Statistical Analysis Plan

Protocol Title:	A Phase 2 Study to Evaluate the Efficacy, Safety, and Tolerability of TERN-601 in Adults with Overweight or Obesity
Compound:	TERN-601
US FDA IND	[redacted]
ClinicalTrials.gov Identifier:	NCT06854952
Protocol Versions and Dates:	Amendment 2, 04 June 2025
Phase:	2
Methodology:	Dose-ranging, Randomized, Double-blind, Placebo-controlled
Sponsor:	Terns Pharmaceuticals, Inc. 1065 E. Hillsdale Blvd. Suite 100 Foster City, California 94404
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Analysis Plan Version:	Final

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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 TERN601-2003. 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 13. Any post-hoc or unplanned analyses, or significant changes from the planned analysis in this SAP, performed to provide results for inclusion in the 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 and Endpoints

Primary Objective	**Primary Endpoint**
To evaluate the effect of TERN-601 on body weight relative to placebo	• Percent change in body weight from baseline at Week 12
	Secondary Endpoints
	• Change in body weight from baseline at Week 12 • Proportion of participants achieving ≥5% weight loss
	Exploratory Endpoint
	• Proportion of participants achieving ≥10% or ≥15% weight loss
Secondary Objective	**Secondary Endpoints**
To assess the safety and tolerability of TERN-601	• Participant incidence of TEAEs • Change from baseline in laboratory parameters • Change from baseline in ECG parameters • Change from baseline in vital sign parameters
Exploratory Objectives	**Exploratory Endpoints**
To evaluate the PK of TERN-601	• PK parameters (e.g., AUC, C_{max}, C_{tau})
To assess the effect of TERN-601 on glycemic control	• Change from baseline in fasting glucose and HbA1c
To evaluate the effect of TERN-601 on waist circumference	• Change from baseline in waist circumference and waist-to-hip ratio

To evaluate the effect of TERN-601 on quality of life	• Change from baseline in IWQOL-Lite-CT
To evaluate the effect of TERN-601 on cardiovascular risk factors	• Change from baseline in fasting lipids, NT-proBNP, hs-CRP, and blood pressure
To evaluate the effect of different titration schedules of TERN-601 on GI tolerability	• Nausea burden score

AUC = area under the concentration-time curve; C_{max} = maximum observed plasma concentration; C_{tau} = steady-state plasma dosing concentration at the end of the dosing interval; ECG = electrocardiogram; GI = gastrointestinal; HbA1c = hemoglobin A1c; hs-CRP = high-sensitivity C-reactive protein; IWQOL-Lite-CT = Impact of Weight on Quality of Life - Lite - Clinical Trials Version; NT-proBNP = N-terminal pro-B-type natriuretic peptide; PK = pharmacokinetic; TEAE = treatment emergent adverse event

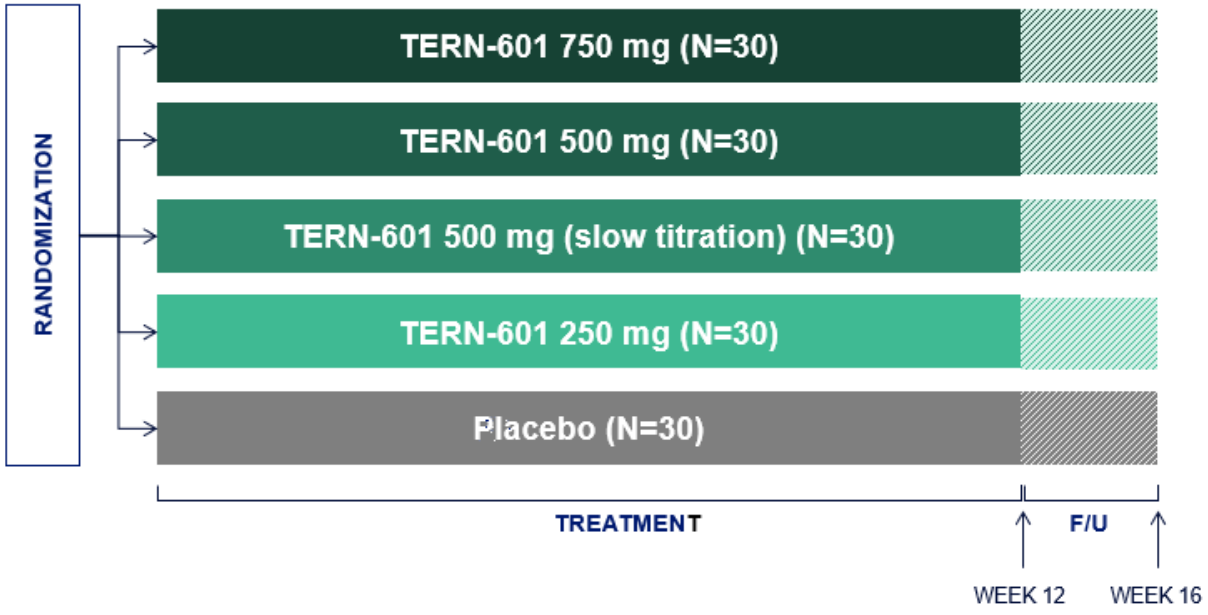
2.2. Study Design

This is a Phase 2, multi-center, dose-ranging, randomized, double-blind study of TERN-601 in non-diabetic adults with overweight or obesity. Treatment with study drug is for 12 weeks, including the titration period, with a 4-week post-treatment follow-up period.

Approximately 150 participants will be randomly assigned to one of four titration schedules of TERN-601 or placebo-to-match for an estimated total of 30 evaluable participants per intervention group. The optional PK sub-study will consist of approximately 30 participants.

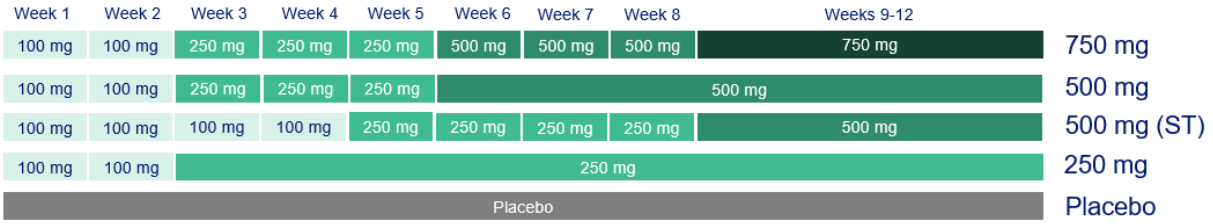
Each participant will be randomly assigned to one of five treatment arms in a 1:1:1:1:1 manner. All treatments will be administered orally once daily without regard to food. Dose interruptions and/or dose reductions will be allowed for the management of adverse events (AEs). Each participant will be on study approximately 20 weeks, including a ≤ 4-week screening period, a 12-week treatment period, and a 4-week follow-up period.

Figure 1: Treatment Arms



F/U = Follow-up

Figure 2: Treatment Arm Dose Titration Schedules



ST = slow titration

2.2.1. Randomization and Blinding

Participants will be randomized to 1 of 4 TERN-601 arms (i.e., 250 mg, 500 mg (ST), 500 mg, or 750 mg) or placebo using an Interactive Response Technology (IRT) system.

Approximately 150 participants will be randomized 1:1:1:1:1 into one of the 5 treatment groups (N=30 per group) to receive TERN-601 or placebo once daily. Randomization will be stratified. by body mass index (BMI) (≤35, >35 kg/m^2 at Randomization) and sex (female, male) to ensure a similar distribution of BMI and an approximately equal distribution of female participants across the 5 treatment groups. Note, this stratification does not require an equal distribution of males and females in the study as a whole. Because this study involves blinded dose titration, which varies by treatment group, Investigators will use IRT to assign the kit(s) numbers to each participant at visits as defined in the Schedule of Activities (SoA). Each kit will be uniquely labeled with a randomized kit number and will contain three bottles which will have an assigned bottle number for each bottle. The bottle number will be derived from the randomized kit number followed by an -A, -B or -C. For each dose administration, the participant should be instructed to take a single tablet from each of the three bottles (3 tablets total) each day.

All personnel directly involved in the conduct of the study (i.e., Investigators, participants, all study personnel, Medical Monitor, and the Sponsor) will remain blinded to each participant's assigned treatment and dosage throughout the course of the study. Individuals in investigational product (IP) packaging and labeling who have Unblinded Inventory Manager role in the IRT for study drug inventory management will remain unblinded. Individuals at the PK bioanalytical laboratory will remain unblinded to facilitate sample processing, as placebo samples will not be analyzed for PK. Study drug will be dispensed at the designated study visits as summarized in the SoA. Returned study drug should be quarantined for study drug accountability and should not be re-dispensed to participants.

2.2.2. Study Procedures

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

2.2.3. Description of Study Drug

Study drug is defined as any investigational intervention(s), marketed product(s), or placebo intended to be administered to a study participant according to the study protocol. Study drug information is provided in Table 1.

TERN-601 and matching placebo will be provided in weekly kits. Each kit contains 3 bottles with 10 tablets per bottle. Bottles contain 10 tablets to account for a maximum 3-day visit window to prevent participants from missing doses even if visits and/or dose escalation is delayed. Participants should return bottles and unused tablets at each scheduled visit with study drug dispensing/return.

Table 1: Study Drug Information

Intervention Name	TERN-601	Placebo (identical in shape, size, appearance, and color to TERN-601)
Type	Drug	Drug
Dose Formulation	tablet	tablet
Unit Dose Strength(s)	100 mg or 250 mg*	placebo*
Route of Administration	oral	oral
Use	experimental	placebo
Sourcing	Provided centrally by the Sponsor	Provided centrally by the Sponsor
Packaging and Labeling	Study drug will be provided in a labelled carton containing three HDPE bottles (10 tablets per bottle) for 1-week use. Each bottle and carton will be labeled as required per country requirements.	Study drug will be provided in a labelled carton containing three HDPE bottles (10 tablets per bottle) for 1-week use. Each bottle and carton will be labeled as required per country requirements.

Abbreviations: HDPE = High Density Polyethylene; IMP = Investigational Medicinal Product; NIMP = Non-Investigational Medicinal Product

*TERN-601 100 mg, 250 mg and placebo tablets are identical in shape, size, and appearance

2.2.4. Study Drug Administration

Participants will be instructed to take one tablet from each bottle (3 bottles per weekly kit) by mouth daily with a glass of water, at approximately the same time each day, for a total of 3 tablets each day as shown in Table 2. Study drug may be taken with or without food. For participants participating in the optional PK sub-study, study drug should be administered approximately 24 hours prior to their Week 12 visit. Participants should be instructed to hold their dose on days where fasting is required, however, lab samples or assessments that are collected or performed post dose will not be considered a protocol deviation.

Table 2: Study Drug by Dose Level

Dose Level	TERN-601	Placebo to Match
Placebo QD	None	Three placebo tablets
100 mg QD	One 100-mg tablet	Two placebo tablets
250 mg QD	One 250-mg tablet	Two placebo tablets
500 mg QD	Two 250-mg tablets	One placebo tablet
750 mg QD	Three 250-mg tablets	None

Abbreviations: QD = once a day

3. SAMPLE SIZE DETERMINATION

Approximately 150 participants will be randomly assigned to study drug (n=30 per group) to achieve 120 participants (n=24 per group) completing Week 12, assuming a dropout rate of 20%.

The power estimation was based on the treatment effect of TERN-601 observed in the Phase 1 FIH trial (TERN601-1013). Assuming a pooled standard deviation of 5.75%, with a two-sided alpha of 0.10, a mean percent difference in body weight at Week 12 of 5% between placebo (n=30) and TERN-601 (n=30) will provide approximately 90% power.

4. GENERAL STATISTICAL METHODS

4.1. Reporting Conventions

Individual participant data obtained from electronic case report forms (eCRFs), central laboratories (e.g., PK), external sources, and any derived data will be presented in data listings by participant. 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 (1996), 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 (2024Guidance 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 2024.).

For categorical variables, summary tabulations of the number and percentage of participants 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.

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 participants discontinue due to "Lost to Follow-up," this reason will be included in the table with a count of 0. Percentages will be rounded and 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 participants, mean, standard deviation (SD), median, 25^{th} (Q1) and 75^{th} (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 displayed 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 plasma 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_{last}, and $t_{1/2}$ will be presented to 2 decimal places and all other plasma 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 shells. 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).

4.2. Computing Environments

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

Plasma PK parameters for TERN-601 will be estimated using non-compartmental methods with Phoenix WinNonlin® Version 8.6 or higher.

Medical history and AEs will be coded using Medical Dictionary for Regulatory Activities (MedDRA) version 27.1. Concomitant medications will be coded using World Health Organization Drug Dictionary (WHODD) Global B3, September 1, 2024.

4.3. Partial Dates

Imputation of partial AE and concomitant medication dates are specified in Appendix 1, respectively.

4.4. Data Conventions

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

Quantitative safety laboratory test results 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 purposes, 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.

Laboratory reference range values that contain less than (<) and greater than (>) symbols will be imputed for analysis purposes in the following manner:

- For values with <, the imputed value will be the numeric portion + $10^{(-1 \times NUMDEC)}$, where NUMDEC is the same number of decimal places as the raw data.
- For values with >, the imputed value will be the numeric portion - $10^{(-1 \times NUMDEC)}$, where NUMDEC is the same number of decimal places as the raw data.

PK imputation of values below the limit of quantification (BLQ) are specified in Section 10.1, 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

- Weeks – A duration expressed in weeks is calculated as the number of days divided by 7
- Months – A duration expressed in months is calculated as the number of days divided by 28
- 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) – Change will be calculated as:

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

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

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

- Temperature reported in °F will be converted to °C using the following formula:

  Temperature (°C) = (Temperature (°F) − 32) × 5/9.

- Estimated glomerular filtration rate (eGFR) will be calculated using the CKD-EPI (2021) equation:

  $eGFR_{cr} = 142 \times \min(S_{cr}/\kappa, 1)^{\alpha} \times \max(S_{cr}/\kappa, 1)^{-1.200} \times 0.9938^{Age} \times 1.012$ [if female], where

  S_{cr} = standardized serum creatinine in mg/dL
  κ = 0.7 (females) or 0.9 (males)
  α = -0.241 (female) or -0.302 (male)
  $\min(S_{cr}/\kappa, 1)$ is the minimum of S_{cr}/κ or 1.0
  $\max(S_{cr}/\kappa, 1)$ is the maximum of S_{cr}/κ or 1.0
  Age = age at collection in years

4.6. Treatments

Table 3 lists the order and labelling of the treatment and dose groups to be presented in tables, figures and listings (TFLs). Unless otherwise stated, the treatment groups presented will be the randomized treatment groups. The TERN-601 Pooled 500 mg and Total groups will not be included in listings or in the efficacy, PK or PD tables or figures. An overall column will be added to the summaries described in Section 7. Screen failures will be presented on disposition, visit dates, informed consent and eligibility listings.

Table 3: Treatment Group Labels and Ordering

Treatment Group	Dose Level	Order on TFLs
Placebo		1
TERN-601	250 mg	2
	500 mg (ST)	3
	500 mg	4
	Pooled 500 mg	5
	750 mg	6
	Total	7

4.7. Visits

4.7.1. Windows

Each visit will be denoted by its visit as “Week x” or “Follow-Up”. Tables will be summarized using the scheduled visit as collected unless the study day for that visit falls outside of the analysis visit window identified in

Table 4. In the event of scheduled assessments occurring outside of the analysis visit window or unscheduled or early end of treatment (EEOT) or early termination (ET) post-baseline assessments, these will be reassigned to scheduled (analysis) visits for analyses. Analysis visits will be assigned using the analysis visit windows provided in

Table 4. After reassignment, if multiple assessments occur within a single visit window, 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: Analysis Visit Windows by Assessment

Analysis Visit	Analysis Target Day	Analysis Visit Window (Days)			
		Weight and BMI, Vital Signs Chemistry, Hematology, Fasting Lipid Profile, PHQ-9, C-SSRS Since Last Visit	Waist and Hip Circumference, Waist to Hip Ratio, ECGs, Calcitonin, Amylase/Lipase	Coagulation, NT-proBNP, hs-CRP, TSH	HbA1c, IWQOL-Lite-CT
Week 2	14	2 to 21	N/A	N/A	N/A
Week 4	28	22 to 42	2 to 42	N/A	N/A
Week 8	56	43 to 70	43 to 70	N/A	N/A
Week 12	84	71 to 98	71 to 98	2 to 98	≥ 2
Follow-Up	112	≥ 99	≥ 99	≥ 99	N/A

4.7.2. Definition of Baseline

The baseline value for statistical analyses of quantitative laboratory parameters and vital signs (excluding weight and BMI) is defined as the mean of all available evaluations, including any unscheduled or repeat assessments, prior to the first administration of study drug.

Baseline values for waist and hip circumference will be the average value, as provided on the eCRF, of 2 measurements taken at the latest visit prior to first administration of study drug. If only one measurement is taken and no average result is recorded, then the single measurement will be used for baseline. Baseline waist-to-hip and waist-to-height ratios will be calculated based on the average values (if available) or on the single measurement(s), if only one measurement is taken.

Baseline values for glycemic control and lipids will be based on fasted results only, except HbA1c, which does not need to be collected fasted.

Baseline values for 12-lead ECGs will be calculated as the average of the non-missing triplicate results taken at the latest visit prior to first administration of study drug.

Otherwise, the baseline value for weight and other parameters is defined as the latest assessment value prior to the first administration of study drug.

Unscheduled and repeat assessments prior to the first administration of study drug will be included in the derivation of baseline.

5. ANALYSIS SETS

Table 5 defines the analysis sets to be used.

Table 5: Analysis Sets

Analysis Set	Description
Screened	All participants who sign the informed consent form (ICF).
Safety	All participants who receive any amount of study drug (TERN-601 or placebo).
Intent-to-Treat (ITT)	All randomized participants who receive any amount of study drug (TERN-601 or placebo).
Pharmacokinetic (PK)	All randomized participants who receive any amount of TERN-601 and have evaluable PK data.
PK Sub-Study	All participants who consented to and participated in the PK sub-study, were dosed with TERN-601 on the day of PK sub-study participation, and for whom at least one PK parameter can be calculated.
Pharmacodynamic (PD)	All randomized participants who receive any amount of study drug (TERN-601 or placebo) and for whom at least one PD marker can be evaluated at baseline and post-baseline.

6. EXAMINATION OF SUBGROUPS

Subgroups in this study will include the following:

- Sex (male or female)
- BMI ($\leq$35 kg/m^2 or >35 kg/m^2)
- MyPhenome^{TM} Phenotype (Hungry Gut Positive vs Negative)

Subgroup analyses will be performed for the primary, secondary and exploratory efficacy endpoints. Participants in each subgroup category will be analyzed separately using the same analysis models (after removing randomized strata) used for the primary, secondary and exploratory efficacy analyses, excluding the sensitivity and supplemental analyses. Analyses using a stratified Cochran-Mantel-Haenszel (CMH) test for calculating p-values will be modified to use a chi-square test instead for the subgroup analyses.

7. STUDY POPULATION

7.1. Participant Disposition

Participant disposition will be summarized for all participants by treatment group and overall. The summary will include:

- Number of participants screened (screened analysis set).
- Number and percentage of screen failures and reasons for screen failure. The denominator used for percentage of screen failures will be the number of participants screened. The denominator used for the percentage for screen failure reasons will be the number of screen failures.
- Number of randomized participants.
- Number and percentage of participants in each analysis set. The denominator used for the percentages will be the number of randomized participants.
- Number and percentage of participants who completed and discontinued treatment early. The denominator used for the percentages will be the number of participants in the safety analysis set. Additionally, the reasons for early treatment discontinuation, including AE relationship to study drug where the discontinuation reason is AE, will be presented. The denominator used for the percentage of reasons for early discontinuation of treatment will be the number of participants who discontinued treatment early.
- Number and percentage of participants who completed and discontinued the study early. The denominator used for the percentages will be the number of participants in the ITT analysis set. Additionally, the reasons for early study discontinuation, including AE relationship to study drug where the discontinuation reason is AE, will be presented. The denominator used for the percentage of reasons for early discontinuation of the study will be the number of participants who discontinued the study early.

A summary of the number and percentage of participants in each randomization strata as assigned in IRT vs. the strata assigned based on actual values recorded in EDC will be provided.

A by-participant data listing of study disposition information, including the reasons for treatment and/or study termination, and a listing of analysis sets will be presented.

Additionally, by-participant listings of randomization codes and treatment assignments, visit dates, informed consent and re-consent dates, study eligibility status and any eligibility criteria not met, participants meeting Inclusion Criterion 3b, and any participant unblinding will be presented.

7.2. Demographics and Baseline Characteristics

Demographic variables to be summarized include the following:

- Age at screening including the subgroups of <65 years vs ≥65 years
- Sex
- Ethnicity
- Race

Other baseline characteristics will include the following:

- Height (cm)
- Weight (kg)

- BMI including the subgroups of ≤35.0 kg/m^2 vs. >35.0 kg/m^2
- BMI categories (25 to <30, 30 to <35, 35 to <40, and ≥40 kg/m^2)
- Waist Circumference (cm)
- Hip Circumference (cm)
- Waist-to-Hip Ratio
- Waist-to-Height Ratio
- HbA1c including categories of <5.7% vs. 5.7 to <6.5%
- MyPhenome™ phenotype (Hungry Gut Positive vs. Hungry Gut Negative)

Demographics and baseline characteristics will be summarized by treatment group and overall for the safety, ITT, PK, PK sub-study, and PD analysis sets. The number and percentage of participants will be summarized by category for age, sex, race, ethnicity, BMI, HbA1c and phenotype. The remaining characteristics will be summarized using descriptive statistics.

All demographic and baseline characteristics data, including childbearing potential, will be presented in a by-participant data listing. A separate listing of MyPhenome™ genetic analysis results will also be provided.

7.3. Protocol Deviations

Protocol deviations will be identified and documented in the clinical trial management system (CTMS). Important protocol deviations are a subset of protocol deviations that may significantly impact the completeness, accuracy, and/or reliability of key study data or that may significantly affect a participant's rights, safety, or well-being. CSR reportable deviations from the protocol deviation plan are considered important protocol deviations.

All important protocol deviations will be summarized by treatment group and overall for each deviation category using the safety analysis set.

All protocol deviations will be presented in a by-participant data listing. A separate listing of important protocol deviations will also be provided.

7.4. Medical History

All medical history terms will be coded using MedDRA. Medical history will be summarized by treatment group and overall using the safety analysis set. Summaries will be ordered by descending order of the overall incidence of system organ class (SOC) and descending order of the overall incidence of preferred term (PT) within each SOC.

All medical history data will be presented in a by-participant data listing.

7.5. Medications

7.5.1. General Prior, Concomitant and Follow-Up 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. Follow-up medications are defined as medications that started after the last study drug administration. 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 1.

Prior, concomitant, and follow-up medications will be summarized separately by treatment group and overall. The number and percentage of participants who took at least one prior (concomitant, follow-up) medication as well as the number and percentage of participants 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 participant has more than one occurrence of the same preferred name, then the preferred name will be counted only once for that participant. Similarly, if a participant has more than one preferred name within ATC Level 4 or ATC Level 4 within ATC Level 2, then the participant will be counted only once in that ATC Level 4 or ATC Level 2.

All medication data will be provided in a by-participant listing.

7.5.2. Antiemetic Medications

In addition to summaries of prior and concomitant medications, separate summaries of post-baseline antiemetic medication use, based on the safety analysis set, will be provided. The number and percentage of participants who were administered antiemetic medications, as well as the total number of antiemetic dose administrations, will be summarized by treatment group. The total number of antiemetic doses administered by week as well as overall will be summarized using descriptive statistics. The value for week will be calculated as

(dose date of antiemetic medication - first dose date of study drug + 1) / 7

and rounded up to the nearest integer.

A summary of the administration of antiemetic medications will also be presented by indication (AE, medical history, procedure, prophylactic, and/or other) and treatment group. Antiemetic medications administered due to an AE will also be categorized and summarized based on the AE relationship to study treatment.

A separate listing of all participants who used antiemetic medications will be provided.

8. EFFICACY ANALYSES

8.1. Adjustments for Covariates

Change from baseline analysis models of body weight, fasting glucose, HbA1c, waist circumference, hip circumference, waist-to-hip ratio, waist-to-height ratio, BMI, fasting lipids, blood pressure, NT-proBNP, and hs-CRP will use applicable baseline values as a covariate.

8.2. Handling of Dropouts or Missing Data

The efficacy analyses will be based on observed data. Sensitivity and supplemental analyses imputing missing data are described separately in each section.

8.3. Interim Analyses and Data Monitoring

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

8.4. Multicenter Studies

The small sample sizes precludes analyses by site. Randomization is not stratified by site. Likewise, analyses of study data will not be stratified by study site.

8.5. Use of an "Efficacy Subset" of Participants

Not Applicable.

8.6. Multiple Comparisons/Multiplicity

No adjustments for multiplicity will be made.

8.7. Efficacy Analyses

Efficacy analyses will use the ITT analysis set. Subgroup analyses specified in Section 6 will be performed where sufficient sample size exists. In case randomized strata was assigned in error or participants were not randomized based on randomization stratification factors, i.e., replacement participants, the strata based on actual values will be presented for all analyses that include randomization strata.

8.7.1. Study Estimands

The study estimands are described in

Table 6.

Table 6: Estimands

Estimand	Population	Treatment	Intercurrent Events	Variable of Interest	Population-Level Summary
Primary	Adults with overweight or obesity and without diabetes	TERN-601 or placebo	Permanent treatment discontinuation (treatment policy strategy)	Percent change in body weight at Week 12	Least-squares mean difference

Estimand	Population	Treatment	Intercurrent Events	Variable of Interest	Population-Level Summary
Secondary 1	Adults with overweight or obesity and without diabetes	TERN-601 or placebo	Permanent treatment discontinuation (treatment policy strategy)	Change in body weight at Week 12	Least-squares mean difference
Secondary 2	Adults with overweight or obesity and without diabetes	TERN-601 or placebo	Permanent treatment discontinuation (treatment policy strategy)	Proportion of participants with ≥5% change in body weight	Difference in proportion of responders

8.7.2. Primary Efficacy Analysis

The primary objective of this study is to evaluate the effect of TERN-601 on body weight relative to placebo and the primary endpoint is percent change in body weight from baseline at Week 12. The primary statistical analysis will test whether the mean percent change from baseline in body weight is (H1) or is not (H0) different between placebo and TERN-601.

The null hypothesis (H0) will be evaluated by an analysis of variance (ANOVA) model. The ANOVA model will include treatment group and randomization strata (sex [male or female] and BMI [$\leq$35 kg/m^2 or >35 kg/m^2]) as fixed effects, and percent change from baseline as the dependent variable. The analysis of the primary efficacy endpoint will be conducted using a two-sided test with an alpha of 0.1. Missing Week 12 results will not be imputed for the primary analysis.

Observed baseline and post-baseline values as well as change from baseline and percent change from baseline values will be summarized at each visit by treatment group using the ITT analysis set. The estimates of least-square (LS) means, standard errors (SEs), and 90% confidence intervals (CIs) will be presented by treatment group at each visit. Estimates of the LS mean differences between each TERN-601 treatment group (excluding total) and placebo, along with the associated SEs and 90% CIs of the differences, as well as non-adjusted p-values, will be presented at each visit. Estimates for the TERN-601 pooled 500 mg treatment group will be calculated based on the individual TERN-601 500 mg (ST) and 500 mg treatment groups.

LS mean (±SE) percent change in body weight over time will be plotted by treatment group. Forest plots of LS mean differences (90% CIs) between each TERN-601 treatment group vs. placebo will be presented by subgroup (see Section 6 for subgroups).

All body weight data along with change and percent change calculations will be presented in by-participant listings.

8.7.2.1. Sensitivity Analyses of the Primary Endpoint

8.7.2.1.1. Mixed Model Repeated Measures Analysis

Percent change in body weight will also be evaluated using a restricted maximum likelihood (REML) based mixed model repeated measures (MMRM) approach. The mixed effect model will handle missing data based on a likelihood method under the missing at random (MAR) assumption.

The model will include the following fixed effects:

- Treatment group (5 levels: placebo [0 mg], 250 mg, 500 mg (ST), 500 mg, 750 mg)
- Visit
- Treatment group by visit
- Randomization strata

The dependent variable will be the percent change from baseline in body weight. Only visits in the treatment period, from baseline up to Week 12, will be presented.

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.

The estimates of LS means, SEs, and 90% CIs estimated by the model will be presented by treatment group (excluding total) at each visit. Estimates of the LS mean differences between each TERN-601 treatment group and placebo, along with the associated SEs and 90% CIs of the differences, as well as non-adjusted p-values with an alpha of 0.1, will be presented at each visit. Estimates for the TERN-601 pooled 500 mg treatment group will be calculated based on the individual TERN-601 500 mg (ST) and 500 mg treatment groups.

8.7.2.1.2. Analysis Based on TERN-601 Treatment Adherence

To explore the potential effects of dose modifications on the primary endpoint of percent change from baseline in body weight, an additional sensitivity analysis will be performed. In this case, the following types of dose modifications as collected on the Study Drug Accountability CRF page will be summarized in the analysis as "Any Dose Modification" including the following possible individual dose modifications: Reduce one dose level, Return to Week 2 dose, Remain on current dose, do not titrate. If sufficient sample size ($n \geq 5$) exist in each individual dose modification, additional analyses may be performed using the individual dose modification group.

For the analysis of treatment adherence, each participant will be assigned to a dose modification subgroup category (reduce one dose level, return to Week 2 dose, remain on current dose, do not titrate, any dose modification, no dose modifications) based on their study drug accountability

records. Placebo participants will be assigned to the no dose modifications subgroup category. Each dose modification subgroup category will be summarized separately using the same ANOVA method used for the primary analysis. If there are not enough participants in a subgroup category (<5 participants per treatment group) to perform the ANOVA analysis, the ANOVA results for that subgroup category will be excluded from the summary.

8.7.2.2. Supplemental Analysis of the Primary Endpoint

The following supplemental analyses may be performed to assess the robustness of the treatment policy strategy approach to the handling of intercurrent events (ICEs) for the primary estimand. The supplementary analysis will be conducted for the ITT Analysis Set.

A pattern mixture model (PMM) will be used to model the predictive distribution of missing data conditional on the observed data (Little, R.J.A. (1993). Pattern-mixture models for multivariate incomplete data. Journal of the American Statistical Association, 88, 125-134., Little, R.J.A. (1994). A class of pattern-mixture models for normal missing data. Biometrika, 81, 471-483.). In this analysis, missing patterns will be defined according to the reasons for early discontinuation from study drug as reported on the electronic case report form (eCRF). Any data that is collected after treatment discontinuation will not be included in this analysis. The following two patterns will be considered:

1. Participants who discontinue study drug due to reasons that may be related to efficacy or safety, including:
    - Lack of Efficacy per the Investigator
    - Investigator Discretion (comments will be reviewed prior to database lock to determine if related to efficacy or safety)
    - Withdrawal by Subject (comments will be reviewed prior to database lock to determine if related to efficacy or safety)
    - Change in Clinical Status (comments will be reviewed prior to database lock to determine if related to efficacy or safety)
    - Protocol Deviation (comments will be reviewed prior to database lock to determine if related to efficacy or safety)
    - Adverse Event
    - Death
    - Other

    2. Participants who discontinue study drug due to reasons that are unlikely related to efficacy or safety, including:

    - Lost to Follow-Up
    - Investigator Discretion (comments will be reviewed prior to database lock to determine if related to efficacy or safety)
    - Pregnancy
    - Withdrawal by Subject (comments will be reviewed prior to database lock to determine if related to efficacy or safety)
    - Non-Compliance with Study Drug

- Change in Clinical Status (comments will be reviewed prior to database lock to determine if related to efficacy or safety)
- Protocol Deviation (comments will be reviewed prior to database lock to determine if related to efficacy or safety)
- Prohibited Medication
- Study Terminated by Sponsor

The pattern (time and rate) of study drug discontinuation will be displayed by a Kaplan-Meier survival curve for each missing pattern within each treatment group. For each survival curve, participants who discontinue study drug for reasons not included in the pattern definition will be censored at their time of study drug discontinuation. All participants who complete study drug will be censored at their last dose of treatment.

Participants who discontinue study drug due to reasons related to efficacy or safety will be penalized and their missing post-treatment data will be imputed using the copy reference method (Section 8.7.2.2.1). Participants who discontinue study drug due to reasons that are unlikely related to efficacy or safety will have their missing post-treatment data imputed using an MAR assumption (Rubin D.B. Multiple Imputation for Nonresponse in Surveys. John Wiley & Sons. 1987.). This MAR assumption will also be used to impute data missing prior to study drug discontinuation (such as assessment not performed, out of window, etc.). Both methods involve multiple imputation.

Participants randomized to placebo will have all missing data imputed using the MAR assumption. The use of the copy reference method is limited to imputing missing data for participants randomized to TERN-601 and only for their missing results following discontinuing study drug for reasons related to efficacy or safety.

Prior to implementing either method of multiple imputation, a Markov Chain Monte Carlo (MCMC) method that assumes multivariate normality will be used to impute the intermediate missing values and produce a monotone missing pattern (data with only terminal missing and no intermediate missing) (Li, K. H. (1988), "Imputation Using Markov Chains," Journal of Statistical Computation and Simulation, 30, 57-79., Schafer J.L. Analysis of Incomplete Multivariate Data. Chapman and Hall, New York. 1997.). The results used to generate this intermediate dataset with monotone missingness will be limited to measurements collected prior to study drug discontinuation for participants randomized to TERN-601, but will include all available results from the placebo participants through and including Week 12, regardless of whether they discontinued study drug prior to Week 12.

The copy reference model will be run on all ITT participants who have at least a baseline result, using SAS PROC MI. Treatment group (TRTPN) and randomization strata (sex [male or female] and BMI [$\leq$35 kg/m^2 or >35 kg/m^2]) will be included in the CLASS statement. The VAR statement will include the variables for strata, baseline result, and post-baseline results ordered by visit. The copy reference model will include a monotone regression of the post-baseline visits and an MNAR MODEL statement that contains all of the post-baseline results ordered by visit and that uses placebo group observations to impute the values (MODELOBS = (TRTPN =’1’)). As indicated for the intermediate dataset, the copy reference model will be run using the results

collected prior to study drug discontinuation for the TERN-601 participants and all available results collected up and through Week 12 for the placebo participants.

The model assuming MAR will be run separately on the same initial dataset used for the copy reference model. Similar to the copy reference method, the MAR model will be run with all ITT participants who have a non-missing baseline result using SAS PROC MI, will include TRTPN and the randomization strata in the CLASS statement, and will include a monotone regression of the post-baseline visits. Unlike the code used for the copy reference model, the VAR statement will also include the variable TRTPN in addition to the strata, baseline results, and post-baseline results ordered by visit. No MNAR model statement will be included in the SAS PROC MI As indicated for the intermediate dataset and the copy reference model, this MAR model will be run using the results collected prior to study drug discontinuation for the TERN-601 participants and all available results collected up and through Week 12 for the placebo participants.

Note: If the MCMC model used to create a monotone missing pattern in the initial dataset fails to converge due to a lack of observations in the randomization strata, the monotone regression statements used in the copy reference-based (and MAR-based) models will be replaced with fully conditional specification (FCS) regression.

Both models will be run separately for a set number of times (e.g., NIMPUTE=100) with the seed (e.g., SEED=62341), resulting in two series of complete datasets. For each individual imputation, a missing result will be replaced by the one generated by either the MNAR or MAR method, and the choice will use the randomized treatment group, the timing of the missing result relative to the discontinuation of study drug, and the reason for discontinuing study drug. For example, all post-baseline results from visits that would have occurred prior to the date of study drug discontinuation will be imputed from the MAR method, regardless of the randomized treatment group. For participants randomized to TERN-601, post-baseline results scheduled to occur after the date of study drug discontinuation will be chosen based on the reason for study drug discontinuation. All missing results for participants randomized to placebo will be imputed using the MAR model.

The final imputed dataset, which is a hybrid of MNAR and MAR imputed results as described above, will then be analyzed using the same ANOVA model as described in Section 8.7.2. The analyzed results from the imputed datasets will be combined based on Rubin's rules (Rubin D.B. Multiple Imputation for Nonresponse in Surveys. John Wiley & Sons. 1987.). The pooled estimates (LS Means [90% CI], LS Mean differences [90% CI], and p-values using alpha of 0.1) from the multiple ANOVA results, along with descriptive statistics, will be summarized in the same manner as the primary analysis.

8.7.2.2.1. Copy Reference Method

The copy reference method may be applied to impute the post-treatment discontinuation data for any TERN-601 treated participant who discontinues study drug early based on data from the placebo group rather than the participant's own randomized treatment group. Specifically, for a participant on TERN-601 who discontinues study drug early, their mean trajectory after early study drug discontinuation is assumed to be parallel to the mean trajectory of the placebo group, and the difference between the two means is the same as the difference at the time of withdrawal. This method assumes that any benefit gained from previous treatment will be retained, but

participants progress as if they were on placebo after discontinuation from study drug. For any participant on placebo who discontinues early from study drug, his or her post-withdrawal profile will be imputed following the MAR principle.

8.7.3. Secondary Efficacy Analyses

8.7.3.1. Change in Body Weight (kg) from Baseline at Week 12

The secondary efficacy endpoint of change in body weight from baseline at Week 12 will be analyzed using an analysis of covariance (ANCOVA) model include treatment group and randomization strata (sex [male or female] and BMI [≤35 kg/m^2 or >35 kg/m^2]) as fixed effects, baseline weight (kg) as a covariate, and change from baseline as the dependent variable. The analysis of the primary efficacy endpoint will be conducted using a two-sided test with an alpha of 0.1. In this case, the statistical analysis will test whether the mean change from baseline in body weight (kg) is (H1) or is not (H0) different between placebo and TERN-601.

The estimates of LS means, SEs, and 90% CIs will be presented by treatment group at each scheduled visit. Estimates of the LS mean differences between each TERN-601 dose level and placebo, along with the associated SEs and 90% CIs of the differences, as well as non-adjusted p-values, will be presented at each scheduled visit.

LS mean (SE) change in body weight over time will be plotted by treatment group.

8.7.3.1.1. Sensitivity Analysis

The same method used for the sensitivity analysis of the primary endpoint (REML-based MMRM and ANCOVA analysis of treatment adherence, with the addition of baseline weight (kg) as a covariate) (Section 8.7.2.1) will be used for the sensitivity analysis of change in body weight from baseline at Week 12.

8.7.3.1.2. Supplemental Analysis

The same methods used for the supplemental analysis of the primary endpoint (multiple imputation method) (Section 8.7.2.2) will be used for the supplemental analysis of change in body weight from baseline at Week 12.

8.7.3.2. Proportion of Participants Achieving ≥5% Weight Loss at Week 12

The secondary efficacy endpoint of the proportion of participants achieving ≥5% weight loss will be analyzed using a stratified Cochran-Mantel-Haenszel (CMH) test. This statistical analysis will test whether the proportion of weight loss responders (decrease of ≥5%) is (H1) or is not (H0) different between placebo and TERN-601. For the analysis, responders will be defined as any participant achieving a decrease of at least 5% (PCHG ≤ -5%). Non-responders will be defined as any participant who did not have a decrease in weight of at least 5%. Missing Week 12 results will not be imputed for analysis.

The number and percentage of responders and non-responders at each visit along with two-sided exact (Clopper-Pearson) 95% CIs for the percentages will be presented for the ITT analysis set. For each pairwise comparison (TERN-601 dose level vs. placebo), the difference in percentage of responders, 90% CIs for the difference (estimated using the Meittinen-Nurminen score

method), and two-sided p-values with alpha of 0.1 (using CMH test stratified for randomization stratification factors) will be provided.

8.7.4. Exploratory Efficacy Analyses

8.7.4.1. Proportion of Participants Achieving ≥10 or ≥15% Weight Loss

The exploratory efficacy endpoint of proportion of participants achieving ≥10% or ≥15% weight loss will be analyzed at each visit and presented in the same manner as the secondary efficacy endpoint ie, proportion of participants achieving ≥5% weight loss.

Plots of the percentage of participants achieving 5%, 10%, and 15% weight loss will be presented by treatment group and visit.

8.7.4.2. Changes from Baseline in Markers of GLP-1R Agonism

The exploratory efficacy endpoints of change from baseline in fasting glucose, HbA1c, waist circumference, hip circumference, waist-to-hip ratio, waist-to-height ratio, and BMI will be analyzed and presented in the same manner as the secondary efficacy endpoint, change in body weight from baseline. HbA1c will not be analyzed using the REML-based MMRM model because only one post-baseline on-treatment visit (Week 12) is conducted for that parameter. Separate by-visit and shift from baseline summaries of the number and percentage of participants in each of the HbA1c and BMI categories (as defined in Section 7.2) will also be presented. A category of <25 kg/m^2 will be added to the BMI summaries if any participant has a result falling into that category at a post-baseline visit. The maximum and minimum values of all individual post-baseline assessments will be presented by category in the BMI categorical summaries.

8.7.4.3. Impact of Weight on Quality of Life - Lite - Clinical Trials Version (IWQOL-Lite-CT)

The IWQOL-Lite-CT is a 20-item measure that yields a total score and five composite scores as described in Table 7. It assesses 2 primary domains of obesity- and health-related quality of life: physical (7 items) and psychosocial (13 items). A 5-item subset of the physical domain, the physical function composite is also supported. Items in the physical-function composite describe physical impacts related to general and specific physical activities. All items are rated on either a 5-point frequency (1="never" to 5="always") scale or a 5-point truth (1="not at all true" to 5="completely true") scale (Kolotkin R.L., Ervin C.M., Meincke H.H., et al. Development of a clinical trials version of the Impact of Weight on Quality of Life-Lite questionnaire (IWQoL-Lite Clinical Trials Version): results from two qualitative studies. Clin Obes. 2017;7(5):290-299., Kolotkin R.L., Williams V., Ervin, C.M., et al. Validation of a new measure of quality of life in obesity trials: IWQOL – Lite Clinical Trials Version. Clinical Obesity. 2019;9(3) https://doi.org/10.1111/cob.12310.).

Table 7: IWQOL-Lite-CT Total and Composite Scores

Score	Number of Items	Items Included in Score	Minimum Raw Score	Maximum Raw Score	Raw Score Range
Total	20	1-20	20	100	80
Physical	7	1-5, 16-17	7	35	28

Score	Number of Items	Items Included in Score	Minimum Raw Score	Maximum Raw Score	Raw Score Range
Physical Function	5	1-3, 16-17	5	25	20
Psychosocial	13	6-15, 18-20	13	65	52

The IWQOL-Lite-CT total and composite standardized scores range from 0 to 100, with higher scores reflecting better levels of functioning. Scores for each subscale are computed if a minimum of 50% of the items for that subscale are non-missing, and for the IWQOL-Lite-CT total score if a minimum of 75% of all items are non-missing. To compute the total and composite scores, follow the 3 steps below for each score identified in the above table:

1. If the minimum number of items are answered, compute the average of the valid item responses.
2. Multiply the average calculated in Step 1 by the total number of items. Round to the nearest integer.
3. To convert the IWQOL-Lite-CT raw score in Step 2 to the 0 (worst) to 100 (best) metric:
   a. Subtract the raw score from the maximum raw score.
   b. Divide the difference in (a) by the raw score range.
   c. Multiply the total in (b) by 100.

Observed baseline and post-baseline as well as change from baseline values for the IWQOL-Lite-CT total, composite and individual item scores, will be summarized by treatment group and visit using descriptive statistics for the ITT analysis set. Change in IWQOL-Lite-CT total score at Week 12 will be analyzed and presented in the same manner as the secondary efficacy endpoint, change in body weight from baseline. IWQOL-Lite-CT will not be analyzed using the REML-based MMRM model because only one post-baseline on-treatment visit (Week 12) is conducted. Individual item scores will not be included in the plots or the supplemental analysis. All IWQOL-Lite-CT individual responses and calculated total and composite scores will be provided in by-participant listings.

8.7.4.4. Nausea Burden Score

Nausea burden score is defined as the sum across all TEAEs having a preferred term of "Nausea" (per MedDRA), weighted by TEAE severity, divided by the duration of treatment (days). Only TEAEs that occur during the dosing period, starting from Day 1 to Week 12 or end of treatment, inclusive, will be included in the overall nausea burden score. TEAEs that are still ongoing at end of treatment will have an AE end date imputed to treatment end date. Duration of treatment (days) is defined as last dose date of study drug – first dose date of study drug + 1. Nausea burden score will also be calculated based on week of occurrence and continuation, where week is calculated as

(date of nausea onset/continuation - first dose date of study drug + 1) / 7

and rounded up to the nearest integer.

For weighting of each preferred term of nausea, the recorded severity of each event will be assigned a score: mild = 1, moderate = 2, severe = 3, life-threatening = 4 and death = 5. Before

summing across all nausea TEAEs, each individual event will first be multiplied by its assigned severity score as well as duration in days. The duration of the event may be greater than 12 weeks, depending on the end date. Participants who experience no nausea TEAEs will be assigned to a nausea burden score of 0. Additional details on the definition of TEAE and imputation of missing or partial dates can be found in Section 11.2.

Overall (on-treatment) and weekly nausea burden score will be summarized by treatment group using descriptive statistics for the ITT analysis set. A by-participant listing of nausea burden scores will be provided.

9. PHARMACODYNAMIC (PD) ANALYSES

The pharmacodynamic endpoints for this study are change (percent change) from baseline in cardiovascular risk markers: fasting lipids (HDL, Non-HDL cholesterol, LDL, Total cholesterol, Triglycerides, VLDL, ApoB), blood pressure (systolic and diastolic), NT-proBNP, and hs-CRP. Observed baseline and post-baseline values as well as change from baseline and percent change from baseline values of each PD marker will be summarized by treatment group and scheduled visit using the PD analysis set. Any lipid marked as not fasting will be excluded from analyses.

Change from baseline will be analyzed at applicable visits using the same models specified for the secondary endpoint of change in body weight (Section 8.7.3.1). Percent change from baseline will be analyzed at applicable visits using the same models specified for the primary endpoint (Section 8.7.2). NT-proBNP and hs-CRP will not be analyzed using the REML-based MMRM model because only one post-baseline on-treatment visit (Week 12) is conducted for those parameters. Plots for NT-proBNP and hs-CRP will exclude results at the Follow-Up visit.

NT-proBNP values may be log-transformed in the models and back-transformed in the presentation of the treatment effect if NT-proBNP is not normally distributed.

A by-participant listing of pharmacodynamic endpoints will be provided.

10. PHARMACOKINETIC ANALYSES

All PK endpoints, recorded and derived, will be presented in by-participant data listings. 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. The actual TERN-601 dose amount administered in relation to the PK draw will be presented as the treatment group in the PK TLFs.

10.1. Below the Limit of Quantification (BLQ) Values

For the purposes of plasma concentration summaries, TERN-601 plasma concentrations defined as BLQ will be summarized as 0 for all values prior to first measurable concentration and as LLOQ (1 ng/mL) multiplied by 0.5 for all values after the first measurable concentration.

For the purposes of plasma PK parameter calculations, TERN-601 plasma concentration values defined as 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 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 (Section 10.2), they will be set to missing.

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

10.2. 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.

10.3. Concentration-Time Data

Individual plasma concentration data will be listed for the PK analysis set. Week 12 PK concentrations for the PK sub-study analysis set and sparse PK concentrations for the PK analysis set will be summarized separately by nominal sampling time point and TERN-601 dose level with descriptive statistics (number of non-missing observations, number of BLQ values, arithmetic mean, arithmetic SD, arithmetic CV%, median, Q1, Q3, minimum, maximum, geometric mean and geometric CV%).

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.

- 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 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 (LLOQ), these values will be presented as zero and the geometric mean and geometric CV% will be denoted as NC.

Individual participant and arithmetic mean concentration-time profiles for each TERN-601 dose level will be presented graphically on linear and semi-logarithmic concentration scales at Week 12 using the PK sub-study analysis set. Data on individual participant plots will be presented by actual sampling time and data on mean concentration plots will be presented by nominal

sampling time. Time will be presented in hours and a reference line for LLOQ will be included on all plots.

Concentration data in listings will be presented to the same number of significant figures as provided by the analytical laboratory.

10.4. Plasma PK Parameters

Plasma PK parameters will be calculated from the individual plasma concentrations at Week 12 for the PK sub-study analysis set using a non-compartmental approach. The actual PK sampling times will be used for the PK parameter analysis, with the exception of the predose time, which will be set to 0. If actual PK sampling times are missing, nominal times will be used. If the predose sample is collected significantly out of window or is missing, the 24 hour post-dose sample concentration may be used in its place, if available and appropriate, with the time set to 0. Similarly, if the 24 hour post-dose sample is collected significantly out of window or is missing, the predose sample concentration may be used in its place, if available and appropriate, and the actual postdose time will be used.

Table 8 presents the plasma PK parameters to be calculated.

Table 8: Plasma PK Parameters

Abbreviation	Parameter Definition
AUC_{0-t}	Area under the plasma concentration curve over from time 0 to time t, e.g. from 0 to 48 hours.
AUC_{tau}	Area under the plasma concentration curve over a dosing interval, i.e. from 0 to 24 hours.
C_{max}	Maximum observed plasma concentration, obtained directly from the plasma concentration-time profiles within the sampling interval, i.e. calculated across all samples at Week 12. In the case where multiple peaks are of equal magnitude, the earliest peak concentration will be reported as C_{max}.
C_{tau}	Plasma concentration at the end of the dosing interval, ie, 24 hrs postdose
T_{max}	Time of the maximum observed plasma concentration, obtained directly from the plasma concentration-time profiles within the sampling interval, i.e. calculated across all samples at 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_{last}	Time of the last quantifiable plasma concentration, obtained directly from the plasma concentration-time profiles within the sampling interval, i.e. calculated across all samples at Week 12.
$t_{1/2}$	Apparent plasma terminal elimination half-life, calculated as $\ln(2) / \lambda_z$.
CL_{ss}/F	Apparent total plasma clearance at steady-state calculated as Dose / AUC_{tau}.
V_z/F	Apparent volume of distribution, calculated as Dose / (λ_z * AUC_{tau}).
C_{last}	Observed drug concentration corresponding to T_{last}
λ_z	Apparent terminal rate constant (listed only)

Additional PK parameters may be determined where appropriate.

10.4.1. Pharmacokinetic Parameter Data Handling

10.4.1.1. Calculation of AUC

AUCs will be calculated using linear up / log down trapezoidal rule. For any partial AUC determination (i.e., AUC over a dosing interval), nominal time will generally be used for the end of the interval. 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}.

10.4.1.2. Criteria for Calculation and Goodness of Fit

Values for λ_z, $t_{1/2}$, $AUC_{0-\infty}$, CL/F, and V_z/F 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.
- $r^2_{adj} \geq 0.70$ for the regression of the log-concentration time data during the terminal elimination phase.
- Negative slope for log regression fit.

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

10.4.2. Statistical Methods for PK Parameters

Plasma PK parameters will be summarized by TERN-601 dose level using descriptive statistics (number of non-missing observations, arithmetic mean, SD, median, Q1, Q3, minimum, maximum, geometric mean, and geometric CV%). The 500 mg dose groups will be pooled for PK summaries and analyses.

For the calculation of summary statistics, all NR and NC values in a data series will be set to missing.

11. SAFETY ANALYSES

All safety analyses will be conducted using the safety analysis set.

11.1. Extent of Exposure and Treatment Compliance

Participants will be dispensed and administered study drug during their study visits and will self-administer study drug at home. Participants will be asked to maintain records of study drug administration in a dosing diary. Dosing diary records will not be used for analysis of exposure and compliance. The number of study drug tablets dispensed and returned, including kit and

bottle numbers, will be recorded at each visit (scheduled and unscheduled). Any dose modifications by modification type and reason will also be recorded. The study drug administration start and stop dates, including dates of missed doses, drug overdoses, incorrect doses, drug interruptions, reason for drug interruptions and number of tablets taken based on a review of the dosing diary and the dispense/return information will be recorded in the eCRF. Actual dose amounts dispensed will be recorded in the IRT.

The Study Drug Administration and Study Drug Accountability CRF pages as well as the IRT data will be used for determining the extent of exposure to study drug. The duration of treatment, cumulative dose (planned and actual), dose intensity (planned and actual), and relative dose intensity will be summarized by treatment group for the safety analysis set.

11.1.1. Duration of Treatment

Duration of treatment (weeks) will be calculated as:

(last dose date of study drug - first dose date of study drug + 1) / 7.

The last dose date will be the latest stop date recorded on the Study Drug Administration CRF page or the date of last dose of study drug recorded on the end of treatment CRF page, whichever occurs later. Descriptive statistics will be provided for duration of treatment by treatment group. Duration of treatment will also be summarized categorically with the number and percentage of participants with ≥1 day, ≥28 days (4 weeks), ≥56 days (8 weeks), and ≥84 days (12 weeks) of treatment.

The following additional durations will be calculated and summarized separately:

- Duration of drug interruptions and missed doses (days) based on the Study Drug Administration CRF page
- Duration of drug interruptions and missed doses (days) based on the dispensing/return data from Study Drug Accountability CRF page
- Duration of treatment, excluding drug interruptions and missed doses, (weeks) based on the Study Drug Administration CRF page
- Duration of treatment, excluding drug interruptions and missed doses, (weeks) based on the dispensing/return data from Study Drug Accountability CRF page

11.1.2. Cumulative Dose

Planned cumulative dose (mg) is defined as the sum of all doses of study treatment that should have been taken by the participant according to their randomized treatment assignment. Planned dose amounts will be calculated based on the dosing titration schedule and the number of days for which the participant was assigned a dose according to the IRT.

Table 9: Planned Daily Cumulative Dose Amounts

Dispensing Visit (Dosing Weeks)	Placebo	TERN-601 Treatment Groups			
		250 mg	500 mg (ST)	500 mg	750 mg
Randomization (Weeks 1-2)	0 mg	100 mg	100 mg	100 mg	100 mg

Week 2 (Weeks 3-4)	0 mg	250 mg	100 mg	250 mg	250 mg
Week 4 (Week 5)	0 mg	250 mg	250 mg	250 mg	250 mg
Week 5 (Week 6-8)	0 mg	250 mg	250 mg	500 mg	500 mg
Week 8 (Weeks 9-12)	0 mg	250 mg	500 mg	500 mg	750 mg

For each scheduled dispensing visit, planned cumulative dose amounts will be calculated as the planned daily dose (see

Table 9 for values) times the number of days from the date of the visit until the day before the next scheduled visit. For participants who started treatment after the Randomization dispensing visit, the date of first dose recorded in the study drug administration CRF will be used as the dispensing date at Randomization. The overall planned cumulative dose will be the sum of the planned cumulative dose amounts at each visit.

Planned cumulative dose (mg) accounting for modifications made by the Investigator will be calculated in a similar manner. Any modified dose amounts will replace the planned daily dose in the above table for scheduled visits. If dose modifications occur at an unscheduled visit, the number of days of the previous visit will be adjusted to end the day before the unscheduled visit and the number of days of the unscheduled visit will be from the date of the visit until the next dispensing visit. The modified dose amount will be applied only to the unscheduled visit duration. After calculating the cumulative dose for the unscheduled visit, the unscheduled visit will then be added to the cumulative dose of the previous scheduled visit and be windowed to that scheduled visit. Planned cumulative dose (by dosing week interval and overall) will be calculated using the modified dose amounts.

For participants who discontinue treatment early, only time up to discontinuation of study drug will be included in the planned cumulative dose calculation. For example, if a participant in the 250 mg treatment group discontinues treatment at dosing Week 3, the planned cumulative dose amount for dispensing Week 2 will be calculated as the planned daily dose times the number of days from the date of the visit until the date of last dose.

Actual cumulative dose (mg) is defined as the sum of all doses of study treatment actually taken based on the study drug accountability CRF and the actual dose amount as recorded in IRT. For each dispensing visit, including unscheduled visits, the actual cumulative dose amount will be calculated in the following manner:

1. For each kit dispensed, calculate the total number of tablets taken by subtracting the total number of tablets returned from 30.
2. Divide the sum calculated in #1 by 3 to get the number of doses taken until the next dispensing visit.
3. Multiply the number of doses calculated in #2 by the actual dose amount recorded in IRT for that kit.
4. Re-assign the unscheduled visit to the previous scheduled visit.
5. Sum the total dose amounts for each kit to get the cumulative dose amount for the visit.

If a bottle was not returned, then it will be assumed that the participant was compliant with the study drug and took 1 tablet each day from that bottle during the visit, after first taking into

consideration any return data from the other kits or bottles. If the last dose date is unknown because the participant is lost to follow-up, the date of last contact will be used as the date of last dose and it will be assumed that the participant took 1 dose each day until their date of last contact or until they would have run out of doses, whichever occurs first.

Planned and actual cumulative dose will be summarized for each dosing week interval and overall by treatment group using descriptive statistics.

11.1.3. Dose Intensity

Planned dose intensity (PDI) (mg/day) is defined as the planned cumulative dose divided by the duration of treatment in days. Actual dose intensity (ADI) (mg/day) is defined as actual cumulative dose divided by the duration of treatment in days. Descriptive statistics will be provided for PDI and ADI for each dosing week interval (after first calculating treatment duration in days for each dispensing visit) and overall by treatment group.

Relative dose intensity (RDI) (%) is calculated as (ADI / PDI) × 100. Descriptive statistics will be provided for RDI for each dosing week interval and overall by treatment group.

11.1.4. Dose Modifications

The number and percentage of participants with any dose modifications as defined below will be summarized by treatment group.

From the Study Drug Administration CRF:

- Drug interruption
- Single missed dose
- Drug overdose
- Incorrect dose

From the IRT:

- Modifications Requested by the Investigator
  - Reduce one dose level
  - Return to Week 2 dose
  - Remain on current dose, do not titrate
- Up-titration

The total number of missed doses, dose modifications and types of modification based on source will be summarized by treatment group.

11.1.5. Treatment Compliance

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

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

- [(duration of exposure (days) - duration of drug interruptions and single missed doses (days)) / duration of exposure (days)] × 100

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

- [(sum of tablets dispensed – sum of tablets returned) / (3 tablets × duration of exposure (days))] × 100

Number and percentage of participants in each of the following compliance categories will be summarized by treatment group and overall total:

- <80%
- 80% to ≤100%
- >100%.

Study drug administration and accountability as well as derived values related to exposure and compliance will be presented in data listings.

11.2. Adverse Events

Adverse event verbatim terms on eCRFs will coded using MedDRA. All AEs will be listed, but summaries will be restricted to TEAEs, defined as AEs with a start date on or after the date of first dose of study drug through 30 days after the last dose of study drug. 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 1. Each summary will be displayed by treatment group.

Selected gastrointestinal (GI) AEs will be summarized by MedDRA PT. Adverse events with a preferred term of Nausea, Vomiting, Diarrhoea, Constipation or Eructation will be included in the summaries.

For summaries based on relationship to study treatment, treatment-related AEs are defined as those with relationships reported as “Related”, “Probably Related” or missing. At each level of participant summarization, a participant is classified according to the closest relationship to study drug if the participant reported 1 or more events.

For summaries based on severity, at each level of participant summarization, a participant is classified according to the highest grade if the participant reported 1 or more events. AEs with a severity of severe, life-threatening, or death will be pooled together and summarized on the tables as ‘≥ Severe’. AEs with missing severity will be considered Severe.

11.2.1. Overall Summary of Treatment Emergent Adverse Events

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

- TEAE
- GI TEAE
- TEAE by maximum severity

- ≥ Severe TEAE
- Serious TEAE
- TEAE leading to death
- TEAE by closest relationship to study drug
- Treatment-related TEAE
- Treatment-related ≥ Severe TEAE
- Treatment-related serious TEAE
- Treatment-related TEAE leading to death
- TEAE related to study procedures
- TEAE leading to dose modification (reduction or interruption)
  - TEAE leading to dose reduction
  - TEAE leading to study drug interruption
- TEAE leading to study drug discontinuation
- TEAE leading to study discontinuation
- Treatment-related TEAE leading to dose modification (reduction or interruption)
  - Treatment-related TEAE leading to dose reduction
  - Treatment-related TEAE leading to study drug interruption
- Treatment-related TEAE leading to study drug discontinuation
- Treatment-related TEAE leading to study discontinuation

11.2.2. Participant Incidence of Treatment Emergent Adverse Events

The following summaries of participant incidence will be presented:

- TEAEs by MedDRA SOC and PT
- TEAEs by MedDRA PT
- Non-Serious TEAEs by MedDRA SOC and PT (for the purpose of clinicaltrials.gov)
- GI TEAEs by MedDRA PT
- TEAEs by MedDRA SOC, PT, and maximum severity
- Serious TEAEs by MedDRA SOC and PT
- Serious TEAEs by MedDRA PT
- ≥ Severe TEAEs by MedDRA SOC and PT
- Treatment-related TEAEs by MedDRA SOC and PT.
- Treatment-related GI TEAEs by MedDRA PT
- Treatment-related Serious TEAEs by MedDRA SOC and PT
- Treatment-related Serious GI TEAEs by MedDRA PT
- Treatment-related ≥ Severe TEAEs by MedDRA SOC and PT
- Treatment-related ≥ Severe GI TEAEs by MedDRA PT
- TEAEs related to study procedures
- TEAEs leading to dose modification (reduction or interruption) by MedDRA SOC and PT
- TEAEs leading to dose reduction by MedDRA SOC and PT
- TEAEs leading to study drug interruption by MedDRA SOC and PT
- TEAEs leading to study drug discontinuation by MedDRA SOC and PT

- TEAEs leading to study discontinuation by MedDRA SOC and PT

Summaries will be ordered by descending order of incidence of SOC and PT within each SOC based on the incidence of all TERN-601 combined for the safety analysis set.

An additional summary of participant incidence of GI TEAEs will be presented by week of onset and maximum grade. The value for week of onset will be calculated as

(date of onset - first dose date of study drug + 1) / 7

and rounded up to the nearest integer. The TEAEs will also be counted in each week of continuation up to the end of study date. Percentages for each week will be based on the number of participants who were still on study at that time.

The following listings will be presented by treatment group and participant, including the duration of event:

- All AEs
- Deaths
- Serious TEAEs
- TEAEs leading to study drug discontinuation
- ≥ Severe TEAEs (including events with missing severity)
- Treatment-related TEAEs (including events with missing relationship)
- GI TEAEs
- TEAEs related to study procedures
- TEAEs leading to dose modification (reduction or interruption)
- TEAEs leading to study discontinuation
- TEAEs leading to death (where AE outcome is “Fatal” or severity is “Death” or seriousness criteria is Death)

11.3. Clinical Safety Laboratory Evaluations

All laboratory assessments are specified in the study protocol. Laboratory parameters will be summarized in conventional units.

Fasting glucose and HbA1c are markers of GLP-1R agonism and will be summarized separately as part of the exploratory efficacy analyses (Section 8.7.4.2). Lipids, NT-proBNP, and hs-CRP are PD endpoints and will be summarized separately as part of the pharmacodynamic analyses (Section 9). Fasting glucose and lipids will be included in safety summaries of treatment emergent laboratory abnormalities and CTCAE grade shift tables.

Glomerular filtrate rate (GFR) will be estimated and provided by the central lab, using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) for estimated glomerular filtrate rate (eGFR) formula. If local labs are collected, eGFR will be derived using the same formula if serum creatinine is collected.

Quantitative hematology, serum chemistry, coagulation, thyroid (TSH and calcitonin) and pancreatic (amylase/lipase) results will be summarized by treatment group using descriptive statistics at baseline and at each post-baseline visit. Change from baseline values will also be summarized.

All clinical safety laboratory data will be presented in by-participant data listings. Any laboratory values that fall outside of the normal range will be presented in a separate listing. All laboratory normal ranges by lab category, lab parameter, lab type (central vs. local), sex, and age, will also be presented in a listing.

11.3.1. Treatment Emergent Abnormalities

Quantitative laboratory tests will be assigned grades based on NCI CTCAE, version 5. Grade 0 will be assigned for all non-missing values not graded as 1 or higher. Grade 5 will not be used.

Some lab tests include additional clinical criteria which *cannot be determined programmatically*. Table 10 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

Albumin (Hypoalbuminemia) • *Grade 4: Life-threatening consequences; urgent intervention indicated.*
Amylase (Serum amylase increased) and Lipase (Lipase increased) • Grade 2: >1.5 - 2.0 x ULN; >2.0 - 5.0 x ULN *and asymptomatic* • Grade 3: >2.0 - 5.0 x ULN *with signs or symptoms*; >5.0 x ULN *and asymptomatic*. • Grade 4: >5.0 x ULN *and with signs or symptoms.* As Grade 2 and Grade 3 cannot be differentiated programmatically, the lowest grade (Grade 2) will be assigned unless otherwise directed by a Medical Monitor. Similarly, as Grade 3 and Grade 4 cannot be differentiated programmatically, the lowest grade (Grade 3) will be assigned unless otherwise directed by a Medical Monitor.
Bicarbonate (Blood bicarbonate decreased): • Grade 1: <LLN *and no intervention initiated*.
eGFR (Chronic Kidney Disease): • Grade 4: <15 mL/min/1.73m^2; *dialysis or renal transplant indicated*
Eosinophils (Eosinophilia) • *Grade 3: Steroids initiated*
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*
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*
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*
Triglycerides (Hypertriglyceridemia) • Grade 4: >1000 mg/dL; >11.4 mmol/L; *life-threatening consequences*
Leukocytes (Leukocytosis) • *Grade 4: Clinical manifestations of leucostasis; urgent intervention indicated*

Abbreviations: LLN = lower limit of normal; ULN = upper limit of normal

For each applicable laboratory test, a treatment emergent abnormality will be defined as a post-baseline CTCAE grade worsening of ≥2 grades.

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

Newly observed or worsened laboratory abnormalities with grade 3 or 4 will be presented separately. Any laboratory toxicity will be defined as being newly occurring or worsening grade 3 or 4 if:

- Participants have baseline result missing or a grade 0, 1 or 2 and then develop grade ≥ 3, or
- Participants have baseline result of a grade 3 and then develop grade 4.

Listings will be presented for participants with any treatment emergent laboratory abnormality.

11.3.2. Shifts in CTCAE Grade

Quantitative laboratory tests will be assigned grades based on NCI CTCAE, version 5. See Section 11.3.1 for details on how grades will be assigned. Shifts in CTCAE grade of laboratory tests will be presented from baseline to worst post-baseline value, as well as at each visit. Denominators for percentages will be the number of participants with non-missing data at the specific timepoint and baseline.

11.3.3. Special Assessments of Potential Hepatoxicity

Modified Hy's rule by Björnsson (Björnsson, E and R Olsson, 2005, Outcome and Prognostic Markers in Severe Drug-Induced Liver Disease, Hepatology, 42(2):481-9.) is defined as participants with ALT or AST values >3× ULN and total bilirubin >2× 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).

The number and percentage of participants who meet the criteria in Table 11, based on their maximum post-baseline value, will be presented to assess any potential for drug-induced hepatotoxicity or liver injury per Guidance for Industry: Drug Induced Liver Injury: Premarketing Clinical Evaluation, CDER, FDA (Guidance for Industry: *Drug Induced Liver Injury: Premarketing Clinical Evaluation*, CDER, FDA (2009).

). Any participant meeting the criteria will be presented in a by-participant listing.

Table 11: Potential Hepatoxicity Laboratory Abnormalities

Hepatocellular Injury and Liver Function Tests	Range of Test Values
ALT	>3 to 5 × ULN
	>5 to 8 × ULN
	>8 to 10 × ULN
	>10 to 20 × ULN
	>20 × ULN
	>2 × Baseline, if Baseline >ULN
AST	>3 to 5 × ULN
	>5 to 8 × ULN
	>8 to 10 × ULN
	>10 to 20 × ULN
	>20 × ULN
	>2 × Baseline, if Baseline >ULN
ALT or AST	>3 to 5 × ULN
	>5 to 8 × ULN
	>8 to 10 × ULN
	>10 to 20 ×ULN
	>20 × ULN
	>2 × Baseline, if Baseline >ULN
Total bilirubin	> ULN
	>1.5 × ULN
	>2 × ULN
ALP	>1.5 × ULN
	>2 × ULN
ALT or AST plus total bilirubin	>3 × ULN (ALT or AST) plus >1.5 × ULN Total Bilirubin, and <2 × ULN ALP
	>3 × ULN (ALT or AST) plus >2 × ULN Total Bilirubin, and <2 × ULN ALP

ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; ULN = upper limit of normal

Liver enzymes (ALT, AST, ALP) and Total Bilirubin will be evaluated in terms of upper limits of normal (ULN). The result will be divided by the ULN and summarized, along with change from baseline, by treatment and visit using descriptive statistics.

An additional summary of participants meeting the liver function test increased monitoring criteria listed in Appendix Table 9 of the protocol will be presented by treatment group. The number and percentage of participants meeting each individual criteria as well as any of the criteria will be summarized based on their maximum post-baseline results.

eDISH (evaluation of Drug-Induced Serious Hepatotoxicity) scatter plots will be provided for each of the following:

- maximum post-baseline ALT/AST vs. maximum post-baseline total bilirubin
- maximum on-treatment ALT/AST vs. maximum on-treatment total bilirubin
- post-treatment ALT/AST vs. post-treatment total bilirubin,

where post-baseline is collection any time after first dose of study drug, on-treatment is defined as collection any time after first dose of study drug up to the last dose of study drug, and post-treatment is defined as collection any time after last dose of study drug. Values presented on the plots will be the ratio of results to ULN.

11.4. Vital Signs

Blood pressure (systolic and diastolic) will be summarized as part of the pharmacodynamic analysis (Section 9) and not included in safety analyses.

The following vital sign parameters will be included in safety analyses: pulse rate (beats/minute) and body temperature (˚C). Descriptive statistics will be provided by treatment group and scheduled visit. Changes from baseline by visit will also be presented. Repeat assessments will be averaged for the by-visit analyses. The maximum and minimum change from baseline of all individual assessments will be presented using descriptive statistics.

All vital signs observed, change from baseline, and average values will be presented in by-participant data listings.

11.5. Electrocardiograms

Electrocardiogram (ECG) parameters include QT interval corrected by the Fridericia's formula [QTcF] (msec), QT (uncorrected) interval (msec), heart rate (beats/min), RR interval (msec), PR interval (msec), and QRS duration (msec). Overall interpretation results are collected as normal, abnormal not clinically significant (NCS), and abnormal clinically significant (CS).

Electrocardiogram values for heart rate, QRS Duration and RR, PR, QT, and QTcF intervals will be taken in triplicate. The average value of the triplicate results will be summarized using descriptive statistics by treatment group and scheduled visit including change from baseline. If the number of non-missing values recorded at a visit is less or more than 3, the average of those values will still be included in the analysis. The maximum change from baseline will also be summarized using descriptive statistics.

A categorical summary of abnormal QTcF values will be presented by treatment group, in accordance with ICH E14 (Note for guidance on the clinical evaluation of QT/QTc interval prolongation and proarrhythmic potential for non-antiarrhythmic drugs, CHMP/ICH/2/04). The number and percentage of participants with observed QTcF values of >480 and >500 msec and increase from baseline values of >30 and >60 msec will be presented for each study visit and maximum post-baseline value/increase during the study.

All ECG data and changes from baseline will be presented in a by-participant data listing. For any participants with a QT or QTcF >500 msec, or QTcF change from baseline of >60 msec, a separate listing of all ECG data for these participants will be provided.

11.6. Patient Health Questionnaire 9 (PHQ-9)

The PHQ-9 includes 9 direct questions related to depression, sleep issues and suicidal thoughts. A follow-up non-scored question screens and assigns weight to the degree to which depressive problems have affected the participant's level of function. An example of the questionnaire is provided in Appendix 6 of the protocol. The score for each of the 9 questions in the PHQ-9 ranges from 0 ("Not at all") to 3 ("Nearly every day"). The total score is the sum of the 9 individual question scores (range from 0 to 27). The total score and the individual question scores as well as changes from baseline will be summarized using descriptive statistics by treatment group and scheduled visit. All PHQ-9 results will be provided in a by-participant listing.

11.7. Columbia-Suicide Severity Rating Scale (C-SSRS)

The C-SSRS measures four elements: the severity of ideation, the intensity of ideation, behavior and lethality. The C-SSRS consists of 10 categories, with a binary response option (yes/no). At screening, the "Baseline/Screening" version will be administered and at all other visits, the "Since Last Visit" version will be administered. For the "Baseline/Screening"' version participants will report on ideation and behavior for their lifetime and for the previous 1 year. For "Since Last Visit" versions, participants will be asked to report on ideation and behavior since the last scheduled C-SSRS assessment.

C-SSRS data will be listed by treatment, participant and visit. Participants who report any suicidal ideation, defined as a response of "yes" to any question under the Suicidal Ideation section, or suicidal behavior, defined as a response of "yes" to any question under the Suicidal Behavior section, will also be listed separately.

12. OTHER ASSESSMENTS

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

- Alcohol/substance abuse
- Concomitant procedures
- Urinalysis and urine microscopic examination
- Pregnancy testing
- Follicle stimulating hormone (FSH)
- Urine drug and alcohol screen
- Serology
- Physical examination

- Comments

13. CHANGES TO PROTOCOL PLANNED ANALYSES

Hip circumference, waist-to height ratio and BMI were added to the list of exploratory endpoints to evaluate the effect of TERN-601 on markers of GLP-1R agonism. These parameters are not included in the protocol as exploratory endpoints for analysis, but they are included in the SAP for completeness.

The definition of the PK sub-study analysis set was updated to include additional criteria: “and for whom at least one PK parameter can be calculated” to account for participants with sparse PK data.

14. REFERENCES

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15. APPENDICES

APPENDIX 1. 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, CM = concomitant medication, Dec = December, Jan = January		

APPENDIX 2. ABBREVIATIONS

Abbreviation or Special Term	Explanation
A1C	Akaike's information criterion
ADI	actual dose intensity
AE	adverse event
ALT	alanine transaminase
ANOVA	analysis of variance
ANCOVA	analysis of covariance
ApoB	apolipoprotein B
AR	autoregressive
AST	aspartate transaminase
ATC	Anatomic Therapeutic Class
AUC	area under the concentration-time curve
BMI	body mass index
BLQ	below the limit of quantification
CHMP	Committee for Medicinal Products for Human Use
CI	confidence interval
C_{max}	maximum observed plasma concentration
CMH	Cochran-Mantel-Haenszel
CRF	case report form
C-SRSS	Columbia Suicide Severity Rating Scale
CS	compound symmetry
CSR	clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
CTMS	clinical trial management system
CV	coefficient of variation
eGFR	estimated glomerular filtration rate
eCRF	electronic case report form
eDISH	evaluation of Drug-Induced Serious Hepatotoxicity
ECG	electrocardiogram
EEOT	early end of treatment
ET	early termination
FDA	Food and Drug Administration
FSH	follicle stimulating hormone
F/U	follow-up
GI	gastrointestinal

Abbreviation or Special Term	Explanation
HbA1c	hemoglobin A1c
HCS	heterogeneous compound symmetry
HDL	high-density lipoprotein
HDPE	high density polyethylene
hs-CRP	high-sensitivity C-reactive protein
ICE	intercurrent event
ICF	informed consent form
ICH	International Council for Harmonisation
IMP	investigational medicinal product
IP	investigational product
INR	international normalized ratio
IRT	interactive response technology
ITT	intent-to-treat
IWQOL-Lite-CT	Impact of Weight on Quality of Life - Lite - Clinical Trials Version
LDL	low-density lipoprotein
LLN	lower limit of normal
LLOQ	lower limit of quantitation
LS	least square
MAR	missing at random
MCMC	Markov Chain Monte Carlo
MedDRA	Medical Dictionary for Regulatory Activities
MI	multiple imputation
MMRM	mixed model repeated measures
MNAR	missing not at random
NC	not calculated
NCI	National Cancer Institute
NIMP	non-investigational medicinal product
NR	no result
NT-proBNP	N-terminal pro-B-type natriuretic peptide
PD	pharmacodynamic(s)
PDI	planned dose intensity
PHQ-9	Participant Health Questionnaire 9
PK	pharmacokinetic(s)
PMM	pattern mixture-model
PT	preferred term

Abbreviation or Special Term	Explanation
Q1	25th percentile, first quartile
Q3	75th percentile, third quartile
QD	once daily
REML	restricted maximum likelihood
SAP	statistical analysis plan
SD	standard deviation
SE	standard error
SoA	schedule of activities
SOC	system organ class
ST	slow titration
TEAE	treatment emergent adverse event
ULN	upper limit of normal
VLDL	very low-density lipoprotein
WBC	white blood cell
WHODD	World Health Organization Drug Dictionary

APPENDIX 3. DOCUMENT HISTORY

Version	Date	Author	Description
1.0	29SEP2025	[redacted]	Final Version 1

APPENDIX 4. APPROVAL PAGE

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

APPROVALS		
[redacted] I am the author of this document 29-Sep-2025 | 15:46 PDT AD461B5892E140B2A5FFA774D67614A5		29-Sep-2025 | 15:46 PDT
[redacted] Principal Statistician [redacted] *<<See Electronic Signature Page at end of document>>*		**Date** (dd-mmm-yyyy)
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[redacted] Chief Medical Officer Terns, Inc *<<See Electronic Signature Page at end of document>>*		**Date** (dd-mmm-yyyy)
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