Statistical Analysis Plan

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

This statistical analysis plan (SAP) document outlines the statistical methods to be implemented during the analyses of Study Protocol TERN201-1007. The purpose of this plan is to provide specific guidelines from which the analyses will proceed. Any deviations from these guidelines will be documented in the clinical study report (CSR).

This SAP supersedes the statistical considerations identified in the protocol; where considerations are substantially different, they are identified in Section 11. Any post-hoc or unplanned analyses, or significant changes from the planned analysis in this SAP performed to provide results for inclusion in the clinical study report (CSR) but not included in this SAP, will be clearly identified in the CSR. Changes to planned analyses do not require an updated SAP but should be included in the CSR if significant.

2. INFORMATION FROM THE STUDY PROTOCOL

2.1. Study Objectives

Primary Objective:

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

Secondary Objectives:

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

Exploratory Objectives:

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

2.2. Study Design

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

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

Part 1

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

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

Part 2

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

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

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

2.2.1. Study Procedures

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

2.2.2. Study Population

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

2.2.3. 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

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

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

Patients will be instructed to take capsules as shown in Table 2.

Table 2: Study Administration by Dose Group

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

Abbreviations: QD = once per day

2.2.4. Treatment Assignment, Blinding, and Randomization Methodology

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

Up to approximately 80 patients will be enrolled in this study. In Part 1, approximately 30 patients will be randomized at a ratio of 2:1 to receive TERN-201 10 mg (n = 20) or matching

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

The randomization codes will be provided to bioanalytics to allow for the exclusion of placebo patients from the PK assay. Bioanalytics will not disclose the randomization code or the results of their measurements 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.

2.3. Study Endpoints

2.3.1. Primary Endpoints

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

2.3.2. Secondary Endpoints

- Plasma and urine PK parameters for TERN-201
- Percent change from baseline in plasma VAP-1/SSAO activity

2.3.3. Exploratory Endpoints

- Plasma and urine PK parameters for TERN-201 metabolites (including TRN-001021 and TRN-001744)
- Change from baseline in corrected T1 (cT1) by magnetic resonance imaging (MRI)
- Change from baseline in liver fat content by magnetic resonance imaging-proton density fat fraction (MRI-PDFF)
- Change from baseline in stiffness by transient elastography
- Change from baseline in alanine aminotransferase (ALT)
- Change from baseline in gamma-glutamyl transpeptidase (GGT)
- Change from baseline in aspartate aminotransferase (AST)
- Change from baseline in NASH and fibrosis biomarkers including cytokeratin-18 (CK-18) (M30 and M65), procollagen III n-terminal propeptide (PIIINP), tissue inhibitor of metalloproteinases-1 (TIMP-1), hyaluronic acid (HA), pro-peptide of type III collagen (PRO-C3), and type III collagen (C3M). Other non-invasive tests for NASH fibrosis may also be assessed including the fibrosis-4 (FIB-4) index, enhanced liver fibrosis (ELF) test, NAFLD fibrosis score (NFS), and PRO-C3/C3M ratio.
- Change from baseline in inflammatory biomarkers including high sensitivity C-reactive protein (hs-CRP), interleukin-6 (IL-6), intercellular adhesion molecule-1 (ICAM-1), and vascular cell adhesion molecule-1 (VCAM-1)

- Change from baseline in estimated glomerular filtration rate (eGFR), urine protein including urine protein-to-creatinine ratio (UPCR), and urine albumin-to-creatinine ratio (UACR)
- Change from baseline in plasma methylamine levels (PD marker of VAP-1/SSAO inhibition)
- Exposure-response and dose-response relationship of TERN-201 over 12 weeks, as applicable
- Exposure-response and dose-response relationship, as applicable, of TERN-201 and baseline patient characteristics such as sVAP-1, BMI, diabetes mellitus, and others

3. SAMPLE SIZE JUSTIFICATION

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

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

4. GENERAL STATISTICAL METHODS

4.1. Reporting Conventions

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 Harmonisation (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. If there are missing values, the number missing will be presented, but without a percentage. 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 T_{max}, T_{min}, T_{last}, and $t_{1/2}$ will be presented to 1 decimal place and all other plasma and urine PK parameters will be presented to 3 significant figures.

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 3 or more values are 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 two-sided 90% and 95% CIs comparing groups will be provided.

Other general programming specifications are provided in Appendix 1.

4.2. 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-201 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 24.0. Concomitant medications will be coded using World Health Organization Drug Dictionary (WHODD), B2 Enhanced March 2021.

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.

4.3. Partial Dates

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

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

4.4. 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 8.7.1 and Section 8.8.1, 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, $\log_{10}$).

4.5. 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) = weight (kg) / ([height (cm)/100]^2)

- Change (CHG; equivalent to absolute change for liver fat content [LFC]) – Change will be calculated as:

  Change = later value – earlier (i.e., baseline) value

- Percent change (PCHG; equivalent to relative change for LFC) – Percent change will be calculated as:

  Percent change = ([Change] / earlier [i.e., baseline] value) × 100

4.6. Treatments

Table 3 presents how the dose groups will be presented on TFLs as treatment groups, including the order. If Part 2 enrolls, placebo patients from Part 1 and Part 2 will be pooled.

Table 3: Treatment Group Labels and Ordering

Treatment Group Label	Order on TFLs
Placebo	1
4 mg	2
10 mg	3
20 mg	4
All TERN-201	5
Overall (where specified)	6

All TERN-201 will not be included on efficacy, PK, or PD tables. Screen failures will be presented on by-patient listings where data is available.

4.7. Visits

4.7.1. Windows

Each visit will be denoted by its visit "Week". The first dose day is denoted as Day 1. In data listings, the relative study day of all dates from first dose will be presented.

In the event of unscheduled visits or early treatment termination (ET) assessments, these will be reassigned to a scheduled visit for analysis purposes according to Table 4 for on treatment assessments. If multiple assessments occur within a single visit window, after reassignment of unscheduled visits and ET assessments, the assessment closest to the target day of the visit window will be used in the analysis. If there is a tie, the later assessment will be used in the analysis.

Table 4: Treatment Period Visit Windows

Target Scheduled Visit	Target Study Day [a]	Analysis Window Study Day [a]	
		Low	High
Baseline[b]	1	See Section 4.7.2	
Week 2	15	2	22
Week 4	29	23	36
Week 6	43	37	50
Week 8	57	51	71
Week 12[c]	85	72	92[c]

[a] Study day will be calculated from first dose of study drug.
[b] Baseline is defined in Section 4.7.2.
[c] LFC and cTI by MRI will have no upper limit on Week 12.

The follow up visit (Week 16) will not be windowed. As described in Section 8.10.3.1, sensitivity analyses will be conducted including only Week 16 assessments which are at least 22 days from last dose.

4.7.2. Definition of Baselines

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, unless otherwise specified. If there is only one evaluation prior to the first administration of study drug, then the available data from this evaluation will be used as the baseline value.

For glucose and lipid parameters, only assessments taken while fasting for at least 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 height, weight, body mass index (BMI), waist circumference, and electrocardiogram parameters is defined as the last evaluation prior to the first administration of study drug.

The baseline value for pharmacodynamic analytes is defined as the Week 0/Day 1 predose value.

4.7.3. Definition of End of Treatment

The End of Treatment value will be defined as the Week 12 value, either scheduled or windowed per Table 4. If a Week 12 value is not available, the last non-missing on or before the last dose date will be used.

5. ANALYSIS SETS

Table 5 defines the analysis sets to be used.

Table 5: Analysis Sets

Analysis Sets	Description
Screened	All patients who sign the informed consent form (ICF).
Randomized	All patients 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-201 and have evaluable PK data. Evaluable PK data is defined in Section 8.7.
Pharmacodynamic (PD)	All randomized patients who received at least 1 dose of study drug (TERN-201 or placebo) and for whom at least one post baseline assessment of VAP-1/SSAO activity and methylamine is available. Treatment assignment will be based on the treatment actually received.
PK/PD Substudy	All patients who consented to the PK/PD substudy, were randomized into the PK/PD substudy, and received at least 1 dose of study drug (TERN-201 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.
Per Protocol (PP)	All randomized patients who have completed the study without any major protocol deviations. Treatment assignment will be based on the treatment actually received.
Treatment Completer	All patients who complete 12 weeks of treatment with at least 80% compliance based on study drug accountability. Treatment assignment will be based on the randomized treatment.

6. EXAMINATION OF SUBGROUPS

No analyses based on subgroups will be conducted.

7. STUDY POPULATION

7.1. Patient Disposition

Patient disposition will be summarized for the Screened 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.
- 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 for the Safety Analysis Set. 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.

7.2. 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 subgroup: <30, ≥30 - <35, ≥35 - <40, ≥40 kg/m^2
- Waist circumference (cm)
- Baseline liver stiffness by transient elastography (kPa)
- Baseline Controlled Attenuation Parameter by transient elastography (CAP; dB/m)
- Baseline LFC (%) by MRI-PDFF
- Baseline cTI (msec) by MRI including the following subgroup: Elevated (>800 – 900 msec) and High (>900 msec)
- Liver biopsy within 2 years of randomization
  - Baseline fibrosis stage (F1, F2, F3)
  - Baseline NAFLD Activity Score (NAS)
- 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.
- 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"
  - 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"

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

- Baseline plasma VAP-1/SSAO activity
- Baseline soluble VAP-1 (sVAP-1) concentration
- Baseline ALT level:
  - ≤60 U/L versus >60 U/L (overall and by sex)
- Baseline AST level: The same subgroups as specified for ALT above will be used.
- Baseline GGT level: ≤ULN, >ULN
- Baseline ALP level: ≤ULN, >ULN

- Baseline total bilirubin level: ≤ULN, >ULN
- Screening HbA1c: < 7%, ≥ 7%
- Baseline platelet count: ≤ULN, > ULN

Demographics and baseline characteristics will be summarized by treatment group and overall, for Efficacy, Safety, PP, and Treatment Completer Analysis Sets. The Safety, PP, and Treatment Completer Analysis Sets will only be presented if the analysis set differs from the Efficacy Analysis Set by more than 10% total.

All demographic and baseline characteristics data will be presented in by-patient data listings using the Efficacy Analysis Set.

No inferential statistical comparisons will be performed.

7.3. 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 major protocol deviations will be summarized 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. A separate listing for COVID-19 protocol deviations will be presented.

7.4. 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 total incidence of system organ class and preferred term within each system organ class.

7.5. 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. 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, ATC Level 4, 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 4 or ATC Level 4 within ATC Level 2, then the patient will be counted only once in that ATC Level 4 or ATC Level 2.

8. EFFICACY ANALYSES

8.1. Adjustments for Covariates

For comparison of treatment groups with respect to change and percent change from baseline, analysis of covariance (ANCOVA) and restricted maximum likelihood (REML) based mixed model repeated measures (MMRM) models will be used. The corresponding baseline value will be used as a covariate in the model.

8.2. Handling of Dropouts or Missing Data

Primary analyses will be based on observed data. Sensitivity analyses will be conducted for patients who do not have data at the Week 12 visit, where the last on treatment value will be used for Week 12.

8.3. Interim Analyses and Data Monitoring

No data monitoring committees are planned for this study.

An interim analysis will be performed after all patients in Part 1 have completed Week 6 assessments. Blinded adverse event and laboratory data will be reviewed. PK and PD data will be provided to the Sponsor with a dummy subject identification and treatment assignment. If robust VAP-1/SSAO activity suppression is observed, and available PK suggest a lower dose may also possibly lead to robust VAP-1/SSAO activity suppression, enrollment in Part 2 with 4 mg TERN-201 may be initiated. Additionally, if safety data indicates 10 mg TERN-201 is overall safe and well-tolerated and anticipated exposures with a higher dose remain below the exposure limit (see section 4.3 of the protocol), enrollment in Part 2 to assess a dose up to 20 mg TERN-201 in Part 2 may be initiated.

Additionally, an interim analysis will be conducted after the completion of Part 1. All data from Part 1 will be cleaned and locked prior to unblinding and analyses.

8.4. Multicenter Studies

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

8.5. Use of an "Efficacy Subset" of Patients

Not Applicable.

8.6. Multiple Comparisons/Multiplicity

There will be no adjustment for multiplicity. Statistical testing will be considered nominal, descriptive and exploratory.

8.7. Pharmacokinetic (PK) Analyses

Analyses of trough PK concentrations will use the PK Analysis Set. Analyses of intensive PK concentrations and PK parameters will use the PK/PD Substudy Analysis Set. All PK endpoints, recorded and derived, will be presented in by-patient data listings.

Plasma and urine TERN-201 and metabolite (TRN-001021 and TRN-001744) concentrations will be used as supplied by the analytical laboratory for PK analysis. The units of concentration and resulting PK parameters, with amount or concentration in the unit, will be presented as they are received from the analytical laboratory, with the exception of metabolite to parent ratios which will be corrected for differences in molecular weight. Urine volume will be presented with urine concentrations. Urine collection dates and times from the EDC will be used for analyses, otherwise plasma collection dates and times from the central vendor will be used.

Blood and urine samples will be collected at the timepoints specified in Appendix 2 of the study protocol.

8.7.1. Below the Quantification Level (BLQ) Values

Plasma concentration values that are BLQ will be set to zero, with defined exceptions as follows:

- Any embedded BLQ value (between 2 quantifiable concentrations) and BLQ values following the last quantifiable concentration in a profile will be set to missing for the purposes of PK analysis. If an embedded BLQ value is considered anomalous within the concentration time profile, this value will be excluded as well.
- If there are late positive concentration values following 2 BLQ concentration values in the apparent terminal phase, these values will be evaluated. If these values are considered to be anomalous (see Section 8.9.2), they will be set to missing.

If an entire plasma concentration-time profile is BLQ, the profile will be excluded from the PK analysis.

Urine concentrations below lower limit of quantification (LLOQ) will be treated as numerical zero for the calculation of the urine parameters.

8.7.2. Anomalous Values

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

8.7.3. Concentration-Time Data

Individual plasma TERN-201 and metabolite (TRN-001021 and TRN-001744) concentration data will be listed separately for trough concentrations (PK Analysis Set) and trough and intensive concentrations (PK/PD Substudy Analysis Set). Concentrations will be summarized by nominal sampling time point and treatment with descriptive statistics (number of non-missing observations, arithmetic mean, arithmetic SD, arithmetic coefficient of variation [CV%], median, Q1, Q3, minimum, maximum, geometric mean and geometric CV%). The number of values below quantification limit (BLQ) will be presented for all patients and separately for PK/PD substudy patients. Individual urine TERN-201 and metabolite (TRN-001021 and TRN-001744) concentrations and sample volume will be listed for each patient.

The following rules will be applied in the presentation of plasma concentration data if there are values that are BLQ or if there are missing values (e.g., no result [NR]) in a plasma concentration data series to be summarized.

- For the calculation of summary statistics, BLQ values will be set to zero.
- For the calculation of PK parameters, BLQ values will be set to zero prior to the first measurable concentration and set to missing after a measurable concentration is observed.
- If an embedded BLQ value is considered anomalous within the concentration time profile, this value will be excluded from the summary statistics.
- 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.
- If all the values are BLQ, then the arithmetic mean, arithmetic SD, median, minimum and maximum will be presented as zero, and the geometric mean and geometric CV% will be denoted as NC.
- If the value of the arithmetic mean or median is below the lower limit of quantification, these values will be presented as zero and the geometric mean and geometric CV% will be denoted as NC.

Individual patient and arithmetic mean concentration-time profiles, for TERN-201 and its metabolites (TRN-001021 and TRN-001744), for each TERN-201 dose, will be presented graphically on linear and logarithmic concentration scales separately for trough concentrations (PK Analysis Set) and trough and intensive concentrations (PK/PD Substudy Analysis Set) for Week 0/Day 1 and Week 12. A reference line for LLOQ will be included on graphs.

Concentration data in listings will be presented to the same number of significant figures as provided by the analytical laboratory. Descriptive statistics will be displayed according to the rules outlined in Section 3.2.

8.7.4. Plasma Pharmacokinetic Parameters

Sparse PK samples may be used to calculate PK parameters using population pharmacokinetic (Pop PK) modeling. Data from the study may be combined with data from other studies for the

purposes of Pop PK modeling. If Pop PK modeling is performed, the process will be described in a separate analysis plan.

For the purposes of this SAP, plasma PK parameters will be computed for the PK/PD sub-study patients only. Plasma PK parameters for TERN-201 and its metabolites (TRN-001021 and TRN-001744) will be calculated from the individual plasma concentrations using a non-compartmental approach for Week 0/Day 1, Week 6, and Week 12. Week 0/Day 1 and Week 6 will include pre dose and all post dose assessments prior to the next dose. Week 12 will include pre dose and all post dose assessments. The actual PK sampling times will be used for the PK analysis. If actual PK sampling times are missing, nominal times will be used. If the 24 hr sample is missing at Week 6 or Week 12, the predose sample concentration may be re-used for the 24 hr sample for the purposes of calculating PK parameters, if appropriate.

Table 6 presents the plasma PK parameters for TERN-201 and its metabolites (TRN-001021 and TRN-001744) to be calculated.

Table 6: Plasma Pharmacokinetic Parameters

Abbreviation	Parameter Definition
$AUC_{0-\infty}$	For Week 0/Day 1 only, area under the drug concentration-time curve from time zero to infinity, calculated using the linear trapezoidal rule for increasing concentrations and the logarithmic rule for decreasing concentrations as $AUC_{0-tlast} + C_t / \lambda_z$.
$\%AUC_{extrap}$	For Week 0/Day 1 only, percentage of AUC that is due to extrapolation from the last measurable concentration to infinity
AUC_{0-t}	For Week 0/Day 1 only, area under the plasma concentration curve over from time 0 to time t, i.e. from 0 to 24 hours, calculated using the linear trapezoidal rule for increasing concentrations and the logarithmic rule for decreasing concentrations.
AUC_{0-8hr}	For Week 0/Day 1 and Week 6, area under the plasma concentration curve over from time 0 to 8 hours, calculated using the linear trapezoidal rule for increasing concentrations and the logarithmic rule for decreasing concentrations.
AUC_{tau}	For Week 6 and Week 12, area under the plasma concentration curve over a dosing interval, i.e. from 0 to 24 hours, calculated using the linear trapezoidal rule for increasing concentrations and the logarithmic rule for decreasing concentrations.
C_{max}	Maximum observed plasma concentration, obtained directly from the plasma concentration-time profiles within the sampling interval, i.e. calculated for each intensive sampling visit separately (Week 0/Day 1, Week 6, Week 12). In the case where multiple peaks are of equal magnitude, the earliest peak concentration will be reported as C_{max}.
C_{min}	Minimum observed plasma concentration, obtained directly from the plasma concentration-time profiles at steady state, within the sampling interval, i.e. calculated for each intensive sampling visit separately (Week 6 Week 12). In the case where multiple minimums are of equal magnitude, the latest minimum concentration will be reported as C_{min}.

Abbreviation	Parameter Definition
T_{max}	Time of the maximum observed plasma concentration, obtained directly from the plasma concentration-time profiles within the sampling interval, i.e. calculated for each intensive sampling visit separately (Week 0/Day 1, Week 6, Week 12). In the case where multiple peaks are of equal magnitude, the time of the earliest peak will be reported as the $t_{max.}$
T_{min}	Time of the minimum observed plasma concentration, obtained directly from the plasma concentration-time profiles at steady state, within the sampling interval, i.e. calculated for each intensive sampling visit separately (Week 6 Week 12). In the case where multiple minimums are of equal magnitude, the time of the latest minimum will be reported as T_{min}.
T_{last}	Time of the last quantifiable plasma concentration, obtained directly from the plasma concentration-time profiles within the sampling interval, i.e. calculated for each intensive sampling visit separately (Week 0/Day 1, Week 6, Week 12).
$t_{1/2}$	Apparent plasma terminal elimination half-life, calculated as ln(2) / λ_z.
CL/F	Apparent total plasma clearance calculated as Dose / $AUC_{0-\infty}$ for Week 0/Day 1
CL_{ss}/F	Apparent total plasma clearance at steady state, calculated as Dose / AUC_{tau} for Week 6 and Week 12.
V_z/F	Apparent volume of distribution, calculated as Dose / (λ_z * $AUC_{0-\infty}$) for Week 0/Day 1
V_{ss}/F	Apparent volume of distribution, calculated as Dose / (λ_z * AUC_{tau}) for Week 6 and Week 12.
RA_{AUCtau}	Observed accumulation ratio based on AUC_{tau} calculated as $AUC_{tau\ (Week\ 6\ and\ Week\ 12)}$ /$AUC_{0\text{-}24hr\ (Day\ 1)}$.
RA_{Cmax}	Observed accumulation ratio based on C_{max}, calculated as $C_{max\ (Week\ 6\ and\ Week\ 12)}$ /$C_{max\ (Day\ 1)}$.
LR	Linearity ratio calculated as $AUC_{tau\ (Week\ 6\ and\ Week\ 12)}$ / $AUC_{0-\infty\ (Day\ 1)}$
C_{avg}	Average observed drug concentration at steady state (Week 6 and Week 12 only)
C_{24}	For Week 0/Day 1, observed drug concentration at the end of the dosing interval, e.g. from 0 to 24 hours
C_{tau}	Observed drug concentration at the end of the dosing interval, e.g. from 0 to 24 hours (Week 6 and Week 12 only)
λ_z	Apparent terminal rate constant (listed only)

In addition, the metabolite-to-parent ratios will be calculated for AUC_{tau}, C_{tau}, and C_{max}. Metabolite-to-parent ratios will be corrected for molecular weight differences by multiplying the ratio by a correction factor. The correction factor for TRN-001021 ratios is 1.05 and the correction factor for TRN-001744 ratios is 1.42.

Additional PK parameters may be determined where appropriate.

8.7.4.1. Pharmacokinetic Parameter Data Handling

8.7.4.2. 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. Actual times for partial AUC intervals may be used at the discretion of the pharmacokineticist.

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}.

8.7.4.3. Criteria for Calculation and Goodness of Fit

Values for λ_z, $t_{1/2}$, $AUC_{0-\infty}$, CL/F and CL_{ss}/F, V_z/F and V_{ss}/F, and LR will only be reported if the following criteria for the terminal elimination phases (log-linear phase) for the concentration-time data are met:

- A minimum of 3 measurable concentration-time-points during the log-linear portion of the terminal elimination phase (after T_{max}), excluding C_{max}.
- $r^2_{adj} \geq 0.80$ for the regression of the log-concentration time data during the terminal elimination phase.
- Negative slope for log regression fit.

$AUC_{0-\infty}$ values where the percentage extrapolation is greater than 30% will be reported and flagged but excluded from descriptive statistics. Parameters affected by $AUC_{0-\infty}$ such as $t_{1/2}$, CL/F, V_z/F, and LR will be handled the same way as $AUC_{0-\infty}$.

Additional analyses will be performed as deemed necessary upon review of the data.

8.7.5. Statistical Methods for Pharmacokinetic Parameters

Plasma PK parameters will be summarized by treatment group using descriptive statistics (number of non-missing observations, arithmetic mean, SD, median, Q1, Q3, 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.

8.7.6. Urine Pharmacokinetic Parameters

Table 7 presents the urine TERN-201 and its metabolites (TRN-001021 and TRN-001744) PK parameters to be calculated.

Table 7: Urine Pharmacokinetic Parameters

Abbreviation	Parameter Definition
CL_R	Renal clearance, calculated over 0-8 h interval by dividing $Ae_{0\text{-}8h}$ by $AUC_{0\text{-}8h}$, where the 0-8 h interval used is the same for Ae and AUC.
Ae	Amount of drug recovered from urine, amount will be calculated by multiplying urine concentration by urine volume. If the amount of urine is collected as weight rather than volume, Ae will be calculated by assuming a urine density of 1.0 g/mL.
fe	Percentage of dose recovered from urine, percentages will be calculated as Ae/dose ×100.

8.8. Pharmacodynamic (PD) Analyses

Plasma samples will be collected for measurement of VAP-1/SSAO activity and methylamine levels according to the schedule of activities in Section 1.3 of the protocol.

8.8.1. Below the Quantification Level (BLQ) Values

Plasma concentrations that are BLQ will be set to ½ × BLQ.

8.8.2. VAP-1/SSAO Activity Levels and Methylamine Concentration Time Data

Individual plasma VAP-1/SSAO activity levels and methylamine concentration data will be listed separately for trough timepoints (PD Analysis Set) and trough and intensive timepoints (PK/PD Substudy Analysis Set). VAP-1/SSAO activity levels and methylamine concentrations will be summarized by nominal sampling time point and treatment group with descriptive statistics (number of non-missing observations, arithmetic mean, SD, median, Q1, Q3, minimum, maximum, geometric mean and geometric coefficient of variation [CV%]). The number of values BLQ will be presented for all patients and separately for PK/PD substudy patients.

The following rules will be applied in the presentation of plasma VAP-1/SSAO activity levels and methylamine concentration data if there are values that are BLQ or if there are missing values (e.g., no result [NR]) in a data series to be summarized.

- For the calculation of summary statistics, BLQ values will be set to ½ × BLQ.
- 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.
- If all the values are BLQ, then the arithmetic mean, arithmetic SD, median, minimum and maximum will be presented as ½ × BLQ, and the geometric mean and geometric CV% will be denoted as NC.

Individual patient, arithmetic mean VAP-1/SSAO activity levels and methylamine concentration -time profiles, for each TERN-201 dose, will be presented graphically on linear and logarithmic

scales separately for trough timepoints (PD Analysis Set) and trough and intensive timepoints (PK/PD Substudy Analysis Set) patients for Week 0/Day 1, Week 6, and Week 12. A reference line for LLOQ will be included on graphs.

VAP-1/SSAO activity levels and methylamine concentration data in listings will be presented to the same number of significant figures as provided by the analytical laboratory. Descriptive statistics will be displayed according to the rules outlined in Section 4.1.

8.8.3. Change from Baseline

Descriptive statistics of VAP-1/SSAO activity and methylamine values, change from baseline, and percent change from baseline values will be presented by treatment group for each visit separately using the PD Analysis Set for trough timepoints and using the PK/PD Analysis Set for trough and intensive timepoints. Baseline is defined as the Week 0/Day 1 pre-dose value.

Analyses of change (and separately percent change) from baseline will be carried out using an ANCOVA model at time point with change (and separately percent change) from baseline as the dependent variable including treatment group and randomization strata as fixed effects and baseline as a covariate.

The estimates of least-square (LS) means, standard errors (SE), and 90% 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 90% and 95% CIs of the difference.

Figures of LS mean (±SE) change from baseline, and percent change from the ANCOVA model will be presented over time by treatment group.

Analyses to explore the correlation of plasma VAP-1/SSAO activity and methylamine changes with liver function tests, LFC, cT1, and other biomarker changes may be evaluated.

8.8.4. Plasma PD Parameters

Plasma PD parameters will be computed for PK/PD sub-study patients only. Plasma PD parameters for plasma VAP-1/SSAO activity and methylamine will be calculated from the individual plasma VAP-1/SSAO activities and methylamine concentrations using a non-compartmental approach for Week 0/Day 1, Week 6, and Week 12. Week 0/Day 1 and Week 6 will include pre-dose and all post dose assessments prior to the next dose. 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 8 and Table 9 present the plasma PD parameters to be calculated.

Table 8: VAP-1/SSAO Plasma PD Parameters

Abbreviation	Parameter Definition
$AAUC_{tau}$	Area under curve for VAP-1/SSAO activity, calculated separately for the value, change from baseline, and percent change from baseline over a dosing interval, i.e. from 0 to 24 hours, calculated using the linear trapezoidal rule.

Abbreviation	Parameter Definition
A_{min}	Minimum observed VAP-1/SSAO activity, calculated separately for the value, change from baseline, and percent change from baseline, obtained directly from the plasma VAP-1/SSAO activity time profiles. In the case where multiple minimums are of equal magnitude, the earliest minimum values will be reported as A_{min}.
A_{max}	Maximum observed VAP-1/SSAO activity, calculated separately for the value, change from baseline, and percent change from baseline, obtained directly from the plasma VAP-1/SSAO activity time profiles. In the case where multiple maximums are of equal magnitude, the earliest maximum values will be reported as A_{max}.
AT_{min}	Time of the minimum observed VAP-1/SSAO activity, calculated separately for the value, change from baseline, and percent change from baseline, obtained directly from the plasma VAP-1/SSAO activity time profiles. In the case where multiple minimums are of equal magnitude, the time of the earliest minimum will be reported as the $AT_{min.}$
AT_{max}	Time of the maximum observed VAP-1/SSAO activity (and separately, change and percent change from baseline), obtained directly from the plasma VAP-1/SSAO activity and methylamine concentration-time profiles. In the case where multiple maximums are of equal magnitude, the time of the earliest maximums will be reported as the $AT_{max.}$
AT_{last}	Time of the last quantifiable VAP-1/SSAO activity value
A_{avg}	Average observed VAP-1/SSAO activity, calculated separately for the value, change from baseline, and percent change from baseline at steady state (Week 6 and Week 12 only)

Table 9: Methylamine Plasma PD Parameters

Abbreviation	Parameter Definition
AUC_{tau}	Area under curve for methylamine concentration (and separately, change and percent change from baseline) over a dosing interval, i.e. from 0 to 24 hours, calculated using the linear trapezoidal rule.
C_{min}	Minimum observed methylamine concentration (and separately, change and percent change from baseline) obtained directly from the plasma methylamine concentration-time profiles. In the case where multiple minimums are of equal magnitude, the earliest minimum values will be reported as C_{min}.
C_{max}	Maximum observed methylamine concentration (and separately, change and percent change from baseline) obtained directly from the plasma methylamine concentration-time profiles. In the case where multiple maximums are of equal magnitude, the earliest maximum values will be reported as C_{max}.
T_{min}	Time of the minimum observed methylamine concentration (and separately, change and percent change from baseline), obtained directly from the plasma and methylamine 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}	Time of the maximum observed methylamine concentration (and separately, change and percent change from baseline), obtained directly from the plasma methylamine concentration-time profiles. In the case where multiple maximums are of equal magnitude, the time of the earliest maximums will be reported as the $T_{max.}$
T_{last}	Time of the last quantifiable methylamine concentration
C_{avg}	Average observed methylamine concentration (and separately, change and percent change from baseline) at steady state (Week 6 and Week 12 only)

8.8.4.1. PD Parameter Data Handling

8.8.4.2. Calculation of AUC

AUCs will be calculated using linear 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 VAP-1/SSAO activity or methylamine concentrations above the LLOQ.

8.8.4.3. 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, Q1, Q3, 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 pre-dose/trough values for plasma VAP-1/SSAO activity (A_{avg} and A_{min}) and methylamine (C_{avg} and C_{max}) at Week 0/Day 1, Week 6, and Week 12 will be carried out using an ANCOVA model with the PD parameter as the dependent variable including treatment group as a fixed effect and baseline VAP-1/SSAO activity or methylamine concentration as a covariate. The model will be carried out separately for the PD parameter based on the VAP-1/SSAO activity and methylamine value, change from baseline, and percent change from baseline. The estimates of LS means, SE, and 90% 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 90% and 95% CIs of the difference.

The distribution of parameter values will be evaluated visually for normality assumptions. If normality assumptions are violated, first the data will be natural log transformed and the log transformed data evaluated for normality. If the log transformed data are normally distributed, the same ANOVA model described above will be used.

8.8.4.4. Dose Response

If Part 2 enrolls, dose-response may be evaluated, if the data warrants, based on the pairwise comparisons of pre-dose/trough values for plasma VAP-1/SSAO activity (A_{avg} and A_{min}) and methylamine concentration (C_{avg} and C_{max}) from the ANCOVA models specified above (Section 8.8.4.3). In addition, pre-dose/trough VAP-1/SSAO activity (A_{avg} and A_{min}) and methylamine concentration (C_{avg} and C_{max}) will also be plotted by treatment group based on values, change from baseline, and percent change from baseline.

Dose response will also be evaluated using a REML based MMRM. The dependent variable will be the percent change (separately for change) from baseline for plasma VAP-1/SSAO activity and methylamine. The model will include the following fixed effects:

- Treatment group (4 levels: placebo [0 mg], 4 mg, 10 mg, 20 mg)
- Categorical time
- Treatment group by time interaction
- Baseline value

An unstructured covariance model will be used. If the computational algorithm fails to converge, the following structures will be executed: heterogeneous Toeplitz, heterogeneous First-Order Autoregressive [AR (1)], heterogeneous compound symmetry (HCS), Toeplitz, AR(1), and compound symmetry (CS). The covariance structure converging to the best fit, as determined by Akaike's information criterion (AIC, the smaller the AIC value the better the model fit), will be used. If the model converges with an unstructured covariance matrix, the Kenward and Roger method will be used to calculate the denominator degrees of freedom for the test of fixed effects. If a structured covariance is used, then a robust sandwich estimator will be utilized for estimating the variance of the treatment effect estimate.

8.9. Exposure Response Analyses

The plasma PK parameters AUC_{tau}, C_{max}, and C_{tau} will be used to evaluate exposure-response. PK parameters will be set to 0 for the placebo group for the purpose of PK/PD.

Pharmacodynamic exposure-response analyses of plasma VAP-1/SSAO activity and methylamine concentration PD parameters will be performed using several exposure-response models for the PK/PD Analysis Set, including but not limited to linear, quadratic, exponential, and E_{max}. The best fit significant model will be chosen based on AIC, the smaller the AIC value the better the model fit.

Additional exposure-response and dose-response (as applicable) analyses may be explored for baseline patient characteristics such as sVAP-1, BMI, diabetes mellitus, or other characteristics or additional efficacy, safety, and PD endpoints, as needed. These analyses will be described in a separate document.

8.10. Exploratory Efficacy Analyses

8.10.1. Magnetic Resonance Imaging

MRIs will be evaluated by a central reader. The following analyses of MRI will use the Efficacy Analysis Set. Sensitivity analyses using the PP and Treatment Completer Analysis Sets will be presented if the analysis set differs from the Efficacy Analysis Set by more than 10% total.

8.10.1.1. Corrected T1 (cT1)

cT1 related to the amount of extracellular fluid present in the liver parenchyma. cT1 is derived from T1 and T2* maps. T1 is a measure of the longitudinal (spin-lattice) relaxation time, measured in milliseconds (msec), of a given substance. The T1 of a tissue depends on its free water content, which relates to the proportion of the extracellular fluid in the tissue.

Proton-dense tissues with a low water content, such as fat, have very short T1 values, while tissues with a high water content, such as muscle and the spleen have much longer T1 values. When tissue is inflamed or scarred (fibrotic), changes in the structural organization of the tissue, due to tissue remodeling, mean that the water content increases, leading to longer T1 values.

cT1 is measured in milliseconds (msec). The cT1 metric is calculated from all pixels with whole slice ROIs placed on the cT1 parametric map. The cT1 metric is displayed as a median and IQR, the median will be used in all analyses.

Analyses of cT1 will be based on the Efficacy Analysis Set. Descriptive statistics of the cT1 values, change from baseline, and percent change will be summarized by treatment group and visit.

Analyses of change (and separately percent change) from baseline will be carried out using an ANCOVA model at each scheduled visit with change (and separately percent change) from baseline as the dependent variable including treatment group and randomization strata as fixed effects and baseline as a covariate.

The estimates of least-square (LS) means, standard errors (SE), and 90% 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 90% and 95% CIs of the difference.

The primary analysis of change (and separately percent change) at Week 12 will be carried out using available observed data only, without imputation for missing data. The same ANCOVA

model will be used to present the last on treatment value for Week 12, to be labelled as "Week 12/End of Treatment". For 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.

The distribution of change (percent change) values will be evaluated visually for normality assumptions. If normality assumptions are violated, first the data will be natural log transformed and the log transformed data evaluated for normality. If the data are not normally distributed, a Wilcoxon Rank Sum Test will be used to compare treatment groups. The median differences and 90% and 95% CIs of the median differences between treatment groups will be constructed using Hodges-Lehmann estimate.

Sensitivity analyses using the PP and Treatment Completer Analysis Sets will be presented if the analysis set differs from the Efficacy Analysis Set by more than 10% total.

cT1 will be categorized as low (<800 msec), elevated (800 – 900 msec), and high (>900 msec). A shift table from baseline to Week 6 and baseline to Week 12 will be presented by treatment group.

In addition, cT1 responders will be defined as any patient with a decrease of at least 80 msec. Non-responders will be defined as any patient who did not have at least an 80 msec decrease. For both endpoints, the number and percentage, with associated two-sided exact (Clopper-Pearson) 90 and 95% CIs, of patients in each category will be presented by treatment group at each post-baseline visit. A Chi-square test at each post-baseline visit will be used to compare each pairwise comparison between placebo and each active dose of TERN-201.

The number and percentage of patients who are responders on cT1 and ALT will be summarized and analyzed in the same manner as responders.

8.10.1.2. Liver Fat Content by MRI Proton Density Fat Fraction (PDFF)

Liver fat content (LFC) or proton density fat fraction (PDFF) is an estimate of the percentage of fat within a tissue. It is defined as the proportion of the mobile proton density in the liver attributable to fat. PDFF is quantified from the ratio of fat/(fat+water) components in images and is expressed as a percentage (%). The PDFF metric on the quantitative analysis output is a summarized metric from the individual pixels within all of the region of interests (ROIs) placed on the PDFF parametric map or an average of all the pixels within the contour generated by automatic liver segmentation. The PDFF metric is displayed as a median and interquartile range (IQR), the median will be used in all analyses.

Analyses of liver fat content (LFC) by MRI by MRI-PDFF will be based on the Efficacy Analysis Set. For the purposes of LFC analyses, absolute change is equivalent to change and relative change is equivalent to percent change (see Section 4.5). Descriptive statistics of the LFC by MRI-PDFF results, absolute change from baseline, and relative change will be summarized by treatment group and visit.

LFC by MRI-PDFF will be analyzed in the same manner as LFC (Section 8.10.1.1). LFC by MRI-PDFF responders will be defined as any patient with a relative decrease of at least 30% (i.e., ≤-30%). Non-responders will be defined as any patient who did not have at least a 30% relative decrease (i.e., >-30%). The number and percentage, with associated two-sided exact (Clopper-Pearson) 90% and 95% CIs, of patients in each category (response, nonresponse) will

be presented by treatment group at Week 6 and Week 12. A Chi-square test at Week 6 and Week 12 will be used to compare each pairwise comparison between placebo and each active dose of TERN-201.

8.10.2. Transient Elastography

Liver stiffness and CAP are measured by transient elastography. Descriptive statistics of biomarker values, change from baseline, and percent change from baseline will be presented by treatment group for each visit, at which data are collected, using the Efficacy Analysis Set.

Change (and separately for percent change) from baseline in liver stiffness will be analyzed using the same ANCOVA model presented in Section 8.10.1.1 for each post-baseline and follow up visit using observed data only. Sensitivity analyses using the PP and Treatment Completer Analysis Sets will be presented if the analysis set differs from the Efficacy Analysis Set by more than 10% total.

Assessments of normality will be performed as described in Section 8.10.1.1.

8.10.3. Liver Function Tests

LFTs for efficacy analyses include AST, ALT, and GGT. Descriptive statistics of LFT values, change from baseline, and percent change from baseline values will be presented by treatment group for each visit using the Efficacy Analysis Set.

Change (and separately for percent change) from baseline will be analyzed using the same ANCOVA model presented in Section 8.10.1.1 for each post-baseline and follow up visit using observed data only. Sensitivity analyses using the PP and Treatment Completer Analysis Sets will be presented if the analysis set differs from the Efficacy Analysis Set by more than 10% total.

Assessments of normality will be performed as described in Section 8.10.1.1.

Figures of LS mean (±SE) change from baseline, and percent change from the ANCOVA model will be presented over time by treatment group.

8.10.3.1. Change from End of Treatment in ALT

The change (and separately percent change) from end of treatment to follow up visit (Week 16) will be summarized by treatment group. For patients who complete Week 12, the Week 12 value will be used for End of Treatment. For patients who do not complete treatment, the last value on treatment will be used for End of Treatment. Descriptive statistics of ALT values, change from end of treatment, and percent change from end of treatment will be presented by treatment group for each visit using the Efficacy Analysis Set.

Change (and separately for percent change) from end of treatment in ALT will be analyzed using the same ANCOVA model presented in Section 8.10.1.1 for each follow up visit using observed data only. Assessments of normality will be performed as described in Section 8.10.1.1. Sensitivity analyses using the PP and Treatment Completer Analysis Sets will be presented if the analysis set differs from the Efficacy Analysis Set by more than 10% total.

Sensitivity analyses will be conducted including only Week 16 assessments which are at least 22 days from last dose.

8.10.4. NASH and Fibrosis Biomarkers

Markers of hepatic fibrosis and apoptosis include CK-18 (M30 and M65), PIIINP, TIMP-1, HA, PRO-C3, and C3M. The PRO-C3/C3M ratio will be calculated. Descriptive statistics of biomarker values, change from baseline, and percent change from baseline will be presented by treatment group for each visit using the Efficacy Analysis Set.

Change (and separately for percent change) from baseline will be analyzed using the same ANCOVA model presented in Section 8.10.1.1 for each post-baseline and follow up visit using observed data only. Sensitivity analyses using the PP and Treatment Completer Analysis Sets will be presented if the analysis set differs from the Efficacy Analysis Set by more than 10% total.

Assessments of normality will be performed as described in Section 8.10.1.1.

8.10.4.1. Enhanced Liver Fibrosis (ELF) Score

The enhanced liver fibrosis (ELF) score will be calculated as: 2.278+0.851 ln (HA) +0.751 ln (PIIINP) +0.394 ln (TIMP-1). Lab values from the same visit will be used to calculate the ELF score. The ELF score will be calculated at baseline and each post-baseline visit.

The ELF score will be analyzed in the same manner as specified in Section 8.10.4.

8.10.4.2. 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: [Age (years) × AST (U/L)] ÷ [Platelet Count (10^9/L) × ALT (U/L)$^{0.5}$]. Age at screening will be used. Lab values at each visit, from the same visit, will be used. The FIB-4 score will be calculated at baseline and each post-baseline visit.

The FIB-4 score will be analyzed in the same manner as specified in Section 8.10.4.

8.10.4.3. 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/m^2) + 1.13 × diabetes status (yes = 1, no = 0) + 0.99 × AST/ALT ratio - 0.013 × Platelet Count (10^9/L) - 0.66 × Albumin (g/dL). Age and diabetes status at informed consent will be used. BMI at each visit will be calculated using the weight from that visit and height from screening. Lab values at each visit, from the same visit, will be used. The NAFLD fibrosis score will be calculated at baseline and each post-baseline visit.

The NAFLD fibrosis score will be analyzed in the same manner as specified in Section 8.10.4.

8.10.5. Inflammation Biomarkers

Markers of inflammation include hs-CRP, IL-6, ICAM-1, and VCAM-1, which will be analyzed in the same manner as specified in Section 8.10.4.

8.10.6. Proteinuria Biomarkers

Proteinuria biomarkers include estimated glomerular filtration rate (eGFR), urine protein including urine protein-to-creatinine ratio (UPCR), and urine albumin-to-creatinine ratio (UACR), which will be analyzed in the same manner as specified in Section 8.10.4.

8.10.7. Anthropometric Measures

Anthropometric measures include body weight (kg) and BMI (kg/m^2). BMI will be programmatically calculated for every visit where there is a weight collected, using the screening height. Weight will be analyzed in the same manner as specified in Section 8.10.4.

Percent change in weight will be categorized as follows:

- At Least 5% Decrease
- All Other Patients (minor decrease [up to 5%], stable, or increase)

The number and percentage, with associated two-sided exact (Clopper-Pearson) 90 and 95% CIs, of patients in each category will be presented by treatment group. P-values from a Chi-square test will be presented for each pairwise comparison.

8.10.8. Dose Response

Dose-response analyses for ALT, AST, GGT, cT1, MRI-PDFF, CK-18 (M30 and M65), PRO-C3, C3M, and PROro-C3/C3M ratio will be performed using the same methodology specified in Section 8.8.4.4.

9. SAFETY ANALYSES

Safety analyses will be conducted using the Safety Analysis Set.

No inferential comparison of safety endpoints will be performed, unless otherwise specified.

9.1. 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 (last date study drug administration – the first date study drug administration + 1) – 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.

Treatment compliance will be calculated based on the Study Drug Administration and Study Drug Interruptions CRFs and separately based on the Study Drug Accountability CRF.

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 missed dose durations) / (last date study drug administration – the first date study drug administration + 1)].

Compliance based on study drug accountability will be calculated as:

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

For Part 2, capsules will be summed across the 2 bottles at each week.

For subjects in Part 1, expected taken is calculated as the study day of the last dose date. For subjects in Part 2, expected taken is calculated as the study day of the last dose date × 2. Each treatment compliance will be summarized with descriptive statistics by treatment group. Number and percent 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 compliances will be presented in by-patient data listings. Compliance with fasting conditions will be presented in a separate by-patient data listings.

9.2. 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 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.

9.2.1. 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
- TEAE by Maximum Severity
- 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 discontinued
- TEAE leading to discontinuation from the study

9.2.2. Patient Incidence of Adverse Events

Summaries will be displayed by SOC and PT, and will be ordered by descending order of all TERN-201 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 non-COVID TEAEs for patients who have a TEAE of COVID-19.
- 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.
- Patient incidence of TEAEs leading to study drug discontinued by MedDRA SOC and PT. This is a subset of the AEs where Action Taken with Study Drug is checked as “Drug Withdrawn.”

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").
- 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 "Related" or "Possibly Related").
- 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 discontinued (subset of the AEs where Action Taken with Study Drug is checked as "Drug Withdrawn").
- Adverse events leading to death (subset of the AEs where outcome is indicated as "Fatal" or the CTCAE grade is 5 or seriousness criteria is Death).

9.3. 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 serum chemistry, fasting lipids, and hematology 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.

Values determined to be erroneous will be documented in the trial master file and analysis data reviewer's guide. Erroneous values will not be included in summary tables or analyses but will be included in patient listings.

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. Any local laboratory normal ranges for COVID-19 will be presented separately.

9.3.1. 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 worsening of ≥2 grades.

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

Listings will be presented for any patient with any treatment emergent laboratory abnormality (any increase in CTCAE grade). Normal ranges provided by the central laboratory will be presented in a listing.

9.3.2. Assessments of Potential Drug Induced Liver Injury

Modified Hy's rule by Bjornsson (Bjornsson 2005) is defined as patients with ALT or AST values >3x ULN and total bilirubin >2x ULN (based on the same blood draw of ALT, AST, and total bilirubin while on study drug, or within 30 days of last received dose) will be used to assess the potential for study drug-induced liver toxicity. Any patient meeting the criteria will be presented in a by-patient listing.

The criteria for increased laboratory monitoring or consideration for study drug discontinuation on study are specified in protocol appendix 3 and will be included in the analysis dataset and listed.

9.3.3. Shifts in CTCAE Grade

Quantitative laboratory tests will be assigned grades based on National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) Version 5. Shifts in CTCAE grade of laboratory tests will be presented from baseline to worst post-baseline value. Summaries will present the number and percentage of patients with shifts in laboratory grade by treatment group. Denominators for percentages will be the number of patients with non-missing data at the specific assessment and baseline.

Some lab tests include additional clinical criteria which cannot be determined programmatically. Table 10 below specifies the grade with clinical criteria in italics. The text in italics will not be considered when assigning grades programmatically.

Table 10: CTCAE Laboratory Tests with Clinical Criteria

Bicarbonate (Blood bicarbonate decreased): • Grade 1: <LLN *and no intervention initiated*.
Prothrombin Time (PT)/International Normalized Ratio (INR) (INR increased): • Grade 1: >1.2 - 1.5; *>1 - 1.5 x baseline if on anticoagulation; monitoring only indicated* • Grade 2: >1.5 - 2.5; *>1.5 - 2.5 x baseline if on anticoagulation; dose adjustment indicated* • Grade 3: >2.5; *>2.5 x baseline if on anticoagulation; bleeding*
eGFR (Chronic Kidney Disease): • Grade 4: <15 ml/min/1.73m^2; *dialysis or renal transplant indicated*
Glucose (Hypoglycemia): • Grade 4: <30 mg/dL; <1.7 mmol/L; *life-threatening consequences; seizures*.

Potassium (Hypokalemia) • *Grade 2: Symptomatic with <LLN - 3.0 mmol/L; intervention indicated* • Grade 3: <3.0 - 2.5 mmol/L; *hospitalization indicated* • Grade 4: <2.5 mmol/L; *life-threatening consequences*
Potassium (Hyperkalemia) • Grade 2: >5.5 - 6.0 mmol/L; *intervention initiated* • Grade 3: >6.0 - 7.0 mmol/L; *hospitalization indicated* • Grade 4: >7.0 mmol/L; *life-threatening consequences*
Sodium (Hyponatremia) • Grade 2: 125-129 mmol/L *and asymptomatic* • Grade 3: *125-129 mmol/L symptomatic;* 120-124 mmol/L regardless of symptoms • Grade 4: <120 mmol/L; *life-threatening consequences*
Sodium (Hypernatremia) • Grade 2: >150 - 155 mmol/L; *intervention initiated* • Grade 3: >155 - 160 mmol/L; *hospitalization indicated* • Grade 4: >160 mmol/L; *life-threatening consequences*
Albumin (Hypoalbuminemia) • *Grade 4: Life-threatening consequences; urgent intervention indicated.*

9.3.4. COVID-19

SARS-CoV-2 test for active infection and SARS-CoV-2 antibody test results, using central and local labs, will be presented in by-patient listings. A separate listing for central and local laboratory normal ranges by lab test, lab parameter, sex, and age will be presented.

9.4. Vital Signs

Temperature, pulse rate, respiratory rate, and blood pressure will be assessed and maintained in source documentation, not reported in the EDC, and therefore will not be included in analyses. Any clinically significant abnormalities will be reported as adverse events.

9.5. Electrocardiograms

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.

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.

10. 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 and re-consents
- Randomization schema
- Alcohol use
- Physical examination collection information
- Serology
- Pregnancy testing
- FSH test
- Urine drug screen
- Alcohol test
- Urinalysis and Urine Microscopic Examination
- Cardiology consult
- Overdose
- Comments

11. CHANGES TO PROTOCOL PLANNED ANALYSES

Additional exploratory efficacy endpoints were added.

12. REFERENCES

Guidance for Industry *E3: Statistical Principles for Clinical Trials*. U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER), September 1998.

Guidance for Industry *E9: Statistical Principles for Clinical Trials*. U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER), September 1998.

Guidance for Industry: *Drug Induced Liver Injury: Premarketing Clinical Evaluation*, CDER, FDA (2009).

Guidance for Industry: *Providing Regulatory Submissions in Electronic Format — Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications*, Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER), September 2016.

13. APPENDICES

APPENDIX 1. OTHER GENERAL PROGRAMMING SPECIFICATIONS

1. All output will have the following two-line header at the upper left margin:

   ```
   Terns, Inc.
   TERN201-1007
   ```

   and the following header at the upper right margin:

   ```
   DRAFT/FINAL (as appropriate)

   Page x of y
   ```

2. Each table should be identified by in a sequential numeric order, and the table designation should be centered above the title. A decimal system within the numeric numbering (i.e., x.y and x.y.z) should be used to identify tables, listings and figures with related contents. The title is centered in initial capital characters and should include the analysis set analyzed (e.g. SS). The title and table designation are single-spaced, but are separated from the table by at least a double space.

   Table No.
   First Line of Title
   Second Line of Title (if needed)
   (Analysis Set Analyzed)

3. Row labels and column headings will be in title/proper case, unless otherwise specified.
4. For variables with numeric values, include "unit" in the row label or column heading when appropriate.
5. Footnotes should be ordered as follows: abbreviations, single space, general notes, single space, specific numeric footnotes, single space, reference, and with final footnote as program name and date of the program run. The notes are aligned vertically by the left vertical border of the table. All output should have at least the footnote about the program name and date of the program run.

   Abbreviations:

   Notes:

   [1] Footnote 1
   [2] Footnote 2
   [3] Footnote 3

   Reference Listing:
   PROGRAM: program file name DDMMMYYYY HH:MM

6. All tables will include a Reference Footnote. All figures will include a Reference Table.
7. Unless specified otherwise, all data listings should be sorted by treatment group, followed by patient number with the study center, and by visit date within patient, where appropriate.
8. All fractional numeric values should be printed with a zero to the left of the decimal point (e.g., 0.12, 0.3), unless otherwise specified.
9. Missing descriptive statistics due to non-estimability in tables, as well as missing data in patient listings should be represented as either a hyphen ("-") with a corresponding footnote

(“ - = unknown or not evaluated”), or as “N/A” with the footnote “N/A = not applicable” whichever is appropriate.

10. Dates printed as a result in the table, listing, or graph should be printed in SAS DATE9. format (“DDMONYYYY”, e.g. 01JUL2002). Missing portions of dates should be represented on patient listings as dashes (--JUL1999). Dates that are missing because they are not applicable for the patient should be listed as “N/A”, unless otherwise specified.

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/CM 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/CM start date

AE = adverse event, Dec = December, Jan = January

APPENDIX 3. ABBREVIATIONS

Abbreviation or Special Term	Explanation
ADaM	Analysis Data Model
ADL	activities of daily living
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine transaminase
ANCOVA	analysis of covariance
AST	aspartate transaminase
ATC	Anatomical Therapeutic Class
AUC	area under the concentration-time curve
BMI	body mass index
BLQ	below quantification limit
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
C_{max}	maximal concentration
CRF	case report form
CSR	clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
CTMS	clinical trial management system
CYP	Cytochrome P450
CV	coefficient of variation
DBL	database lock
eGFR	estimated glomerular filtration rate
eCRF	electronic case report form
ECG	electrocardiogram
ET	early termination
FDA	Food and Drug Administration
FSH	follicle stimulating hormone
GCP	Good Clinical Practice
GGT	gamma-glutamyl transpeptidase
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

Abbreviation or Special Term	Explanation
INR	international normalized ratio
IWRS	interactive web response system
LDL	low-density lipoprotein
LFC	liver fat content
LFT	liver function test
LLN	lower limit of normal
ln	natural log
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 peptide
PD	pharmacodynamics
PK	pharmacokinetics
PRO-C3	pro-peptide of type III collagen
Q1	25^{th} percentile, first quartile
Q3	75^{th} percentile, third quartile
REML	restricted maximum likelihood
SAE	serious adverse event
SAP	statistical analysis plan
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SD	standard deviation
SDTM	Study Data Tabulation Model
SE	least squares mean standard error
TEAE	treatment emergent adverse event
TIMP-1	tissue inhibitor of metalloproteinases-1
ULN	upper limit of normal
WHODD	World Health Organization Drug Dictionary

APPENDIX 4. DOCUMENT HISTORY

Version	Date	Author	Description
1.0	[redacted]	[redacted] DrPH Statistical Consultant Terns, Inc.	Final Version 1

APPENDIX 5. APPROVAL PAGE

I confirm that I have reviewed this document and agree with the content.

APPROVALS		
Terns, Inc. (Sponsor)		
[redacted] Statistical Consultant DocuSigned by: [redacted] Signer Name: [redacted] Signing Reason: I approve this documen Signing Time: 22-Nov-2021 | 7:26:44 PM PST 2FE1E9C77EE646E3862A1F07DBEFEFC9		**Date** (dd-mmm-yyyy) 22-Nov-2021
[redacted] President & Chief Medical Officer DocuSigned by: [redacted] Signer Name: [redacted] Signing Reason: I approve this document Signing Time: 19-Nov-2021 | 10:30:35 AM PST C0295B0FF2C2450A81545974727EDF5E		**Date** (dd-mmm-yyyy) 19-Nov-2021
[redacted] Executive Director, Clinical Research and Medical Affairs DocuSigned by: [redacted] Signer Name: [redacted] Signing Reason: I approve this document Signing Time: 21-Nov-2021 | 3:39:36 PM PST 15978E5F9A184B9DA6ECA4AD72D4FCF3		**Date** (dd-mmm-yyyy) 21-Nov-2021
[redacted] Senior Director, Clinical Pharmacology DocuSigned by: [redacted] Signer Name: [redacted] Signing Reason: I approve this document Signing Time: 19-Nov-2021 | 1:27:41 PM PST 9FFBBB6BA2554868BCD03D7C85FD2420		**Date** (dd-mmm-yyyy) 19-Nov-2021
[redacted] ***(Contract Research Organization)***		
[redacted] Statistician DocuSigned by: [redacted] Signer Name: [redacted] Signing Reason: I approve this document Signing Time: 28-Nov-2021 | 6:44:57 PM PST A3B474136[redacted]1918B68430790B		**Date** (dd-mmm-yyyy) 28-Nov-2021
[redacted] Vice President, Biometrics [redacted]d by: [redacted] Signing Reason: I approve this document Signing Time: 29-Nov-2021 | 8:57:02 PM EST 668170BCD00947268609A2C5D2CBF6C0		**Date** (dd-mmm-yyyy) 29-Nov-2021