffy facies and loss of eyebrows, periorbital edema, tongue enlargement, dry skin, hoarseness, or edema
- Others such as diastolic hypertension, decreased hearing, myalgia and paresthesia, depression, or arthralgia

Liver function test monitoring criteria include guidance on increased monitoring in the event of alkaline phosphatase elevation (Appendix 3), as hyperthyroidism-associated liver injury may be cholestatic in nature and present with high alkaline phosphatase levels. Study drug discontinuation guidelines for ALP elevations are included in Section 7.1.2.

Thyroid axis testing will be performed as outlined in the Schedule of Activities and Appendix 1. Peripheral thyroid hormone modulation with THR-β agonism may lead to lowering free T4 (prohormone) without changes in T3 (active hormone) or TSH (Section 7.1.2). In the FIH study (Study TERN501-1009), dose-dependent decreases in free T4 were observed without clear changes in T3 or TSH over 14 days of treatment with TERN-501, which appeared consistent with peripheral thyroid hormone modulation with THR-β agonism. While minor fluctuations in thyroid hormone (e.g., ~20%) within the normal range are not considered clinically relevant in euthyroid patients (Dong 2000), overt alterations of TSH could reflect unwanted effects on the central thyroid axis. In the event of systemic thyroid hormone effects of TERN-501, clear TSH decline to below the normal range would be an indicator of likely central thyroid axis suppression. However, clinical manifestations should be considered in determining clinical thyroid status. Similarly, changes in T3 (and/or T4, if unblinded) should be interpreted in the setting of the TSH changes and clinical factors.

TSH or other thyroid axis tests outside the normal range should be confirmed by repeat testing. Repeat testing should be performed within 7 days of the test result. All thyroid axis testing including repeat testing should be performed in the morning, approximately at the same time.

Study drug should be discontinued in a patient with TSH level outside the normal range (confirmed by repeat testing) that is determined to be clinically significant or that warrants initiation of new medications or therapies to treat apparent thyroid dysfunction or hyper/hypothyroidism (Section 7.1.2). T4 will be blinded during the study to avoid potential unblinding of treatment assignment (Section 8.1.9.1). Free T4 and/or total T4 results may be made available at the Investigator's request upon consultation with Medical Monitor as necessary for clinical management for patients.

Ongoing assessment of AEs considered possibly related to thyroid dysfunction should be conducted until symptoms resolve or stabilize. In the event of abnormal thyroid laboratory assessments, repeat assessment should be conducted approximately every 3 to 7 days, at the discretion of the Investigator, until levels normalize. Patients who have thyroid axis tests outside of the normal range at Follow-Up visit that are determined to be clinically significant by the Investigator should be monitored until laboratory values normalize and/or any symptoms are resolved.

For guidance on dose adjustment of thyroid hormone replacement therapy with levothyroxine during the study, see Section 6.6, Concomitant Therapy.

8.1.9. Clinical Laboratory Assessments

See Appendix 1 for the list of clinical laboratory tests to be performed and refer to the Schedule of Activities (Section 1.3) 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.

8.1.9.1. Blinded Laboratory Assessments

Laboratory results that could potentially unblind the study will not be reported to investigative sites or other blinded personnel until the study has been unblinded unless deemed necessary for patient safety or clinical decision-making during the study. This includes all PD analyses listed in Appendix 2. All clinical safety laboratory assessments listed in Appendix 1 will be available to investigative sites for safety monitoring, except for the analytes noted below.

Analyte and Rationale for Blinding	Details and Risk Mitigation, if Needed
Fasting lipids Lipid profile changes are an important PD marker of THR-β agonism. TERN-501 led to significant decreases in circulating lipid levels including LDL cholesterol, Apo B, total cholesterol, and triglycerides in the FIH study (Study TERN501-1009).	While a standard lipid panel will be included as part of the chemistry panel for eligibility, the lipid parameters collected as TERN-501 PD markers listed in Appendix 2 will be blinded. Declines in lipid parameters including LDL cholesterol, Apo B, total cholesterol, and triglycerides are not expected to pose a safety risk to patients during study participation. However, in the event of LDL cholesterol elevation > 100 mg/dL that is >20% increase from baseline, LDL cholesterol values will be made available to the Investigators, along with the Medical Monitor and Sponsor, to help guide clinical decision making.
Sex hormones THR-β agonism upregulates SHBG expression, and a significant increase in SHBG was demonstrated in the FIH study (Study TERN501-1009). With an increase in SHBG, increases in total testosterone levels were also observed.	Sex hormones including total and free testosterone, estradiol, FSH, and luteinizing hormone (LH) will be blinded. Possible changes in sex hormone levels would need to be interpreted in the context of SHBG levels and are not expected to pose a safety risk to patients during study participation. Sex hormone results may be made available at the Investigator's request upon consultation with Medical Monitor as needed for management of clinical concerns consistent with sex hormone abnormalities.
Postdose T4 In the FIH study (Study TERN501-1009), dose-dependent decreases in free T4 were observed without clear changes in T3 or TSH, which appeared consistent with peripheral thyroid hormone modulation with THR-β agonism leading to lowering free T4 (prohormone) without changes in T3 (active hormone) or TSH.	Postdose T4 will remain blinded, as isolated T4 changes are not expected to affect clinical decision making or pose a risk to patients during study participation. Free T4 and/or total T4 values may become available at Investigator's request upon consultation with Medical Monitor as needed for management of clinical concerns consistent with thyroid dysfunction or hyper/hypothyroidism (see Section 8.1.8.).
Reverse T3 Reverse T3 (rT3) will be assessed as an exploratory biomarker of THR-β agonism.	No clinical decision making is anticipated based on rT3 values, and thus this exploratory biomarker will remain blinded.
Bone Turnover Markers Serum procollagen type I N propeptide (sPINP) is a marker of bone formation and serum C-terminal cross-linking telopeptide of type I collagen (sCTX) is a marker of bone resorption.	No clinical decision making is anticipated based on these results, and thus will remain blinded.

8.1.9.2. Liver Function Tests

ALT and/or AST stability should be evaluated prior to randomization, if applicable, per Section 5.

During the course of the study, LFTs will be monitored per the Schedule of Activities (see Section 1.3). 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.

8.1.9.3. Bone Turnover Markers

While bone loss may occur in the event of thyroid hormone excess, this is mediated largely through THR-α (Sinha 2019; Gorka 2013). Although no significant effects on bone mineral density was observed at Week 36 in the phase 2 resmetirom study (Harrison 2019) and no TERN-501 data available to date suggest an adverse thyromimetic effect on bone, samples to measure serum bone turnover markers will be collected in this study. Specifically, serum procollagen type I N propeptide (sPINP) as a marker of bone formation and serum C-terminal cross-linking telopeptide of type I collagen (sCTX) as a marker of bone resorption will be assessed at visits specified in the Schedule of Activities (Section 1.3).

8.1.10. Transient Elastography and Controlled Attenuation Parameter by FibroScan®

Liver stiffness by TE and CAP may be assessed at Screening to determine study eligibility (Section 5.1). If TE and CAP were performed at Screening, these parameters do not need to be repeated on Day 1. TE and CAP will also be conducted at Week 12, and at ET only if not done within the prior 4 weeks, and the patient has had at least 4 weeks of dosing (see Section 1.1).

The transient elastography requirement is intended to select for patients likely to have at least F1 fibrosis. The protocol excludes patients with cirrhosis based on medical history or clinical signs or symptoms (Exclusion criteria #2). Prior studies indicate variability in the ranges of liver stiffness measured by transient elastography in NASH patients with fibrosis or cirrhosis. In STELLAR-3, which enrolled patients with bridging fibrosis, median liver stiffness at baseline was approximately 13 kPa, with an interquartile range between 10 and 17 kPa (Harrison 2020). In STELLAR-4, which enrolled patients with cirrhosis, median liver stiffness at baseline was approximately 20-21 kPa, with an interquartile range between 14 and 30 kPa (Harrison 2020). The utility of transient elastography to diagnose cirrhosis in the setting of NASH also appears limited based on the low positive predictive value (PPV) of even relatively high kPa thresholds. For a threshold of 21 kPa, the upper limit for this study, the PPV for F4 fibrosis (i.e., cirrhosis) in the setting of NASH is 0.37 (which may be even lower in a population with low prevalence of cirrhosis, such as one in which cirrhosis is excluded on clinical grounds), with a negative predictive value of 0.96 (Eddowes 2019). This threshold has a sensitivity of 0.59 and a specificity of 0.90 for a diagnosis of cirrhosis in the setting of NASH (Eddowes 2019).

CAP is an assessment of liver steatosis and is generally used to complement the assessment of liver stiffness by transient elastography for evidence of NASH (Eddowes 2019). CAP estimates the total ultrasonic attenuation (go-and-return path), expressed in dB/m, based on the postulate that fat affects ultrasound propagation. A CAP threshold of 274 dB/m has sensitivity of 0.9 and

specificity of 0.6 for identification of liver steatosis of ≥ 5% (Eddowes 2019). The threshold of 300 dB/m was chosen to identify patients who are likely to have elevated liver steatosis, in conjunction with the other imaging assessments at screening, including MRI-PDFF and cT1.

8.1.11. FibroScan-AST (FAST) Score

The FAST score, a number between 0 and 1, uses the liver stiffness by TE and CAP measurements from FibroScan® combined with levels of AST to estimate a patient's risk for NASH. A score ≥ 0.67 has been reported to indicate a high risk for NASH (Newsome 2020). The FAST score will be derived based on TE and CAP by FibroScan® combined with AST value.

8.1.12. Magnetic Resonance Imaging: Proton Density Fat Fraction (MRI-PDFF) and Corrected T1 (cT1)

MRI-PDFF quantifies the relative amount of water vs. fat in a tissue, while cT1 is a novel MRI-based quantitative metric for assessing a composite of liver inflammation and fibrosis.

MRI-PDFF quantifies the relative amount of water vs. fat in a tissue based on signals from proton groups that vary depending on tissue cell type (Caussy 2018). PDFF is expressed as a percentage (range from 0-100%) representing the ratio of density of mobile protons from triglycerides relative to total triglyceride and water mobile proton density (although there are also triglyceride elements that are not visible by magnetic resonance and do not contribute to PDFF determination). In the liver, PDFF correlates with histological assessment of hepatic steatosis, and PDFF has been advanced as a measure of liver fat content to assess treatment response in NASH studies (Caussy 2018). PDFF values correlate with NAS score on liver histology, with a strong correlation with steatosis ($rs = 0.68$, $p < 0.001$) (Dennis 2021). A PDFF ≥ 5% generally reflects abnormal steatosis as seen in NAFLD or NASH (Szczepaniak 2005; Tang 2013). PDFF and cT1 values have been shown to be strongly correlated with each other in NASH patients ($rs = 0.66$, $p < 0.001$) (Dennis 2021). The threshold of MRI-PDFF for study entry ≥ 10 % was chosen to identify patients who are likely to have elevated liver steatosis, in conjunction with the other imaging assessments at screening, including cT1.

Corrected T1 is based on multiparametric MRI data, measuring relaxation time that varies based on extracellular tissue fluid attributed to inflammation and fibrosis, with a longer relaxation time occurring with more extracellular fluid; the measurement is corrected for elevated iron content, which has an opposing effect on relaxation time (Banerjee 2014). Values for cT1 have been shown to correlate with the NAFLD Activity Score (NAS) and its components, as well as with degree of fibrosis by liver histology (Banerjee 2014; Dennis 2021). A population at low risk for NAFLD was found to have values ranging from 573 to 852 msec with a median of 666 msec and interquartile range from 643 to 694 msec, with high cT1 values (e.g. > 875 msec) having been shown to strongly predict liver-related clinical outcomes (e.g., hepatic encephalopathy, variceal bleeding, ascites, death) (Mojtahed 2019). In conjunction with other screening assessments, a threshold of 800 msec for study entry will enrich for a NASH population with fibrosis; this threshold has a sensitivity of 86% and a specificity of 93% for identifying patients with ≥ F1 fibrosis (Banerjee 2014).

MRI-PDFF and cT1 assessments will be performed at Screening. An MRI-PDFF and cT1 scan may proceed based on the initial screening ALT and AST values, given all other eligibility

criteria are met, but randomization should not occur prior to confirmation of ALT and/or AST stability as necessary, per Section 5. The images will be analyzed by a central reader. MRI-PDFF and cT1 will also be conducted at Week 6 and Week 12, or at ET only if not done within the prior 4 weeks, and the patient has had at least 4 weeks of dosing (Section 1.3).

8.2. Pharmacokinetics

Blood samples will be collected for measurement of plasma concentrations of TERN-501, TERN-101, and TERN-101 metabolite TRN-000971 at timepoints specified in Appendix 2 and as specified in the Schedule of Activities (Section 1.3).

Patients in the PK/PD sub-study will undergo intensive and sparse PK sample collection as specified in the Schedule of Activities (Section 1.3) and Appendix 2.

Patients who are not participating in the PK/PD sub-study will undergo sparse PK sampling collection only, as specified in the Schedule of Activities (Section 1.3) 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 as well as actual dosing date and time (24-hours clock time) of the last dose prior to PK sample collection.

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

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

In addition, any remaining (leftover) samples may be stored and used for optional exploratory future research on biomarker variants thought to play a role in NASH or to develop methods or assays related to the disease process or mechanism of action of the study drug. Patients must provide informed consent for optional exploratory future research as specified in Section 10.1.2. Samples collected for pharmacokinetic assessments will be destroyed no later than 15 years after the end of study.

8.3. Pharmacodynamics

Blood samples will be collected for measurement of PD markers of THR-β and FXR agonism at timepoints specified in Appendix 2 and as specified in the Schedule of Activities.

Patients in the PK/PD sub-study will undergo intensive PD sample collection for FGF19, 7αC4, as well as trough PD sample collection for lipid panel, 7αC4, SHBG, and bile acids 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 lipid panel, 7αC4, SHBG, and bile acids as specified in the Schedule of Activities and Appendix 2.

Bile acids will only be tested on Week 0, Week 12, and at ET.

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

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

In addition, any remaining (leftover) samples may be stored and used for optional exploratory future research on biomarker variants thought to play a role in NASH or to develop methods or assays related to the disease process or mechanism of action of the study drug. Patients must provide informed consent for optional exploratory future research as specified in Section 10.1.2. Samples collected for pharmacodynamic assessments, and any remaining samples stored and used for optional exploratory future research will be destroyed no later than 15 years after the end of study.

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 (Section 1.3):

- Blood collection for the following biomarkers: CK-18 (M30 and M65), ELF (PIIINP, TIMP-1, HA), and PRO-C3
- rT3 will be assessed as an exploratory biomarker of THR-β agonism and collected as part of the thyroid axis testing panel

Leftover samples may also be used to assess additional NASH biomarkers based on the safety, efficacy, and PD biomarker results of this study.

The following exploratory fibrosis scores may also be calculated: FIB-4, ELF, and FAST score and. Biomarkers inform exploratory objectives to further understand FXR and THR-β agonism in NAFLD and NASH, and their association with the observed clinical responses to treatment with study drug.

In addition, any remaining (leftover) samples may be stored and used for optional exploratory future research on biomarker variants thought to play a role in NASH or to develop methods or assays related to the disease process or mechanism of action of the study drug. Patients must provide informed consent for optional exploratory future research as specified in Section 10.1.2. The samples collected for biomarkers and any remaining samples stored and used for optional exploratory future research will be destroyed no later than 15 years after the end of study.

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 visit, at every study visit, as specified in the Schedule of Activities (Section 1.1).

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

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

8.5.2. Method of Detecting AEs and SAEs

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

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

8.5.3. Follow-up of AEs and SAEs

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

8.5.4. Regulatory Reporting Requirements for SAEs

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

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

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

An Investigator who receives an investigator safety report describing a SAE or other specific safety information (e.g., summary or listing of SAEs) from the sponsor will review and then file it along with the Investigator's Brochure and will notify the IRB/IEC, if appropriate according to local requirements.

8.5.5. Pregnancy

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

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

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

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). A qualified staff member will administer the Pruritus Numerical Rating Scale (Appendix 8) at each study visit when pruritus is reported or noted as ongoing. If pruritus is reported (either ongoing or at any time since the last visit), the clinical site will provide details on these events in the AE eCRF page.

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 and study stopping rules.

8.6. Treatment of Overdose

Overdose with TERN-501 monotherapy, TERN-101 monotherapy, or TERN-501+TERN-101 has not been reported. Neither the effect of overdose nor antidote are known. The maximum amount of TERN-101 that can be safely administered in a single dose has not been determined. The highest single dose of TERN-101 in clinical studies was 25 mg in the tablet formulation and 600 mg in the capsule formulation (see Section 2.2.2.2) and the highest single dose of TERN-501 in clinical studies was 60 mg. The highest single dose of TERN-501+TERN-101 was 3mg and 15mg respectively. Patients who receive higher than the protocol-defined dose should be carefully monitored for AEs, and the quantity of the excess dose and duration of excess dose should be documented in the eCRF; the Medical Monitor should be notified immediately. Refer to Appendix 6 for additional information on AE reporting.

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

8.7. Medical Resource Utilization and Health Economics

Medical resource utilization and health economics parameters are not evaluated in this study.

9. Statistical Considerations

9.1. Statistical Hypotheses

The primary statistical analysis will test whether the mean relative change from baseline in MRI-PDFF is (H_1) or is not (H_0) different between placebo and TERN-501 monotherapy. Secondary statistical analyses will test whether the mean relative change from baseline in MRI-PDFF is (H_1) or is not (H_0) different between placebo and TERN-501+TERN-101. Similarly, statistical analyses of cT1 will test whether the mean change from baseline is (H_1) or is not (H_0) different between placebo and TERN-501 monotherapy and between placebo and TERN-501+TERN-101. In addition, exploratory analyses will evaluate all pairwise comparisons between the different TERN-501 doses and of TERN-101 compared to placebo and will be considered nominal and descriptive.

9.2. Sample Size Determination

Approximately 140 patients will be randomized into one of the 7 groups (n=20 each) to detect a clinically meaningful difference in the primary endpoint and secondary endpoints of MRI-PDFF relative reduction at Week 12 and secondary endpoints of cT1 reduction at Week 12 between placebo and TERN-501 monotherapy and separately between placebo and TERN-501+TERN-101.

Power was estimated based on published literature for THR-β agonist resmetirom (to estimate TERN-501 effect) and clinical data for TERN-101 (Study TERN101-2001). Assuming a pooled standard deviation of 22% (Study TERN101-2001 final analysis), with a two-sided alpha of 0.05, a mean relative reduction difference in MRI-PDFF at Week 12 of

- 23% between placebo (n=20) and TERN-501 monotherapy (n=20) will provide approximately 90% power (Harrison 2019).
- 36% between placebo (n=20) and TERN-501+TERN-101 (n=20) will provide >90% power, based on placebo treatment effect from resmetirom (Harrison 2019) and sum of treatment effects from resmetirom (to estimate TERN-501 effect) and minimum treatment effect for TERN-101 (Study TERN101-2001), assuming an additive effect of the two agents in combination.

Assuming a pooled standard deviation of 82 msec (Study TERN101-2001 final analysis), with a two-sided alpha of 0.05, a mean reduction difference in cT1 at Week 12

- of 77 msec between placebo (n=20) and TERN-501 monotherapy (n=20) will provide approximately 82% power (Harrison 2018).
- 134 msec between placebo (n=20) and TERN-501+TERN-101 (n=20) will provide >90% power, based on placebo treatment effect from resmetirom (Harrison 2019) and sum of treatment effects from resmetirom (to estimate TERN-501 effect) and minimum treatment effect for TERN-101 (Study TERN101-2001), assuming an additive effect of the two agents in combination.

Patients who are randomized but do not receive study drug for any reason may be replaced. In addition, patients who discontinue treatment early for reasons other than safety (i.e., withdrawal

of consent, lost to follow-up, patient relocated, etc.) may also be replaced, at the Sponsor's discretion. Replacement patients will receive the same treatment assignment as the patient that discontinued treatment early.

9.3. Analysis Sets

The following analysis sets are defined:

Analysis Sets	Description
Screened	All patients who sign the ICF
Randomized	All patients who are randomized into any one of treatment groups. Treatment assignment will be based on the randomized treatment.
Pharmacokinetic (PK)	All randomized patients who received at least 1 dose of TERN-501 and/or TERN-101 and have evaluable PK data. Treatment assignment will be based on the treatment actually received.
Pharmacodynamic (PD)	All randomized patients who received at least 1 dose of study drug (TERN-501, TERN-101, or placebo) and for whom PD markers can be evaluated. Treatment assignment will be based on the treatment actually received.
PK/PD sub-study	All patients who consented to and participated in the PK/PD sub-study and received at least 1 dose of study drug (TERN-501, TERN-101, or placebo). Treatment assignment will be based on the treatment actually received.
Safety	All patients who received at least 1 dose of study drug. Treatment assignment will be based on the treatment actually received.
Efficacy	All randomized patients who received at least 1 dose of study drug. Treatment assignment will be based on the randomized treatment.

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 database lock (DBL).

9.4.1. General Considerations

For continuous data, summary statistics will include the number of non-missing observations (n), arithmetic mean, arithmetic standard deviation, median, 25^{th} percentile (Q1), 75^{th} percentile (Q3), minimum, and maximum. For log-normal data (eg, the PK parameters: AUCs and maximum observed concentration [C_{max}]), 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 for statistical analyses of quantitative laboratory parameters is defined as the mean of all available evaluations, including any unscheduled or repeat assessments, prior to the first administration of study drug. Otherwise, the baseline value is defined to be the latest assessment value prior to the first administration of study drug, unless specified in the SAP.

Missing values will not be imputed for primary analyses. However, sensitivity analyses will be conducted to evaluate the effect of missing data. Further details will be specified in the SAP.

No adjustments for multiplicity will be made.

Data analysis will be performed using SAS® Version 9.4 or higher. Noncompartmental PK parameters will be estimated from individual plasma concentration data using Phoenix® WinNonlin®.

9.4.2. Primary Endpoint

Analyses of MRI-PDFF will be based on the Efficacy Analysis Set. Descriptive statistics of MRI-PDFF results, absolute change from baseline, and relative change from baseline will be summarized by treatment group and visit. Analyses of relative change from baseline will be carried out using an ANCOVA model at Week 12 with relative change from baseline as the dependent variable including treatment group as a fixed effect and baseline as a covariate.

The estimates of least-square (LS) means, standard errors (SE), and 95% confidence intervals (Cis) will be presented by treatment group. Estimates of the LS mean difference between TERN-501 monotherapy and placebo will be presented with the associated standard error of the difference, and 95% CI of the difference.

9.4.3. Secondary Endpoints

9.4.3.1. Change from Baseline in cT1 at Week 12

Analyses of cT1 will be based on the Efficacy Analysis Set. Descriptive statistics of cT1 results, change from baseline, and percent change from baseline will be summarized by treatment group and visit. Corrected T1 will be analyzed in the same manner as MRI-PDFF. Secondary endpoint comparisons will include TERN-501 monotherapy compared to placebo and TERN-501+TERN-101 compared to placebo.

9.4.3.2. Change from Baseline in MRI-PDFF at Week 12

In addition to the primary endpoint comparison, secondary endpoint comparisons include TERN-501+TERN-101 compared to placebo.

9.4.3.3. Treatment-Emergent Adverse Events

Reported AEs will be coded using the latest version of Medical Dictionary for Regulatory Activities. Patient incidence of treatment-emergent AEs (TEAEs) will be summarized by treatment group and MedDRA system organ class (SOC) and preferred term (PT) using the Safety Analysis Set.

9.4.4. Exploratory Endpoints

9.4.4.1. Efficacy Endpoints

All exploratory efficacy analyses will be performed on Efficacy Analysis Set. Exploratory analyses will evaluate all pairwise comparisons between the 7 treatment groups and will be considered nominal and descriptive.

The primary and secondary endpoints evaluate Week 12 MRI-PDFF and cT1, while exploratory endpoints will summarize and analyze other applicable time points and additional treatment group comparisons of TERN-501+TERN-101 to TERN-501 monotherapy and TERN-101 monotherapy in the same manner specified for the primary and secondary endpoints. Additional details will be specified in the SAP.

Change (and separately percent change) from baseline in liver enzymes, NASH and fibrosis biomarkers, and liver stiffness will be summarized and analyzed at applicable time points using the same ANCOVA model specified for the primary endpoint.

FAST score will be calculated based on liver stiffness and AST values (Newsome 2020).

MRI-PDFF responders will be defined as any patient with a relative decrease of at least 30%. Non-responders will be defined as any patient who did not have at least a 30% relative decrease. The number and percentage, with associated two-sided exact (Clopper-Pearson) 95% CI, of patients in each category (response, nonresponse) will be presented by treatment group at applicable time points. A Chi-square test will be used to compare treatment groups.

cT1 responders will be defined any patient with a decrease of at least 80 msec. Non-responders will be defined any patient who did not have at least an 80 msec decrease. cT1 response will be summarized and analyzed at applicable time points in the same manner as specified for MRI-PDFF.

9.4.4.2. Pharmacokinetic Endpoints

Individual plasma concentrations of TERN-501, TERN-101, and TERN-101 metabolite TRN-000971 will be listed by timepoint and summarized by treatment group. PK of other metabolites may be explored. Individual and mean concentration-time profiles will be presented graphically in linear and semi-log scales.

Derived PK parameters from the PK/PD sub-study will be listed individually and summarized with descriptive statistics, including arithmetic and geometric mean, median, standard deviation, coefficient of variation (CV), geometric CV, minimum and maximum.

9.4.4.3. Pharmacodynamic Endpoints

PD markers of THR-β agonism include SHBG and lipids, while PD markers of FXR agonism include FGF19, 7αC4, and bile acids. Descriptive statistics of PD marker results, change from baseline, and percent change from baseline will be summarized by treatment group and visit. Change (and separately percent change) from baseline will be analyzed at applicable time points using the same ANCOVA model specified for the primary endpoint.

Pharmacodynamic parameters may also be calculated, summarized, and described by plotting the concentration-time curve or time-effect curve.

9.4.5. Safety Endpoints

In addition to the secondary endpoint of patient incidence of TEAEs, patient incidence of TEAEs will also be summarized by maximum intensity and study drug causality. Summaries of treatment-emergent SAEs will be summarized in the same manner as the secondary endpoint.

Vital signs and quantitative safety laboratory measurements will be summarized by treatment group and scheduled time points. Laboratory abnormalities will be graded according to NCI CTCAE Version 5.0, where applicable. The number and percentage of subjects experiencing treatment-emergent graded lab toxicities will be summarized by treatment group and toxicity grade.

9.5. Interim Analyses

No formal interim analyses are planned.

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
- Start and end date (including dose regimen) of study drug administration, including dates of dispensation and return as applicable
- Record of all AEs and other safety parameters (start and end date, and including causality and severity)
- Concomitant medications (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 7 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 and the reference range 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 7 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 Calcium Chloride CPK Creatinine eGFR[4] Glucose Phosphorus Potassium Sodium Total Protein	Liver Function Tests[3]: • ALT • Albumin • AST • ALP • GGT • Total and Direct Bilirubin[5] Lipid Tests: • HDL cholesterol • LDL cholesterol[6] • Total cholesterol[6] • Triglycerides[6] • Non-HDL cholesterol[6] • VLDL cholesterol[6]

Sex Hormone Panel	Free and Total Testosterone	FSH
	Estradiol	LH
Coagulation[3]	aPTT[1]	
	Prothrombin Time (PT)/International Normalized Ratio (INR)	
Thyroid Axis Testing	TSH	Total T4
	TBG[7]	Free T4
	Total T3	rT3[7]
	Free T3	
Bone Turnover Markers	sCTX	
	sPINP	
Urinalysis	• Specific gravity	
	• pH, glucose, protein, blood, ketones, bilirubin, urobilinogen, nitrite, leukocyte esterase by dipstick	
	• Microscopic examination (if blood or protein is abnormal)	
Pregnancy	Highly sensitive serum β-hCG (WOCBP only)	
Other Tests	• FSH (as needed in women of non-childbearing potential only)[1]	
	• Blood alcohol test[1]	
	• Urine drug screen including amphetamines, barbiturates, cocaine, opiates, cannabinoids and benzodiazepines	
	• Serology[1]: HIV antibody, HBsAg, and HCV antibody[8]	
	• 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] Collected per Scheduled of Activities. If significant abnormal liver function is observed, PT/INR and albumin to be repeated as outlined in Appendix 3.
[4] eGFR to be calculated by central lab; refer to Appendix 5 for the formula.
[5] 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.
[6] A standard lipid test will be collected as part of the clinical chemistry at Screening to confirm eligibility. During study treatment, lipid parameters for PD assessments listed in Table 9 of Appendix 2 will be collected and results will be blinded. HDL will remain unblinded and will be collected as part of clinical chemistry at all visits
[7] Only collected Week 0/Day 1, Week 12, and ET.
[8] If HCV antibody positive, conduct HCV RNA test.

Abbreviations: β-hCG = β-human chorionic gonadotropin; ALP = alkaline phosphatase; ALT = alanine transaminase; aPTT = activated partial thromboplastin clotting time; AST = aspartate transaminase; BUN = blood urea nitrogen; CPK = creatine phosphokinase; sCTX = serum C-terminal cross-linking telopeptide of type I collagen; 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; LH = luteinizing hormone; MCH = mean corpuscular hemoglobin; MCV = mean corpuscular volume; sPINP = serum procollagen type I N propeptide; PCR = polymerase chain reaction; RBC = red blood cell; RNA = ribonucleic acid; rT3 = reverse T 3; 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 potentially unblind the study will not be reported to investigative sites or other blinded personnel until the study has been unblinded. See Section 8.1.9.1 for more details.

Appendix 2: Sample Collection for Pharmacokinetics and Pharmacodynamics

Table 8 presents a description of PK/PD sample requirements at each study visit and timepoint.

Table 8 PK/PD Sampling Timepoints

Week	Day	Timepoint	Sample Type
0	1	• Pre-dose (All Patients)	Patients in PK/PD sub-study • TERN-501, TERN-101, and TERN-101 metabolite TRN-000971 PK samples (PK/PD sub-study) • Lipid Panel, 7αC4, FGF19, bile acids, and SHBG PD samples (PK/PD sub-study) Patients not participating in PK/PD sub-study • Lipid Panel, 7αC4, bile acids, and SHBG PD samples
		• Post dose at the following timepoints (PK/PD sub-study only): ○ 1 hour ± 5 minutes ○ 2 hour ± 15 minutes ○ 4 hours ± 15 minutes ○ 6 hours ± 15 minutes ○ 24 hours ± 1 hour prior to dosing on Day 2	• TERN-501, TERN-101, and TERN-101 metabolite TRN-000971 PK samples • 7αC4 and FGF19 PD samples
2	15 ± 3	• Pre-dose (All Patients)	• TERN-501, TERN-101, and TERN-101 metabolite TRN-000971 PK samples • Lipid Panel, 7αC4, and SHBG PD samples
4	29 ± 3	• Pre-dose (All Patients – PD samples) • One sample between 2 and 6 hours post dose (All Patients – PK samples)	• Lipid Panel, 7αC4, and SHBG PD samples • TERN-501, TERN-101, and TERN-101 metabolite TRN-000971 PK samples
6	43 ± 3	• Pre-dose (All Patients)	• TERN-501, TERN-101, and TERN-101 metabolite TRN-000971 PK samples • Lipid Panel, 7αC4, and SHBG PD samples
8	57 ± 3	• Pre-dose (All Patients)	• TERN-501, TERN-101, and TERN-101 metabolite TRN-000971 PK samples
12	85 ± 3	• Pre-dose (All Patients)	Patients in PK/PD sub-study • TERN-501, TERN-101, and TERN-101 metabolite TRN-000971 PK samples • Lipid Panel, 7αC4, FGF19, bile acids, and SHBG PD samples

			Patients not participating in PK/PD sub-study • TERN-501, TERN-101, and TERN-101 metabolite TRN-000971 PK samples • Lipid Panel, 7αC4, bile acids, and SHBG PD samples
		• Post dose at the following timepoints (PK/PD sub-study only): ○ 1 hour ± 5 minutes ○ 2 hour ± 15 minutes ○ 4 hours ± 15 minutes ○ 6 hours ± 15 minutes ○ 24 hours ± 1 hour on Day 86 PK only: ○ 48 hours ± 2 hours on Day 87 ○ 72 hours ± 4 hours on Day 88	• TERN-501, TERN-101, and TERN-101 metabolite TRN-000971 PK samples • 7αC4 and FGF19 PD samples (up to 24 hours ± 1 hour on Day 86 only)
ET	ET	• At the ET Visit, for all patients discontinuing the study at any time for any reason (Early Termination)	• TERN-501, TERN-101, and TERN-101 metabolite TRN-000971 PK samples • Lipid Panel, 7αC4, FGF19, bile acids, and SHBG PD samples

PD Sample Collection

The tests detailed in Table 9 will be performed by the central laboratory, as specified in the Schedule of Activities. The exact times of blood sampling will be recorded in the eCRF.

Table 9 PD Laboratory Assessments

PD Assessments	Parameters	
Lipid Panel	Total cholesterol Triglycerides LDL cholesterol VLDL Non-HDL cholesterol LDL particle number	apo B apo A1 Lipoprotein(a)
SHBG, 7αC4, FGF19, bile acids	SHBG, 7αC4, FGF19, bile acids	

Appendix 3: Liver Chemistry Increased Monitoring Criteria

Table 10 summarizes requirements for follow-up of liver function test abnormalities.

Table 10 Liver Chemistry Increased Monitoring Criterion and Follow-Up

Criterion	Actions
Elevated ALT and/or AST: • Above 2 × Baseline, or • Above 5 × ULN Elevated ALP above 3 × ULN	• Participant can continue study drug at the discretion of the Investigator • Repeat measurement of LFTs (including ALT, AST, ALP, and total bilirubin) will be performed within 48 hours to confirm the abnormalities and to determine if they are increasing or decreasing. If total bilirubin is increased above the upper limit of normal, there should be a reflex to direct and indirect bilirubin. • PT/INR and albumin will be tested when significantly abnormal liver function is observed and repeated with repeat measurement of LFTs. • Upon confirmation of elevated LFTs, close observation by repeating LFTs every 24 to 72 hours will be initiated immediately. • Frequency of monitoring can be decreased as LFTs decrease at the Investigator's discretion. • The Investigator will collect detailed information on concomitant symptoms, new medications, drug or alcohol exposure, etc., to identify possible cause of abnormal LFTs. • Close observation on abnormal LFTs will last until the parameters return to baseline, or to a stable level judged by the Investigator.

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

Note: If any of the following laboratory abnormalities is confirmed by repeat testing, considered related to the study drug and does not have alternative etiology, study drug may be discontinued at the discretion of the Investigator in accordance with Section 7.1.2, and the Medical Monitor should be informed (repeat test should be performed within 48-72 hours once initial abnormality is detected):

- ALT or AST > 8 × ULN
- ALT or AST > 5 × ULN for more than 1 week during study drug administration
- ALT or AST > 2 × Baseline with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (> 5%)
- ALT or AST > 2 × Baseline and total bilirubin > 2 × ULN or INR > 1.5 for more than 1 week, confirmed with a repeat assessment
- ALP > 5 x ULN
- ALP > 3 x ULN and total bilirubin > 2x ULN

Appendix 4: Fridericia's Formula

A single 12-lead ECG will be obtained as outlined in the Schedule of Activities (see Section 1.1) using an ECG machine that automatically calculates the heart rate and measures PR, QRS, and QT intervals. QTc will be calculated using Fridericia's Formula as outlined below.

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

Fridericia's Formula:

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
κ = 0.7 (females) or 0.9 (males)
α = -0.329 (females) or -0.411 (males)
min = indicates the minimum of SCr/κ or 1
max = indicates the maximum of SCr/κ or 1
age = years

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

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

Events Meeting the AE Definition
• Any safety assessment (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.

For detailed organ system AE severity grading, please refer to NCI CTCAE v5.0:
https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5x11.pdf

Assessment of Causality

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

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

Follow-up of AEs and SAEs

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

Reporting of SAEs

SAE Reporting to Sponsor or designee via Paper CRF

- Email transmission of the SAE paper Report Form is the preferred method to transmit this information to the Labcorp Drug Development Patient Safety Group (SAEintake@labcorp.com).
- Notification by facsimile transmission to the Labcorp Drug Development Patient Safety Group is also acceptable (1-888-887-8097)
- Initial notification via telephone or email does not replace the need for the Investigator to complete, sign, and return the SAE report form within the designated reporting time frames.
- Contacts and additional instructions for SAE reporting can be found in in the Study Procedures Manual provided.

Appendix 7: Contraceptive Guidance and Collection of Pregnancy Information

Definitions:

Woman of Childbearing Potential (WOCBP)

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

Women in the following categories are not considered WOCBP

1. Premenopausal female with surgical sterility defined as 1 of the following:
    - Documented hysterectomy
    - Documented bilateral salpingectomy
    - Documented bilateral oophorectomy
2. Postmenopausal female
    - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
        - A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, confirmation with more than one FSH measurement is required.
    - Females on HRT and whose menopausal status is in doubt will be required to follow the protocol-mandated contraception guidance if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

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

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

Contraception Guidance:

Male patients who are sexually active with a female partner of childbearing potential must be either surgically sterile (confirmed by azoospermia > 90 days after the procedure or vasectomy) or follow the guidance per Table 11 during the study and until 30 days following the last dose of study drug. Male patients must not donate sperm from the first dose of study drug until 30 days following the last dose of the study drug.

Female patients of childbearing potential must have negative serum pregnancy test at screening and negative urine pregnancy test at randomization, not be breastfeeding, and not plan to become pregnant during study or within 30 days after dosing of study drug. Female patients of

childbearing potential must either be surgically sterile (documented hysterectomy, bilateral salpingectomy, bilateral oophorectomy) or follow the guidance per Table 11 during the study and until 30 days following the last dose of the study drug.

Table 11 Contraceptive Methods

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

Collection of Pregnancy Information:

Male patients with partners who become pregnant

The Investigator will attempt to collect pregnancy information on any male patient's female partner who becomes pregnant while the male patient is in this study, or if they become pregnant within 30 days following the last dose of the study drug. This applies only to male patients who receive study drug.

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

Female Patients Who Become Pregnant

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

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

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

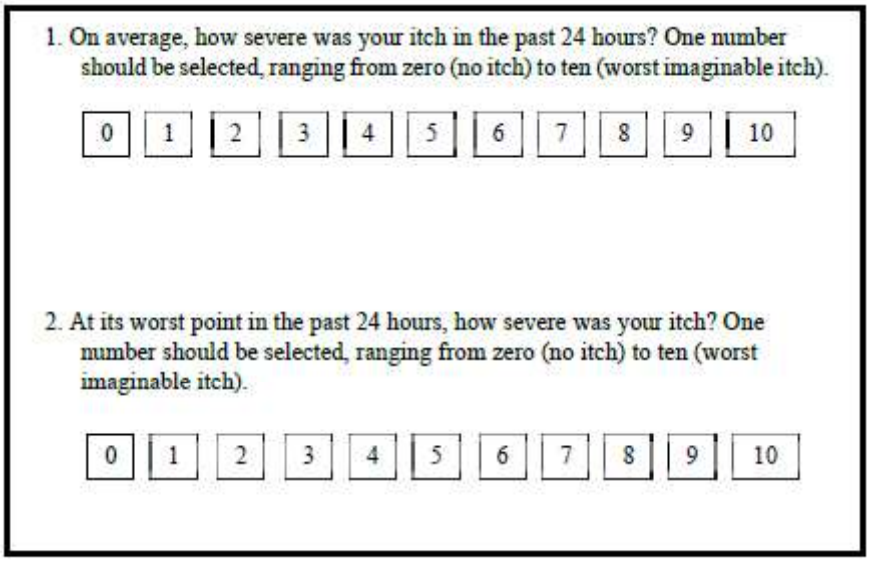
While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE.

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

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

Appendix 8: 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



Appendix 9: COVID-19 Assessments

At Screening:

- SARS-CoV-2 testing to assess for active infection (eg, 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).
- Testing at Screening may be omitted for patients who have completed a COVID-19 vaccination series, with adequate documentation, at the Investigator's discretion

At Weeks 0, 6, and 12:

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

Ad-hoc:

- In the event of symptoms suggestive of COVID-19, ad hoc testing (including molecular test such as PCR or viral antigen serology, and/or antibody testing, 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 (eg, 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
7αC4	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
apo A1	Apolipoprotein A1
apo B	Apolipoprotein B
aPTT	activated partial thromboplastin clotting time
AST	Aspartate transaminase
AUC	Area under the concentration-time curve
BCRP	Breast cancer resistance protein
BMI	Body mass index
BUN	Biliary urea nitrogen
CAP	Controlled attenuation parameter
CCl_4	Carbon tetrachloride
CFR	Code of Federal Regulations
CIOMS	Council for International Organizations of Medical Sciences
CK-18	Cytokeratin-18
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
cT1	Corrected T1
C_{tau}	concentration at the end of the dosing interval
CTCAE	Common Terminology Criteria for Adverse Events
CTX	c-terminal cross-linking telopeptide of type I collagen
CYP	cytochrome P450
CYP3A	cytochrome P450 3A
CV	Coefficient of variation

Abbreviation or Special Term	Explanation
DBL	Database lock
DIO	Diet-induced obesity
eGFR	Estimated glomerular filtration rate
eCRF	Electronic case report form
ECG	Electrocardiographic
ELF	Enhanced liver fibrosis
ET	Early Termination
FAST	FibroScan-AST score
FDA	Food and Drug Administration
FGF	Fibroblast growth factor
FGF-19	Fibroblast growth factor -19
FIB-4	Fibrosis 4
FSH	Follicle stimulating hormone
FXR	Farnesoid X receptor
GCP	Good clinical practice
GGT	Gamma-glutamyl transpeptidase
HA	Hyaluronic acid
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
IMM	Independent Medical Monitor
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

Abbreviation or Special Term	Explanation
LFC	Liver fat content
LH	Luteinizing hormone
LFT	Liver function test
LSM	Least square mean
MCH	Mean corpuscular hemoglobin
MCV	Mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
MRI-cT1	Magnetic Resonance Imaging Corrected T1
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
OATP	Organic anion transporting polypeptide
OCA	Obeticholic acid
PCR	Polymerase chain reaction
PD	Pharmacodynamics
PIIINP	Procollagen III n-terminal propeptide
PINP	Procollagen type I N propeptide
PK	Pharmacokinetics
PO	*Per os* (oral); by mouth
PRO-C3	Pro-peptide of type III collagen
QD	Once daily (quaque die)
RBC	Red blood cell
RNA	Ribonucleic acid
rT3	Reverse triiodothyronine
SAE	Serious adverse event
SAP	Statistical analysis plan
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SCr	Standardized serum creatinine
SD	Standard Deviation
SHBG	Sex hormone binding globulin
SoA	Schedule of Activities

Abbreviation or Special Term	Explanation
SUSR	Suspected unexpected serious adverse reactions
T3	Triiodothyronine
T4	Thyroxine
TBG	Thyroxine binding globulin
TCHO	Total cholesterol
TDI	Time dependent inhibition
TE	Transient elastography
TEAE	Treatment emergent adverse event
TERN-101	An investigational FXR agonist
TERN-501	An investigational THR-β selective agonist
TG	Triglycerides
THC	Tetrahydrocannabinol
THR	Thyroid hormone receptor
THR-α	Thyroid hormone receptor α
THR-β	Thyroid hormone receptor β
TIMP-1	Tissue inhibitor of metalloproteinases-1
TSH	Thyroid stimulating hormone
ULN	Upper limit of normal
US	United States
USPI	United States prescribing information/package insert
VLDL	Very low-density lipoprotein
WBC	White blood cell
WOCBP	Women of childbearing potential

Appendix 11: Investigator Signature Page

A Multicenter, Randomized, Double-Blind, Placebo-Controlled, Phase 2a Clinical Study to Evaluate the Safety, Efficacy, Pharmacokinetics, and Pharmacodynamics of Orally Administered TERN-501 as Monotherapy as well as in Combination with TERN-101 in Noncirrhotic Adults with Presumed Non-Alcoholic Steatohepatitis (NASH)

Protocol Number: TERNCB-2002

Protocol Version/Date: Amendment 2; 18 July 2022

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 18 July 2022) is the Amendment 2, and the document history is below. The Summary of Changes for each amendment listed below will be provided separately.

DOCUMENT HISTORY	
Document	**Date**
Amendment 2	**18 July 2022**
Amendment 1	02 May 2022
Original	16 March 2022

Appendix 13: References

Andronescu CI, Purcarea MR, Babes PA. Nonalcoholic fatty liver disease: epidemiology, pathogenesis and therapeutic implications. *J Med Life*. 2018;11(1):20–23.

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