Statistical Analysis Plan

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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Reviewers

The following reviews of the Statistical Analysis Plan (SAP) were conducted:

Name and Title	Role	Version Last Reviewed	Company / Organization
[redacted]	Peer Review Statistician	0.6	Fortrea (former Labcorp Drug Development)

1. Source Documents

The SAP was written based on the following documentation:

Document	Date	Version
Protocol	16MAR2022	Original
Amendment 1	02MAY2022	Amendment 1
Protocol Amendment	13JUL2022	Amendment 2
eCRF	15JUN2022	1.00

2. Protocol Details

2.1. Overall Study Design

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

Approximately 140 non-cirrhotic 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.

2.1.1. Study Procedures

The overall schedule of activities is outlined in Section 1.3 of the study protocol. See study protocol for complete details.

2.1.2. Study Population

This study includes non-cirrhotic presumed NASH patients. Inclusion and exclusion criteria are provided in Sections 5.1 and 5.2, respectively, of the study protocol.

2.1.3. 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.

Table 1 Study Drug

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.

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 2 Study Drug Administration 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-101 10 mg QD	Not applicable	Two placebo capsules	Two 5 mg tablets	Not applicable
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

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

2.1.4. Treatment Assignment, Blinding, and Randomization Methodology

Patients will be randomized to study drug or placebo using an Interactive Web Response System (IWRS). Approximately 140 patients will be randomized at an overall ratio of 1:1:1:1:1:1:1 into the 7 groups treatment groups as described in Table 2.

Investigators, patients, all study personnel, and the Sponsor will remain blinded to each patient's assigned dose group throughout the course of the study. The randomization codes will be provided to bioanalytics to allow for the exclusion of placebo patients from the PK assay.

Randomization codes will remain blinded until the trial is officially unblinded.

Emergency unblinding procedures are outlined in Section 6.4.1 of the study protocol and in the unblinding plan. Additional unblinding will be reviewed in the medical monitor plan (Maintaining Study Blind and Unblinding Plan).

2.2. Study Objectives

2.2.1. Primary Objective

To evaluate the effect of TERN-501 monotherapy on liver fat content as assessed by MRI-PDFF compared to placebo.

2.2.1.1. Endpoint for the Primary Objective

Relative change from baseline in MRI-PDFF at Week 12 for TERN-501 compared to placebo.

2.2.2. Secondary Objectives

- 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

2.2.2.1. Endpoints for the Secondary Objectives

- 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

2.2.3. Exploratory Objectives

- 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
- To evaluate the pharmacokinetics of TERN-501 and TERN-101 administered alone and in combination

2.2.3.1. Endpoints for the Exploratory Objectives

- 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
- PK parameters (e.g., AUC, C_{max}, C_{tau})

2.3. Sample Size and Power

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.

3. Statistical Methods

3.1. General Principles

All data processing, summarization and analyses will be performed using Labcorp Drug Development's SAS Environment / Version 9.4 (or later) of the SAS® statistical software package.

Individual patient data obtained from electronic case report forms (eCRFs), central laboratories, external sources, and any derived data will be presented in data listings by patient. The primary data source will be used for all analyses. All data listings that contain an evaluation date will contain a relative study day. Pre-treatment and on-treatment study days are numbered relative to the day of the first dose of study drug which is designated as Day 1. The preceding day is Day -1, the day before that is Day -2, etc.

All outputs will be incorporated into Microsoft Word rich text format (.rtf) files, sorted and labeled according to the International Council for Harmonization (ICH) E3 guideline, E3 Structure and Content of Clinical Study Reports, and formatted to the appropriate page size(s), font type, and font size according to Food and Drug Administration (FDA) guidance of Portable Document Format Specifications.

For categorical variables, summary tabulations of the number and percentage of patients within each category of the parameter will be presented. Percentage calculations will be based on non-missing data, unless otherwise specified. For each parameter, the total number of patients with a response will be provided. Percentages are rounded to 1 decimal place, unless otherwise specified.

For frequency counts of categorical variables, categories whose counts are zero will be displayed for the sake of completeness. For example, if none of the patients discontinue due to "Lost to Follow-up," this reason will be included in the table with a count of 0. Percentages will be presented to 1 decimal place, with the exception of 0, which will be presented without percent, and 100, which will be presented without decimal places. Values less than 0.1% will be presented as "<0.1%." Values less than 100% but greater than 99.9% will be presented as ">99.9%."

For continuous variables, the number of patients, mean, standard deviation (SD), median, 25th (Q1) and 75th (Q3) percentiles, minimum, and maximum values will be presented. The precision of summary statistics, unless otherwise specified will be as follows: mean, median, Q1, and Q3 to 1 more decimal place than the raw data, SD to 2 decimal places more than the raw data, and minimum and maximum to the same decimal places as the raw data. In general, the number of decimal places should not exceed 3 decimal places unless appropriate.

For log-normal data (e.g., the PK parameters of area under the concentration-time curve [AUC] and maximum observed concentration [C_{max}]), the geometric mean and geometric coefficient of variation (CV%) will also be presented. The precision of descriptive statistics will be as follows: mean, median, Q1, and Q3 to 1 more decimal place than the raw data, SD to 2 decimal places more than the raw data, the minimum and maximum to the same number of decimal places as the raw data, geometric mean to 3 significant figures, and geometric CV% to 1 decimal place. The PK parameters will be presented to 1 decimal place.

Confidence intervals (CIs) will be provided and will be rounded to 1 decimal place, unless otherwise specified, in the table and listing shell. A full set of summary statistics will only be presented if there are 3 or more values available. If there are less than 3 values, only the min, max, and N will be presented. The other summary statistics will be denoted as not calculated (NC).

For tables where rounding is required, rounding will be done to the nearest round-off unit. For example, when rounding to the nearest integer, values ≥XX.5 will be rounded up to XX+1 (e.g., 97.5 will round up to 98), while values <XX.5 will be rounded down to XX (e.g., 97.4 will round down to 97).

All statistical tests comparing groups will be conducted at the 2-sided, 0.05 level of significance, unless otherwise specified. Summary statistics for each treatment group will be presented, as well as the two-sided 95% CIs for comparing groups.

Specifications for table, figures, and data listing formats can be found in the TFL shells specifications for this study.

All data recorded on the case report form will be included in data listings.

3.2. Computing Environments

All descriptive statistical analyses will be performed using SAS software Version 9.4 or higher, unless otherwise noted.

Plasma PK and PD parameters for TERN-501 and TERN-101 will be estimated using non-compartmental methods with Phoenix WinNonlin® Version 8.3 or higher.

Medical history and AEs will be coded using Medical Dictionary for Regulatory Activities (MedDRA) version 23.0. Concomitant medications will be coded using World Health Organization Drug Dictionary (WHODD), B2 Enhanced March 2020.

Study Data Tabulation Model (SDTM) and Analysis Data Model (ADaM) datasets will be prepared using Clinical Data Interchange Standards Consortium (CDISC) SDTM Implementation Guide (IG) Version 3.3, ADaM Version 2.1, and CDISC ADaM IG Version 1.2 including most current occurrence and time to event IGs.

3.3. Partial Dates

Imputation of partial adverse event and concomitant medication dates are specified in Appendix 2.

All clinical data recorded on the case report form will be included in data listings.

3.4. Missing Data

Treatment end date will be the date of last dose from the End of Study Treatment page of the CRF. If this is missing, then the last date (dispensing or return) from the study drug accountability page will be used.

3.5. Data Conventions

The precision of original measurements will be maintained in summaries, when possible.

Quantitative safety laboratory tests containing less than (<) and greater than (>) symbols are test results that are below and above quantifiable limits, respectively. In order to retain these values for analysis purpose, the following will be imputed and stored within the analysis datasets:

- For values with <, the imputed value will be the numeric portion × 0.9.
- For values with >, the imputed value will be the numeric portion × 1.1.

PK and PD imputation of values below the limitation of quantitation (BLQ) are specified in Section 7.17.4 and Section 7.18, respectively.

Variables with a non-normal distribution that impacts the interpretation or validity of the planned analysis may have a data transformation applied (e.g., ln, log10).

3.6. Standard Calculations

Variables requiring calculation will be derived using the following formulas:

- Days – A duration expressed in days between one date (date1) and another later date (date2) will be calculated using the following formulas:

  duration in days = date2 – date1 + 1, where date1 ≥ first administration date

  duration in days = date2 – date1, where date1 < first administration date
- Months – A duration expressed in months is calculated as the number of days divided by 30.4375
- Years – A duration expressed in years between one date (date1) and another date (date2) is calculated using the following formulas:

duration in years = (date2 – date1 + 1)/365.25, where date1 ≥ first administration date

duration in years = (date2 – date1)/365.25, where date1 < first administration date

- Body Mass Index (BMI) – BMI is calculated using height (cm) and weight (kg) using the following formula:

  BMI (kg/m^2) = body weight (kg) / ([height (cm)/100]^2)

- Change (CHG) will be calculated as:

  Change = later value – earlier baseline value

- Relative change (PCHG or percent change) will be calculated as:

  Relative change = ([Change] / baseline value) × 100

  If a baseline value is 0, the relative change will be missing and not included in summary calculations. Within listings, this value will be displayed as NC (not calculable).

3.7. Treatments

Table 3 presents how the dose groups will be presented in TFLs as treatment groups, including the order.

Table 3 Treatment Group Labels and Ordering

Treatment Group Label	Order on TFLs
Placebo	1
101 10 mg	2
501 1 mg	3
501 3 mg	4
501 6 mg	5
501 3 mg + 101 10 mg	6
501 6 mg + 101 10 mg	7

Screen failures will be presented on by-patient listings where data is available.

3.8. Visits

3.8.1. Windows

In data listings, the relative study day of all dates from first dose will be presented.

Scheduled visit assessments will be determined based on a two-step process using the parameters of exposure to study drug and scheduled visit assessment windows.

Step 1:

- The last dose date (maximum from dates of discontinuation form and exposure data) must be within 14 days, inclusive, of the last assessment of those within the treatment exposure period (12 weeks). If the last dose date is after or within 14 days inclusive of the Week 12 assessment there will be an assumption that all previous assessments were performed while under proper drug exposure. Any assessments performed greater than 14 days of the last dose date will be considered unscheduled irrespective of Table 4 mapping.

Step 2:

- Use Table 4 to initially map the appropriate assessment under consideration
- For multiple assessments mapped to the same scheduled visit interval, select the assessment date that is closest to the target day of the visit window in terms of absolute difference, irrespective of scheduled or unscheduled visit type. Any assessment not selected in the window is considered unscheduled.

In the event of a scheduled visit assessment tie AND the assessment was performed as an original scheduled assessment select this over an unscheduled; if both assessments are unscheduled or scheduled select the first assessment, then classify the other as unscheduled.

Table 4 Treatment Period Visit Windows

Target Scheduled Visit	Target Study Day[a]	Analysis Window Study Day[a]	
		Low	**High**
Targeted physical examination, vital signs, ECG, chemistry and hematology labs			
Baseline	1	See Section 3.6.2	
Week 2	15	2	22
Week 4	29	23	36
Week 6	43	37	50
Week 8	57	51	70
Week 12	85	71	99
Thyroid axis testing			
Baseline	1	See Section 3.6.2	
Week 2	15	2	29
Week 6	43	37	50
Week 12	85	71	99
Weight, MRI-PDFF, MRI-cT1, and fibrosis biomarkers			
Baseline	1	See Section 3.6.2	
Week 6	43	29	57
Week 12[b]	85	71	99
Week 16	For all parameters, use nominal visit as recorded on CRF.		
a Study Day will be calculated from first dose of study drug. Visit windows defined by the low and high values are inclusive.			

3.8.2. Definition of Baselines

The baseline value for statistical analyses of quantitative laboratory parameters is defined as the last non-missing assessment, including any unscheduled or repeat assessments, collected prior to the first administration of study drug, unless otherwise specified.

For glucose and lipid parameters, only assessments taken while fasting for 8 hours will be included in the baseline derivation.

The baseline value for analyses of qualitative parameters (e.g., normal/abnormal) is defined as the last evaluation prior to the first administration of study drug.

The baseline value for analyses of weight, body mass index (BMI), and electrocardiogram parameters is defined as the last evaluation prior to the first administration of study drug.

3.8.3. Definition of End of Treatment

The End of Treatment value will be defined as the Week 12 value, either scheduled or windowed per Table 5. If a Week 12 value is not available, the last non-missing value on or before the last dose date will be used.

4. Analysis Sets

Table 5 defines the analysis sets to be used.

Table 5 Analysis Sets

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, and/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 randomized patients who consented to and participated in the PK/PD sub-study and received at least 1 dose of study drug (TERN-501 and/or TERN-101). Treatment assignment will be based on the treatment actually received.
Safety	All randomized 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.
Per Protocol (PP)	All randomized patients who have completed the study without any major protocol deviations affecting the interpretation of the efficacy, PK, or PD results

5. Examination of Subgroups

Subgroups will be assessed at Baseline and only if there are a sufficient number of patients in each group, i.e., at least 5 patients in each treatment group. Each efficacy analysis description in Section 7 includes the description of subgroup analyses.

Baseline subgroups of interest are as follows:

- Age categories: < 65, ≥ 65 years
- Sex: Male, Female
- Baseline BMI: < 30 kg/m2, ≥30 - < 35 kg/m2, ≥35 - < 40 kg/m2, ≥ 40 kg/m2
- Baseline Comorbidity of diabetes (yes, no) will be based on Medical History case report form, Medical Dictionary of Regulatory Activities (MedDRA) preferred term Baseline use of Statins defined by the WHODD Standardized Drug Grouping (SDG) of 'Statins'. This subgroup will only be used for the safety analysis of lipids (Section8.3.3).
- cT1 classified as elevated (800 – 875 msec) and high (>875 msec)

6. Study Population

6.1. Patient Disposition

Patient disposition will be summarized for the Screening Analysis Set by treatment group and overall total. The summary will include:

- Number of patients screened.
- Number of screen failures, i.e., screened but not randomized, with reasons for screen failure. The denominator for percentage of screen failures will be the number of patients screened. The denominator for percentages for reasons for screen failures will be the number of screen failures.
- Number randomized. The denominator for percentage of randomized patients will be the number of patients screened.
- Number randomized and not treated. The denominator for percentage of randomized and not treated patients will be the number of patients randomized.
- Number in each analysis set. The denominator for percentage in each analysis set will be the number of randomized patients. In addition, the number of patients randomized to the PK/PD substudy will be presented.
- Number who discontinued treatment early and reason(s) for discontinuation of treatment. The denominator for percentages will be the number of randomized and treated patients (Efficacy Analysis Set).
- Number who discontinued from study prior to completing the study and reason(s) for discontinuation. The denominator for percentages will be the number of randomized and treated patients (Efficacy Analysis Set).

A by-patient data listing of study disposition information including the reasons for treatment and/or study termination will be presented. Withdrawal of consent details will also be included, if applicable.

A by-patient data listing including the reasons for exclusion from each analysis set will be presented.

6.2. Demographics and Baseline Characteristics

Demographic variables will include the following:

- Age at informed consent including the subgroup of < 65 years vs ≥ 65 years
- Sex
- Race
- Ethnicity

Other baseline characteristics will include the following:

- Weight (kg)
- Height (cm)
- BMI (kg/m^2) including the following subgroups:
  - < 30,
  - ≥ 30 - < 35
  - ≥ 35 - < 40
  - ≥ 40 kg/m^2
- Baseline liver stiffness measure (LSM) by transient elastography (kPa)
- Baseline Controlled Attenuation Parameter (CAP; dB/m)
- Baseline LFC (%) by MRI-PDFF
- Baseline cTI (msec) by MRI including the following subgroups:
  - Elevated (800 – 875 msec),
  - and High (> 875 msec).
- Liver Biopsy within 1 years of randomization
  - Baseline fibrosis stage (F1, F2, F3)
  - Baseline NAFLD Activity Score (NAS)
- Baseline ELF including the following subgroups:
  - Low (< 7.7)
  - Intermediate (≥ 7.7 to < 9.8)
  - High (≥ 9.8)
- Baseline PRO-C3 including the following subgroups:
  - < 17.5

- ≥ 17.5

- Baseline FAST Score including the following subgroups:
  - < 0.67
  - ≥ 0.67
- Baseline Comorbidities will be based on Medical History case report form, Medical Dictionary of Regulatory Activities (MedDRA) preferred term (PT)
  - Diabetes status (yes, no) will be defined as PT preferred term (PT) includes "diabetes mellitus" or "Diabetic neuropathy" will be assigned yes, otherwise no.
  - Hypertension (yes, no) will be defined as PT of "Hypertension" will be assigned yes, otherwise no.
  - Dyslipidemia (yes, no) will be defined as Standardized MedDRA query (SMQ) of "Dyslipidemia (SMQ)" will be assigned yes, otherwise no.
  - Primary hypothyroidism (yes, no) will be defined as Standardized MedDRA Hypothyroidism (SMQ)
- Baseline medication use, defined as starting prior to first administration of study drug, regardless of end date:
  - Statins defined by the WHODD Standardized Drug Grouping (SDG) of "Statins"
  - PCSK9 inhibitors defined by the WHODD terms "Inclisiran", "Alirocumab", "Evolocumab"
  - Fish oil defined by the WHODD Standardized Drug Grouping (SDG) of "Omega-3 Fatty Acid"
  - Fibrates defined by the WHODD Standardized Drug Grouping (SDG) of "Fibrates"
  - Levothyroxine defined by the WHODD Standardized Drug Grouping (SDG) of Levothyroxine
  - Antihypertension medications defined by the WHODD SDG of "Antihypertensives"

- Antithrombotic medications defined by WHODD SDG of "Antithrombotic drugs"
- Antidiabetic medications defined by the WHODD SDG of "Drugs used in diabetes"
- Hormonal contraceptives defined by the WHODD SDG of "Drugs used in Hormonal contraception"
- Vitamin E defined by the WHODD drug codes beginning in "001105" or if "VITAMIN E" is found in the preferred drug name
- Pioglitazone or other PPARγ agonists defined by WHODD ATC level 4 A10BD and A10BG
- GLP-1 analogues defined by WHODD ATC level 4 code (term) A10BJ (Glucagon-like peptide-1 [GLP-1] analogues)
- DPP-4 inhibitors defined by WHODD ATC level 4 code (term) A10BH (Dipeptidyl peptidase 4 [DPP-4] inhibitors)
- SGLT2 inhibitors defined by WHODD ATC level 4 code (term) A10BK (Sodium-glucose co-transporter 2 [SGLT2] inhibitors)

The following baseline laboratory tests will be summarized as continuous variables and as frequencies for categorizations described:

- Baseline ALT level (U/L):
  - ≤ 60 U/L versus > 60 U/L (overall and by sex)
  - < 2x ULN versus ≥ 2x ULN to < 5x ULN
- Baseline AST level (U/L): The same subgroups as specified for ALT above will be used.
- Baseline GGT level (U/L): ≤ ULN, > ULN
- Baseline ALP level (U/L): ≤ ULN, > ULN
- Baseline total bilirubin level (mg/dL)
- Baseline fasting HDL cholesterol (mg/dL)
- Baseline fasting LDL cholesterol (mg/dL)

- Baseline fasting total cholesterol (mg/dL)
- Baseline fasting triglycerides (mg/dL)
- Baseline fasting glucose level (mg/dL)
- HbA1c (%): < 6.5%, ≥ 6.5%
- Baseline platelet count (10^9/L):
- Baseline free T3 (FT3)
- Baseline total T3
- Baseline free T4
- Baseline total T4
- Baseline TBG
- Baseline rT3
- Baseline FT3/rT3

Demographics and baseline characteristics will be summarized by treatment group and overall, for the Safety, Efficacy, and Per Protocol Analysis Sets.

All demographic and baseline characteristics data will be presented in by-patient data listings.

No inferential statistical comparisons will be performed.

6.3. Protocol Deviations

Protocol deviations will be identified and documented in the clinical trial management system (CTMS). Major protocol deviations that could potentially affect the conclusions of the study will be identified prior to database lock and unblinding of individual patient treatment information.

Major protocol deviations include, but are not limited to

- Patients who entered the study even though they did not satisfy the entry criteria.
- Patients who developed withdrawal criteria during the study but were not withdrawn.
- Patients who received the wrong treatment or were dispensed an incorrect dose.

- Patients who received an excluded concomitant treatment.

All protocol deviations and major protocol deviations will be summarized separately by treatment group and overall total for each deviation category using the Efficacy Analysis Set.

All protocol deviations and separately only major protocol deviations will be presented in a by-patient data listing.

6.4. General Medical History

All medical history conditions will be coded using the Medical Dictionary of Regulatory Activities (MedDRA). Medical history will be summarized by treatment group and overall total by system organ class and preferred term, using the Safety Analysis Set. Summaries will be ordered by descending order of the overall incidence of system organ class and preferred term within each system organ class.

6.5. Prior and Concomitant Medications

Prior medications are defined as medications that started before first study drug administration and either stopped before or continued after first study drug administration. Concomitant medications are defined as medications that are being taken while on study drug through 30 days after last dose or through the Follow-Up Period (Week 16). Medications that are ongoing on the date of the first administration of study drug will be classified as both prior and concomitant. Any medication that cannot be confirmed as stopping before the start of study drug will be classified as both a prior and a concomitant medication. Imputation of partial dates is defined in Appendix 2.

Prior and concomitant medications will be summarized separately and the number and percentage of patients in each treatment group who took at least one prior (concomitant) medication as well as the number and percentage of patients who took each type of medication will be summarized by Anatomic Therapeutic Class (ATC) Level 2 and preferred name for the Safety Analysis Set. If a patient has more than one occurrence of the same preferred name, then the preferred name will be counted only once for that patient. Similarly, if a patient has more than one preferred name within ATC Level 2, then the patient will be counted only once in that ATC Level 2.

Any medications with potential beneficial impact on NASH outcome and steatohepatitis will be presented in a separate by-patient listing.

7. Efficacy Analyses

7.1. Adjustments for Covariates

The Baseline value will be used as a covariate in each ANCOVA model.

7.2. Handling of Dropouts or Missing Data

Primary analyses will be based on observed data. For the primary endpoint, a sensitivity analysis will be conducted for patients who do not complete the Week 12 visit, where the last on-treatment value, including any values collected at unscheduled visits, will be carried forward (LOCF) and used for Week 12.

7.3. Interim Analyses and Data Monitoring

No interim analysis or data monitoring committees are planned for this study.

7.4. Multicenter Studies

The randomization is not stratified by site. Likewise, analyses of data will not be stratified by study site.

7.5. Use of an "Efficacy Subset" of Patients

Not Applicable.

7.6. Multiple Comparisons/Multiplicity

Table 6 depicts the pairwise comparisons which will be performed denoted by "X".

Table 6 Pairwise Comparison for Display

	101	501 (1)	501 (3)	501 (6)	101+501 (3)	101+501 (6)
Placebo	X	X	X	X	X	X
501 (3)					X	
501 (6)						X

Table 7 depicts the order or comparison for the hierarchical testing strategy.

Table 7 Hierarchical Testing Strategy

MRI-PDFF						
	101	501 (1)	501 (3)	501 (6)	101+501 (3)	101+501 (6)
Placebo		3	2	1	5	4
501 (3)					7	
501 (6)						6
cT1						
	101	501 (1)	501 (3)	501 (6)	101+501 (3)	101+501 (6)
Placebo	4	3	2	1	6	5
501 (3)					8	
501 (6)						7

7.7. Analysis and Reporting of Change and Relative Change from Baseline

Analysis of change and relative change will be performed using a type III sum of squares ANCOVA model with treatment group as a fixed effect and baseline covariate, where applicable. Least squares (LS) means and standard errors (SE) as well as 95% confidence intervals (CIs) will be presented for each treatment group at each scheduled visit.

LS estimates of the mean difference, SE, and 95% CI between each TERN active treatment group versus placebo comparison will be presented at scheduled visits. Analyses will include the pairwise comparisons in table 6 of Section 7.6 at week 12, unless otherwise specified. Relative change will include LS means, SE, and 95% CI but only MRI-PDFF relative change will include inferential statistics.

Table displays:

(1) Observed result descriptive statistics, as described in Section 3.1, will be displayed within the same table.

(2) All scheduled visits should be reported.

(3) Pooling of treatment group should not be performed or displayed unless noted otherwise.

7.8. MRI-PDFF Analyses

For all MRI-PDFF analyses, relative change from baseline and absolute change in MRI-PDFF will be analyzed and reported according to Section 7.7 using the pairwise comparisons in Section 7.6 for the efficacy and per protocol analysis sets.

An additional sensitivity analysis of relative change in MRI-PDFF at Week 12 using a last observation carried forward (LOCF) approach will be performed according to Section 7.7 using the pairwise comparisons in Section 7.6 for the efficacy analysis set. The LOCF endpoint will be labelled "End of Treatment". For the LOCF analysis, patients who complete Week 12, the Week 12 value will be used. For patients who do not complete treatment, the last value on treatment will be used. Otherwise, the Week 12 response will be missing.

An analysis of MRI-PDFF relative change responders using the pairwise comparisons in Section 7.6 will be performed using the efficacy analysis set. Responders will be defined as any patient with a relative decrease of at least: (1) 30% (i.e., ≤-30%), (2) 40%, (3) 50% at weeks 6 and 12. Non-responders will be defined as any patient who did not have at least a relative decrease for each specific analysis. The frequency and percentage of responders along with a two-sided exact (Clopper-Pearson) 95% CI for the percentage of responders will be presented. For each pairwise comparison, the difference in percentage of responders, 95% CI, and p-value using a chi-square test will be presented.

7.8.1. cT1

For all cT1 analyses, change from baseline in cT1 will be analyzed and reported according to Section 7.7 using the pairwise comparisons in Section 7.6 for the efficacy and per-protocol analysis sets.

An analysis of cT1 change responders using the pairwise comparisons in Section 7.6 will be performed for the efficacy analysis set. Responders will be defined as any patient with a decrease of at least 80 msec at weeks 6 and 12. Non-responders will be defined as any patient who did not have at least a 80 msec decrease for each specific analysis. The frequency and percentage of responders along with a two-sided exact (Clopper-Pearson) 95% CI for the percentage of responders will be presented. For each pairwise comparison, the difference in percentage of responders, 95% CI, and p-values using a chi-square test will be presented.

7.9. Liver Enzymes (ALT, AST, GGT)

For ALT, AST, and GGT analyses, change from baseline will be analyzed according to Section 7.7 using the pairwise comparisons in Section 7.6 for the efficacy analysis set.

An analysis of ALT change responders using the pairwise comparisons in Section 7.6 will be performed for the efficacy analysis set. Responders will be defined as any patient with a decrease of at least 17 U/L from baseline at weeks 6 and 12. Non-responders will be defined as any patient who did not have at least a decrease for each specific analysis. The frequency

and percentage of responders along with a two-sided exact (Clopper-Pearson) 95% CI for the percentage of responders will be presented. For each pairwise comparison, the difference in percentage of responders, 95% CI, and p-value using a chi-square test will be presented.

7.10. NASH and Fibrosis Biomarkers

Change from baseline in markers of hepatic fibrosis and apoptosis include CK-18 (M30 and M65), PIIINP, TIMP-1, HA, and PRO-C3, will be analyzed according to Section 7.7 and pairwise comparisons in Section 7.6 using the efficacy analysis set.

7.11. Reverse T3 (rT3)

Change in rT3 and FT3/rT3 will be analyzed according to Section 7.7 and pairwise comparisons in Section 7.6 using the efficacy analysis set.

7.12. Fibrosis-4 (FIB-4) Score

The Fibrosis-4 (FIB-4) score helps to estimate the amount of scarring in the liver. The FIB-4 score is calculated as:

$$[\text{Age (years)} \times \text{AST (U/L)}] \div [\text{Platelet Count } (10^9/\text{L}) \times \text{ALT (U/L)}0.5].$$

Age at informed consent will be used. Lab values at each visit, from the same visit, will be used. The central lab calculation of FIB-4 will be used in analyses. The FIB-4 score will be calculated at baseline, Week 6, Week 12, and Week 16.

The change from baseline in FIB-4 score will be analyzed in the same manner as specified in Section 7.7 and pairwise comparisons in Section 7.6 using the efficacy analysis set.

7.13. Enhanced Liver Fibrosis (ELF) Score

The enhanced liver fibrosis (ELF) score will be calculated as:

$$2.278 + 0.851 \ln(\text{HA}) + 0.751 \ln(\text{PIIINP}) + 0.394 \ln(\text{TIMP-1}).$$

Lab values from the same visit will be used to calculate the ELF score. The central lab calculation of ELF will be used in analyses. Programming will also calculate the score programmatically for validation. The ELF score will be calculated at baseline and post-baseline visits Week 6 and Week 12.

The change from baseline in ELF score will be analyzed in the same manner as specified in Section 7.7 and pairwise comparisons in Section 7.6 using the efficacy analysis set.

7.14. Nonalcoholic Fatty Liver Disease (NAFLD) Fibrosis Score

The Nonalcoholic Fatty Liver Disease (NAFLD) fibrosis score will be calculated as:

> -1.675 + [0.037 × Age (years)] + [0.094 × BMI (kg/m2)] + [1.13 × baseline diabetes status (yes = 1, no = 0)] + [0.99 × AST/ALT ratio] – [0.013 × Platelet Count (109/L)] – [0.66 × Albumin (g/dL)].

Age at informed consent and baseline diabetes status will be used. BMI at Screening, Baseline, and Weeks 6, 12, and 16 will be calculated using the weight from that visit and height from screening. Programming will calculate the score at each to be used in analyses. The NAFLD fibrosis score will be calculated at screening, baseline, Week 6, Week 12, and Week 16.

The change from baseline in NAFLD fibrosis score will be analyzed in the same manner as specified in Section 7.7 and pairwise comparisons in Section 7.6 using the efficacy analysis set.

7.14.1.1. AST to Platelet Ratio Index (APRI)

The AST to Platelet Ratio Index (APRI) will be calculated as:

> (AST Level [IU/L] / AST Upper Limit of Normal IU/L]) × 100 / Platelet Count (10^9/L).

Lab values at each visit, from the same visit, will be used. The APRI will be calculated at baseline, Week 6, Week 12, and Week 16.

The change from baseline in APRI will be analyzed in the same manner as specified in Section 7.7 and pairwise comparisons in Section 7.6 using the efficacy analysis set.

7.15. FAST Score

The change from baseline in the FAST score will be analyzed as described in Section 7.7 and pairwise comparisons in Section 7.6 using the efficacy analysis set.

The FAST score was calculated according to the following formula10:

FAST = {exp (–1.65 + 1.07 × ln (LSM) + 2.66 × 10–8 × CAP3 – 63.3 × AST–1)}/{1 + exp (–1.65 + 1.07 × ln (LSM) + 2.66 × 10–8 × CAP3 – 63.3 × AST–1)}.

7.16. TE and CAP

The change from baseline in TE and CAP will be analyzed as described in Section 7.7 and pairwise comparisons in Section 7.6 using efficacy analysis set.

7.17. Pharmacokinetic Analyses

PK Parameter Generation:

The following PK parameters will be determined where possible from the plasma concentrations of TERN-501, TERN-101, and TERN-101 metabolite TRN-000971 using noncompartmental methods in validated software program Phoenix WinNonlin (Certara, Version 8.3.5 or higher) for all patients for the PK Sub-study Analysis Set:

Table 8 PK Profile Day 1*

Parameter	Units[a]	Definition
$AUC_{0\text{-last}}$	h*ng/mL	area under the concentration-time curve from time 0 to the time of the last quantifiable concentration (t_{last})[c]
AUC_{tau}	h*ng/mL	area under the concentration-time curve over a dosing interval (τ)
$AUC_{0\text{-}\infty}$	h*ng/mL	area under the concentration-time curve from time 0 extrapolated to infinity[c]
$\%AUC_{extrap}$	%	percentage of area under the concentration-time curve due to extrapolation from the last quantifiable concentration to infinity
C_{max}	ng/mL	maximum observed concentration
C_{tau}	ng/mL	concentration observed at the end of the dosing interval/immediately prior to dosing
T_{max}	h	time of the maximum observed concentration
T_{last}	h	time of the last quantifiable concentration
$t_{1/2}$	h	apparent terminal elimination half-life
CL/F	L/h	apparent total clearance (parent analyte only)
V_z/F	L	apparent volume of distribution during the terminal phase (parent analyte only)
MR $_{AUC0\text{-}\tau}$		metabolite:parent ratio based on $AUC_{0\text{-}\tau}$
$AUC_{0\text{-tau}}/D$	h*ng/mL/mg	$AUC_{0\text{-}\tau}$ normalized by dose administered[d]
$AUC_{0\text{-last}}/D$	h*xg/mL/xg	$AUC_{0\text{-tlast}}$ normalized by dose administered[d]
$AUC_{0\text{-}\infty}/D$	h*ng/mL/mg	$AUC_{0\text{-}\infty}$ normalized by dose administered[d].
C_{max}/D	ng/mL/mg	C_{max} normalized by dose administered[d]

[a] Units are based on concentration units (provided by the bioanalytical lab or preferred units for presentation of PK parameters) and dose units used in the study.
[b] The AUC will be calculated using the linear trapezoidal rule for increasing concentrations and the logarithmic rule for decreasing concentrations (linear up/log down rule).
[c] Based on the last observed quantifiable concentration
[d] Calculated by dividing the parameter by the dose (mg)
* *Concentration-time profile following dosing on Profile Day 1*

Table 9 PK Profile Week 12*

Parameter	Units[a]	Definition
$AUC_{0\text{-last}}$	h*ng/mL	area under the concentration-time curve from time 0 to the time of the last quantifiable concentration (t_{last})[b]
AUC_{tau}	h*ng/mL	area under the concentration-time curve over a dosing interval (τ)
C_{max}	ng/mL	maximum observed concentration
C_{tau}	ng/mL	concentration observed at the end of the dosing interval/immediately prior to dosing
T_{max}	h	time of the maximum observed concentration
T_{last}		
$t_{1/2}$	h	apparent terminal elimination half-life
CL/F	L/h	apparent total clearance (parent analyte only)
V_z/F	L	apparent volume of distribution during the terminal phase (parent analyte only)
$MR_{AUC0\text{-}tau}$		metabolite: parent ratio based on $AUC_{0\text{-tau}}$
AR_{AUC}		accumulation ratio based on $AUC_{0\text{-tau}}$
AR_{Cmax}		accumulation ratio based on C_{max} during the dosing interval
$AUC_{0\text{-tau}}$/D	h*ng/mL/mg	$AUC_{0\text{-}\tau}$ normalized by dose administered[d]
$AUC_{0\text{-last}}$/D	h*ng/mL/mg	$AUC_{0\text{-tlast}}$ normalized by dose administered[d]
C_{max}/D	ng/mL/mg	C_{max} normalized by dose administered [d]
LR		Linearity ratio

The dosing interval τ is *24* hours.
[a] Units are based on concentration units (provided by the bioanalytical lab or preferred units for presentation of PK parameters) and dose units used in the study.
[b] Area under the concentration-time curve will be calculated using the linear trapezoidal rule for increasing concentrations and the logarithmic rule for decreasing concentrations (linear up/log down rule).
[c] Based on the last observed quantifiable concentration
[d] Calculated by dividing the parameter by the dose (mg)
* Concentration-time profile following multiple dosing on Profile Week 12

Additional PK parameters may be determined where appropriate.

Pharmacokinetic analysis will be carried out where possible using actual dose administered and actual postdose blood sampling times. If an actual time is missing, the sample concentration result will be treated as missing unless there is scientific justification to include the result using the nominal time.

The parameters C_{max}, C_{tau}, t_{last}, and t_{max} will be obtained directly from the concentration-time profiles. If C_{max} occurs at more than 1 timepoint, t_{max} will be assigned to the first occurrence of C_{max}.

The metabolite: parent ratio(s) (MR_{AUC}) will be calculated as follows:

MR_{AUC} = (AUC TRN-000971 / MW TRN-000971) / (AUC TERN-101 / MW TERN-101), where MW is the molecular weight of each analyte.

The molecular weights of parent analyte and metabolite(s) to be used in the adjustment are as follows:

TERN-101 = 540.44 g/mol

TRN-000971 = 716.56 g/mol

The parameter $AUC_{0\text{-}tlast}$ or other common partial area may be used to determine MR_{AUC} if $AUC_{0\text{-}\infty}$ or $AUC_{0\text{-}\tau}$ cannot be reliably calculated for the majority of subjects.

The linearity ratio (LR) will be calculated as ratio of $AUC_{0\text{-}\tau}$ following multiple dosing to $AUC_{0\text{-}\infty}$ following a single dose:

LR = $AUC_{0\text{-}\tau}$ Profile Week 12 / $AUC_{0\text{-}\infty}$ Profile Day 1

7.17.1. Criteria for the Calculation of Apparent Terminal Elimination Rate Constant and Half-life

The start of the terminal elimination phase for each subject will be defined by visual inspection and generally will be the first point at which there is no systematic deviation from the log-linear decline in concentrations.

The apparent terminal elimination rate constant (λz) will only be calculated when a reliable estimate can be obtained using at least 3 data points, preferably not including C_{max}, and the adjusted coefficient for determination of exponential fit (R^2-adj) of the regression line is $\geqslant$ 0.7. Parameters requiring λz for their calculation (eg, $AUC_{0\text{-}\infty}$, $t_{1/2}$, CL/F (Profile Day 1 only), Vz/F) will only be calculated if the R^2-adj value of the regression line is $\geqslant$0.7.

The following regression-related diagnostic PK parameters will be determined where possible:

Parameter	Units	Definition
λ_z	1/h	apparent terminal elimination rate constant
λ_z Upper	h	end of exponential fit
λ_z Lower	h	start of exponential fit
λ_z N		number of data points included in the log-linear regression
λ_z Span Ratio		time period over which λ_z was determined as a ratio of $t_{1/2}$
R^2-adj		adjusted coefficient for determination of exponential fit

Where possible, the span of time used in the determination of λ_z (i.e., the difference between λ_z Upper and λ_z Lower) should be ≥2 half-lives. If the λ_z Span Ratio is <2, the robustness of the $t_{1/2}$ values will be discussed in the clinical study report (CSR).

7.17.2. Criteria for Calculation and Reporting of Area Under the Concentration-time Curve

The minimum requirement for the calculation of AUC will be the inclusion of at least 3 consecutive concentrations above the lower limit of quantification. If there are only 3 consecutive concentrations, at least 1 should follow C_{max}. An exception may be made for metabolite, where C_{max} may be the last timepoint.

If the extrapolated area is >20%, $AUC_{0-\infty}$ (and derived parameters) may be excluded from the summary statistics at the discretion of the sponsor or pharmacokineticist.

If the τ PK blood sample is collected slightly early (i.e., the 24 hours sample), the actual sampling time of the τ sample may be used for the calculation of $AUC_{0-\tau}$. However, the $AUC_{0-\tau}$ parameter will be calculated if the τ sample is within 60 minutes of the nominal sampling time.

7.17.3. Criteria for Handling Concentrations Below the Limit of Quantification or Missing Concentrations for Pharmacokinetic Analysis (i.e., PK Parameter Generation)

For the purposes of PK parameter generation, plasma concentrations below the limit of quantification (BLQ) will be assigned a value of 0 before the first measurable concentration and thereafter BLQ concentrations will be treated as missing. The following rules apply to the specific situations defined below:

- If an entire concentration-time profile is BLQ, it will be excluded from PK analysis.
- Where there is NR, these will be set to missing.
- Where 2 or more consecutive concentrations are BLQ at the end of a profile, the profile will be deemed to have terminated and any further quantifiable concentrations will be set to missing for the calculation of the PK parameters, unless they are

considered to be a true characteristic of the profile of the drug. If a predose plasma concentration is missing, it will be set to 0 by default within Phoenix WinNonlin for the first dosing day (Study Profile Day 1).

- For multiple dose (Study Profile Week 12), if the analyte concentration at τ (i.e., 24 hours postdose for once daily dosing) is missing, this may be substituted with the predose concentration. Similarly, if the predose concentration is missing then this may be substituted with the concentration at τ.

7.17.3.1. Treatment of Outliers in Pharmacokinetic Analysis

If a value is considered to be anomalous due to being inconsistent with the expected PK profile, it may be appropriate to exclude the value from the PK analysis. However, the exclusion of any data must have strong justification and will be documented in the CSR.

Any quantifiable predose concentration value on the first dosing day (Study Profile Day 1) will be considered anomalous and set to missing for the PK analysis if determined as predose after investigation. This will be set to 0 by default in Phoenix WinNonlin.

7.17.4. Presentation of Pharmacokinetic Data

A listing of PK blood sample collection times as well as plasma concentrations will be presented for TERN-501, TERN-101, and TERN-101 metabolite TRN-000971 separately for all patients for the Pharmacokinetics Analysis Set.

Pharmacokinetic concentrations will be summarized for the PK Analysis Set for each timepoint by treatment group using protocol scheduled times and appropriate summary statistics. Individual patient and geometric mean concentration-time profiles, for each TERN-101 dose, will be presented graphically on linear and logarithmic concentration scales for PK/PD substudy patients for Day 1 and Week 12.

If the actual time of sample collection deviates from the nominal time by more than ±10%, the plasma concentration will be flagged and excluded from the summary statistics. Individual concentrations deemed to be anomalous will be flagged in the listings and excluded from the summary statistics. For plasma concentration data, the following rules will apply:

- Values that are BLQ will be set to 0 for the calculation of summary statistics and the number of values that are BLQ will be presented.
- Arithmetic mean or median values that are BLQ will be presented as 0.
- Where there is NR, these will be set to missing

- If there are less than three values in the data series, only the minimum, maximum, and number of observations will be presented. The other summary statistics will be denoted as not calculated (NC). BLQ is considered a value for these purposes.
- If all values are BLQ, then the arithmetic mean, arithmetic SD, median, minimum, and maximum will be presented as 0, and the geometric mean and geometric CV% will be denoted as NC.

For PK parameters, the following rule will apply:

Geometric mean and coefficient of variation will not be calculated for T_{last} or T_{max}.

7.18. Pharmacodynamic Analyses

The pharmacodynamic (PD) endpoints of SHBG, lipid panel, FGF19, 7αC4, and bile acids are collected at the timepoints shown in Table 8 of the protocol.

The change from baseline in SHBG, LDL-c, will be analyzed in the same manner as specified in Section 7.7 and pairwise comparisons in Section 7.6 using the efficacy analysis set.

Plasma concentrations for 7αC4, FGF19, and bile acids that are BLQ will be set to ½ × BLQ. Plasma PD parameters will be computed for PD patients only. Plasma PD parameters for 7αC4 and FGF19 will be calculated from the individual plasma concentrations using a non-compartmental approach for Day 1 and Week 12. Day 1 will include pre dose and all post dose assessments prior to dosing on Day 2. Week 12 will include pre dose and all post dose assessments. The actual PD sampling times will be used for the PD analysis. If actual PD sampling times are missing, nominal times will be used. Table 1 below presents the plasma PD parameters to be calculated.

Table 10 Plasma PD Parameters

Abbreviation	Parameter Definition
$AUEC_{0-24}$	Area under the effect-time curve from time 0 to 24 hours postdose
RAUEC	Ratio of $AUEC_{(Week\ 12)}$ /$AUEC_{(Day\ 1)}$.
C_{min}	For 7αC4 only, minimum observed plasma concentration, obtained directly from the plasma concentration-time profiles. In the case where multiple minimums are of equal magnitude, the earliest minimum concentration will be reported as C_{min}.
RC_{min}	For 7αC4 only, ratio of $C_{min\ (Week\ 12)}$ /$C_{min\ (Day\ 1)}$.
C_{max}	For FGF19 only, maximum observed plasma concentration, obtained directly from the plasma concentration-time profiles. In the case where multiple peaks are of equal magnitude, the earliest peak concentration will be reported as C_{max}.
RC_{max}	For FGF19 only, the ratio of $C_{max\ (Week\ 12)}$ /$C_{max\ (Day\ 1)}$.
t_{min}	For 7αC4 only, time of the minimum observed plasma concentration, obtained directly from the plasma concentration-time profiles. In the case where multiple minimums are of equal magnitude, the time of the earliest minimum will be reported as the t_{min}.
t_{max}	For FGF19 only, time of the maximum observed plasma concentration, obtained directly from the plasma concentration-time profiles. In the case where multiple peaks are of equal magnitude, the time of the earliest peak will be reported as the t_{max}.

7.18.1. PD Parameter Data Handling

7.18.1.1. Calculation of AUC

AUCs will be calculated using linear up / log down trapezoidal rule. For any partial AUC determination (i.e., AUC over a dosing interval), nominal time will generally be used for the end of the interval. The minimum requirement for the calculation of AUC will be the inclusion of at least three consecutive plasma concentrations above the LLOQ, with at least one of these concentrations following C_{max} for FGF19 and C_{min} for 7αC4.

7.18.2. Statistical Methods for PD Parameters

Plasma PD parameters will be summarized by treatment group using descriptive statistics (number of non-missing observations, arithmetic mean, SD, median, minimum, maximum,

geometric mean, and geometric CV%). For the calculation of summary statistics, all NR and not calculated (NC) values in a data series will be set to missing.

Analyses of AUC for both 7αC4 and FGF19, C_{max} for FGF19, and C_{min} for 7αC4 at Day 1 and Week 12 will be carried out using an analysis of variance (ANOVA) model with the PD parameter as the dependent variable including treatment group as a fixed effect. The estimate of the LS means, SE, and 95% CIs will be presented by treatment group. Estimates of the LS mean difference for each pairwise comparison will be presented with associated the standard error of the difference, and 95% CI of the difference.

7.18.3. PK/PD Analyses

For patients in the PK/PD substudy, Day 1 and Week 12 PK and PD (7αC4 and FGF19) concentrations will be plotted together by treatment group over time. Similarly, AUCs, C_{min}, and C_{max} for PK and PD will also be plotted by treatment group.

8. Safety Analyses

All safety analyses will be conducted using the safety analysis set unless otherwise noted.

8.1. Extent of Exposure

Total duration of exposure will be calculated in days as the last date study drug administration – the first date study drug administration + 1. In addition, duration of exposure accounting for days where a dose was missed (referred to as interruptions on CRFs) will be calculated as total duration – sum of (Week X date of resumption – Week X start date of interruption) where X is the week number, i.e., 2, 4, 6, 8, and 12. The dates of interruption are from the Study Drug Interruptions CRF. If dates of missed doses are not available, the number of missed doses will be used. Duration of exposure, total and accounting for missed dosing days, will be summarized with descriptive statistics by treatment group.

The number and percentage of patients with any missed dose and the total duration of days where doses were missed will be summarized with descriptive statistics by treatment group.

Compliance based on the Study Drug Administration and Study Drug Interruptions CRFs will be calculated as:

- 100 × [((last date study drug administration – the first date study drug administration + 1) – sum of durations interrupted) / (last date study drug administration – the first date study drug administration + 1)].

Compliance will be calculated based on the Study Drug Accountability CRF as:

- 100 × [(Sum of tablets or capsules taken during study) / (Expected Taken)]

Tablets and/or Capsules will be summed across all bottles, whether monotherapy or combination, at each week.

Expected taken is calculated as the study day of the last dose date × 4 (number of tablets or capsule taken per day). Treatment compliance will be summarized with descriptive statistics by treatment group. The number and percentage of patients in each of the following compliance categories will be summarized by treatment group and overall total:

- < 80%
- 80% to ≤ 100%
- > 100%.

Study drug administration including missed doses, delays, and overdoses, and study drug dispensing and accountability, calculated durations of exposure, and calculated compliance will be presented in by-patient data listings.

8.2. Adverse Events

Adverse event (AE) verbatim terms on eCRFs will be mapped to preferred terms (PT) and system organ classes (SOC) using MedDRA. AE severity will be categorized using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE, Version 5).

All AEs will be listed, but summaries will be restricted to treatment emergent AEs (TEAEs), defined as any AE with a start date on or after the date of first administration of study drug through 30 days after the last administration of study drug or through the Follow-Up Period (Week 16). Related SAEs after Week 16 will be considered TEAEs. If it cannot be determined whether an AE is treatment emergent due to a partial onset date, then it will be counted as such. Methodology for imputation of partial AE start and stop dates is described in Appendix 2. Each summary will be displayed by treatment group.

8.2.1. Overall Summary of Adverse Events

An overall summary of TEAEs will be presented by treatment group. The number and percentage of patients who experience at least one of the following:

- Any TEAE, All CTCAE grades
- Grade 3 or higher TEAE
- Serious TEAE
- TEAE leading to death
- Treatment-related TEAE, All CTCAE grades
- Treatment-related Grade 3 or higher TEAE
- Treatment-related serious TEAE
- TEAE leading to study drug interruption
- TEAE leading to study drug discontinuation
- TEAE leading to discontinuation from the study

8.2.2. Patient Incidence of Adverse Events

Summaries will be displayed by SOC and PT and will be ordered by descending order of group 7 incidence of system organ class and preferred term within each system organ class. Summaries of the following types will be presented:

- Patient incidence of TEAEs by MedDRA SOC and PT.
- Patient incidence of TEAEs leading to study drug discontinuation by MedDRA SOC and PT. This is a subset of the AEs where Action Taken with Study Drug is checked as "Drug Withdrawn."
- Patient incidence of TEAEs leading to study drug interruption by MedDRA SOC and PT. This is a subset of the AEs where Action Taken with Study Drug is checked as "Drug Interrupted."
- Patient incidence of TEAEs leading to study discontinuation by MedDRA SOC and PT (subset of the AEs where Reason for Discontinuation on the End of Study CRF is "Adverse Event").
- Patient incidence of TEAE leading to death by MedDRA SOC and PT.
- Patient incidence of TEAEs by MedDRA SOC, PT, and highest severity (CTCAE grade). At each level of patient summarization, a patient is classified according to the highest severity if the patient reported 1 or more events. AEs with missing severity (CTCAE grade) will be considered Grade 3 (severe) for this summary.
- Patient incidence of CTCAE Grade 3 or higher TEAEs by MedDRA SOC and PT. At each level of patient summarization, a patient is classified according to the highest severity if the patient reported 1 or more events. AEs with missing severity (CTCAE grade) will be considered Grade 3 (severe) for this summary.
- Patient incidence of treatment-related TEAEs by MedDRA SOC and PT. Related AEs are those with relationships reported as "Related" or "Possibly Related". At each level of patient summarization, a patient is classified according to the closest relationship to study drug if the patient reported 1 or more events. AEs with a missing relationship will be considered related for this summary.
- Patient incidence of treatment-related CTCAE Grade 3 or higher TEAEs by MedDRA SOC and PT. At each level of patient summarization, a patient is classified according

to the highest severity if the patient reported 1 or more events. AEs with missing severity (CTCAE grade) will be considered Grade 3 (severe) for this summary. AEs with a missing relationship will be considered related for this summary.

- Patient incidence of serious TEAEs by MedDRA SOC and PT.

The following listings will be presented by treatment group and patient, include study day event started and the duration of event:

- All adverse events.
- Serious adverse events (subset of the AEs where serious is marked as “Yes”).
- Adverse events leading to study drug interruption (subset of the AEs where Action Taken with Study Drug is checked as “Study drug interrupted”).
- Adverse events leading to study drug discontinuation (subset of the AEs where Action Taken with Study Drug is checked as “Study drug discontinued”).
- Adverse events leading to study discontinuation (subset of the AEs where Reason for Discontinuation on the End of Study CRF is “Adverse Event”).
- CTCAE Grade 3 or higher adverse events (subset of AEs where severity is marked as CTCAE Grade 3, 4, or 5).
- Related adverse events (subset of the AEs where relationship marked as “Definitely Related” or “Possibly Related”).
- CTCAE Grade 3 or higher treatment-related adverse events (subset of AEs where severity is marked as CTCAE Grade 3, 4, or 5).

8.2.3. Pruritus

For patients who report AEs consistent with pruritus at the visit, a qualified staff member will administer the Pruritus Numerical Rating Scale (see Appendix 8 of the study protocol). The Pruritus Numerical Rating Scale assesses a patient’s severity of itching on average and at its worst point, in the past 24 hours, on a scale of 0 (no itching) to 10 (worst imaginable itch). Pruritus events will be identified in the ADAE.

Treatment-emergent pruritus is defined as any preferred term including “Prur”.

A separate by-patient listing for pruritus events will be provided with associated Pruritus Numerical Rating Scale results, if applicable.

8.3. Clinical Safety Laboratory Evaluations

All laboratory assessments are specified in Appendix 1 of the study protocol. Laboratory parameters will be summarized in conventional units. Coagulation parameters, hemoglobin A1c, direct bilirubin, and indirect bilirubin will not be summarized.

Quantitative clinical chemistry, hematology, and urinalysis results will be summarized by treatment group using descriptive statistics at baseline and at each post-baseline visit. The change and percent change from baseline will also be summarized.

Additional summaries will be provided by scheduled visits for the number and percentage of patients with

- Total CK > 5x ULN
- Hg < 10 mg/dL
- HCT < 30%
- platelets < 100,000 /microL
- WBC < LLN

All clinical safety laboratory data will be presented in by-patient data listings. A separate listing for central laboratory normal ranges, by lab category, lab test, lab parameter, sex, and age, will be presented.

8.3.1. Treatment Emergent Abnormalities

Quantitative laboratory tests will be assigned grades based on National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) Version 5. For each applicable laboratory test, a treatment emergent abnormality will be defined as a post-baseline through Week 16 CTCAE grade increase of ≥2 grades.

The number and percentage of patients overall and by laboratory test, with any treatment emergent laboratory abnormality, CTCAE increase of ≥2 grades, will be presented. Similarly, the number and percentage of patients overall and by laboratory test, with CTCAE increase of ≥1 grade will be presented.

Estimated glomerular filtration rate (eGFR) is calculated by the central lab using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation. eGFR does not have a normal range within the central lab data. A normal range will be defined as ≥90 mL/min/1.73m2.

LDL cannot be graded via NCI CTCAE version 5. For the purposes of treatment emergent abnormalities, LDL will be graded as follows:

- Optimal: < 100 mg/dL
- Near or Above Optimal: 100 – 129 mg/dL
- Borderline High: 130 – 159 mg/dL
- High: 160 – 189 mg/dL
- Very High: > 189 mg/dL

Listings will be presented for any patient with any treatment emergent laboratory abnormality (post-baseline through Week 16 CTCAE increase of ≥ 2 grades). Normal ranges provided by the central laboratory will be presented in a listing.

The number and percentage of patients meeting each criterion detailed in Table 11 will be presented. A listing will be presented for any patient meeting any of the criteria in Table 11.

Table 11 Liver Function Tests Potentially Reflecting Hepatoxicity Liver Function Tests

Liver Function Tests	Range of Test Values
ALT or AST	≥ 3 to < 5 x ULN
	≥5 to < 10 x ULN
	≥ 10 to < 20 x ULN
	≥ 20 x ULN
Total bilirubin	> ULN
	≥ 1.5 x ULN
	≥ 2 × ULN
(AST or ALT) plus total bilirubin	≥3 x ULN (ALT or AST) plus ≥ 1.5 x ULN (total bilirubin)
	≥ 3 x ULN (ALT or AST) plus ≥ 2 x ULN (total bilirubin)
ALP	≥ 2 x ULN
ALP and total bilirubin	≥ 2 x ULN (ALP) and ≥ 2 x ULN (total bilirubin)
	< 2 x ULN (ALP) and ≥ 2 x ULN (total bilirubin)
	≥ 2 x ULN (ALP) and < 2 x ULN (total bilirubin)
ALT = alanine aminotransferase; AST = aspartate aminotransferase; ULN = upper limit of normal; ALP = Alkaline phosphatase.	

8.3.2. Thyroid Axis Testing

TSH, free T3, free T4, total T3, total T4, and TBG will be collected at Baseline and Weeks 2, 6, 12, and 16, and/or ET. Estimates of the LS mean difference for the pairwise comparisons detailed in Section 7.7 with the associated standard error of the difference, and 95% CI of the difference, the standard error of the difference, and 95% CI of the difference will be presented. Summary statistics will be provided for the levels at each visit and for change from baseline by treatment groups.

8.3.3. Sex Hormones

Free and total testosterone, estradiol, FSH, and LH will be collected at Baseline and Week 12. Estimates of the LS mean difference for the pairwise comparisons detailed in Section 7.7 with the associated standard error of the difference, and 95% CI of the difference, the standard error of the difference, and 95% CI of the difference will be presented for change from baseline by treatment group and by sex.

8.3.4. Bone Turnover Markers

The bone turnover markers sCTX and sPINP will be collected at Baseline, Week12, and Week 16. Summary statistics will be provided for each parameter at each visit and for change from baseline at each visit.

8.3.5. Shifts in Normal Range

Shift tables for each laboratory test (hematology, chemistry, and urinalysis) showing the shift from normal at baseline to abnormal at each post-baseline visit will be presented by visit. Summaries will present the number and percentage of patients with shifts by treatment group. Denominators for percentages will be the number of patients with non-missing data at the specific assessment and baseline.

8.4. Vital Signs

Vital signs will be collected at each visit. Summary statistics will be provided for systolic and diastolic blood pressure, and heart rate for each visit. Any clinically significant abnormalities will be reported as adverse events.

8.5. Electrocardiograms

Summary statistics will be provided for heart rate, PR interval, QRS interval, QT interval, and QTcF at each visit. The investigator interpretation is collected as normal, abnormal not clinically significant (NCS), or abnormal clinically significant (CS). Patients whose interpretation shifts from normal to abnormal (CS or NCS) will be listed separately including description of the abnormality and any associated comments.

Categorical summaries will for baseline, worst post-baseline, and change from baseline for the following QTcF values will be presented:

- > 450 msec
- > 480 msec
- > 500 msec
- Change from baseline > 30 msec
- Change from baseline > 60 msec

All ECG results will be presented in by-patient data listings. If applicable, cardiologist consult information will be presented in a separate by-patient data listing.

9. Other Assessments

Other assessments will be provided in by-patient data listings only; no summary tables will be provided, including but not limited to the following:

- Eligibility details including unmet eligibility criteria
- Informed consent
- Randomization schema
- Physical examination collection information
- Serology
- Pregnancy testing
- FSH test
- Urine drug screen
- Alcohol test
- Urinalysis and Urine Microscopic Examination
- Coagulation
- Hemoglobin A1c
- Direct bilirubin
- Indirect bilirubin
- Laboratory reference ranges
- Cardiology consult
- Overdose
- Comments

10. Changes to Protocol Planned Analyses

There were no changes from the protocol planned analyses.

11. Appendices

Appendix 1: Document History

Document Version, Status, Date	Summary / Reason for Changes
Version 0.1, Draft, 12AUG2022	Not applicable; the first version
Version 0.2, Draft, 30SEP2022	Addressed sponsor comments from Version 0.1
Version 0.3, Draft, 18JAN2023	Addressed sponsor comments from Version 0.2
Version 0.4, Draft, 13MAR2023	Addressed sponsor comments from Version 0.3
Version 0.5, Draft, 05MAY2023	Addressed sponsor comments from Version 0.4
Version 0.6, Draft, 18JUL2023	Addressed sponsor comments from Version 0.5 and TLF shells version Draft 0.3
Version 1.0, Final: 20July2023.	Comments from version 0.6 addressed and SAP signed off
Version 1.1 Final 26July2023	Additional changes requested by sponsor after sign off.
Version 2.0 final 26Jluy2023	Resolved final formatting comments

APPENDIX 2: IMPUTATION RULES FOR MISSING OR PARTIAL DATES FOR ADVERSE EVENTS AND CONCOMITANT MEDICATIONS

Date	Situation	Imputation Rule
Start Date	Only month and year are known and month and year are prior to first dose date	Use the last day of the month
	Only month and year are known and month and year are the same as first dose date	Use the first study drug administration date
	Only month and year are known and month and year are after first dose date	Use the first day of the month
	Only year is known and year is before first dose date	Use Dec 31 of that year
	Only year is known and year is same as first dose date	Use the first study drug administration date
	Only year is known and year is after first dose date	Use Jan 1 of that year
	Entire date is missing	Use the first study drug administration date
	The estimated start date is after a complete or imputed AE stop date	Use the first day of the month of the AE stop date
Stop/End Date	Only month and year are known and month and year are prior to last dose date	Use the last day of the month
	Only month and year are known and month and year are the same as last dose date	Use the last dose date
	Only month and year are known and month and year are after last dose date	Use the last day of the month
	Only year is known and year is before last dose date	Use Dec 31 of that year
	Only year is known and year is same as last dose date	Use the last study drug administration date
	Only year is known and year is after last dose date	Use Dec 31 of that year
	Entire date is missing	Use the last study drug administration date
	The estimated stop date is before a complete or imputed AE start date	Use the last day of the month of the AE start date
AE = adverse event, Dec = December, Jan = January		

APPENDIX 3: ABBREVIATIONS

Abbreviation or Special Term	Explanation
7αC4	7α-hydroxy-4-cholesten-3-one
ADaM	Analysis Data Model
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine transaminase
ANCOVA	analysis of covariance
AST	aspartate transaminase
ATC	Anatomical Therapeutic Class
AUC	area under the concentration-time curve
BLQ	below limit of quantification
BMI	body mass index
CAP	Controlled Attenuation Parameter
CDISC	Clinical Data Interchange Standards Consortium
CHG	change from baseline ADaM basic dataset structure defined variable
CI	confidence interval
CK-18	cytokeratin-18
COVID-19	Coronavirus disease 2019
Cmax	maximal concentration
CRF	case report form
CSR	clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
CTMS	clinical trial management system
CV	coefficient of variation
DPP-4	Dipeptidyl peptidase 4
eGFR	estimated glomerular filtration rate
eCRF	electronic case report form
ECG	electrocardiogram
ET	early termination
FDA	Food and Drug Administration
FGF	fibroblast growth factor
FIB-4	Fibrosis-4 Score
FSH	follicle stimulating hormone
FXR	farnesoid X receptor
GGT	gamma-glutamyl transpeptidase
GLP-1	Glucagon-like peptide-1
HA	hyaluronic acid
HDL	high-density lipoprotein
hs-CRP	high sensitivity C-reactive protein
ICF	informed consent form
ICH	International Council for Harmonisation
IG	implementation guide
IMP	investigational medicinal product
INR	international normalized ratio
IWRS	interactive web response system
LDL	low-density lipoprotein

Abbreviation or Special Term	Explanation
LFC	liver fat content
LFT	liver function test
LLN	lower limit of normal
ln	natural log
LOCF	Last observation carried forward
LS	least squares
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	mixed model for repeated measures
MRI-PDFF	Magnetic Resonance Imaging Proton Density Fat Fraction
NAFLD	non-alcoholic fatty liver disease
NAS	non-alcoholic fatty liver disease activity score
NASH	non-alcoholic steatohepatitis
NC	not calculated
NCA	noncompartmental analysis
NCI	National Cancer Institute
PCHG	percent change from baseline ADaM basic dataset structure defined variable
PIIINP	procollagen III n-terminal propeptide
PD	pharmacodynamics
PK	pharmacokinetics
PRO-C3	pro-peptide of type III collagen
Q1	25th percentile, first quartile
Q3	75th percentile, third quartile
QTcF	QT corrected for heart rate by Fridericia's cube root formula
REML	restricted maximum likelihood
SAE	serious adverse event
SAP	statistical analysis plan
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SD	standard deviation
SDG	Standardized Drug Grouping
SDTM	Study Data Tabulation Model
SE	least squares mean standard error
SGLT-2	Sodium-glucose co-transporter 2
TEAE	treatment emergent adverse event
TERN-101	investigational agonist of Farnesoid X receptor
TIMP-1	tissue inhibitor of metalloproteinases-1
ULN	upper limit of normal
WHODD	World Health Organization Drug Dictionary