CLINICAL STUDY PROTOCOL

Protocol Title:	A Phase 2 Study to Evaluate the Efficacy, Safety, and Tolerability of TERN-601 in Adults with Overweight or Obesity
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Short Title:	Study of TERN-601 in Adults with Overweight or Obesity
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Sponsor Signatory:

<<See Electronic Signature Page at the end of this document>>

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Chief Medical Officer
Terns, Inc.

Date

Medical Monitor Name and Contact Information will be provided separately.

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1. Protocol Summary

1.1. Synopsis

Protocol Title:

A Phase 2 Study to Evaluate the Efficacy, Safety, and Tolerability of TERN-601 in Adults with Overweight or Obesity

Short Title:

Study of TERN-601 in Adults with Overweight or Obesity

Rationale:

TERN-601 is an orally bioavailable small molecule glucagon-like peptide-1 (GLP-1) receptor agonist that is being developed for chronic weight management in adults. Study TERN601-2003 is a 12-week Phase 2 multicenter, randomized, double-blind, placebo-controlled study designed to evaluate the efficacy and safety of four titration schedules of TERN-601 administered once daily compared with placebo in participants who have overweight or obesity. The primary objective is to demonstrate that at least one treatment arm of TERN-601 is superior to placebo in percent body weight reduction. This study is also designed to inform the dose selection and dose titration schedule for longer term studies.

Objectives:

Primary Objective:

- To evaluate the effect of TERN-601 on body weight relative to placebo

Secondary Objective:

- To assess the safety and tolerability of TERN-601

Exploratory Objectives:

- To evaluate the pharmacokinetics (PK) of TERN-601
- To assess the effect of TERN-601 on glycemic control
- To evaluate the effect of TERN-601 on waist circumference
- To evaluate the effect of TERN-601 on quality of life
- To evaluate the effect of TERN-601 on cardiovascular risk factors
- To evaluate the effect of different titration schedules of TERN-601 on gastrointestinal (GI) tolerability

Endpoints:

Primary Endpoint:

- 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

Safety Endpoint(s):

- Participant incidence of treatment-emergent adverse events
- Change from baseline in laboratory parameters
- Change from baseline in ECG parameters
- Change from baseline in vital sign parameters

Exploratory Endpoints:

- PK parameters (eg, AUC, C_{max}, C_{tau})
- Proportion of participants achieving ≥10% or ≥15% weight loss
- Change from baseline in waist circumference and waist-to-hip ratio
- Change from baseline in fasting glucose and HbA1c
- Change from baseline in IWQOL-Lite-CT
- Change from baseline in fasting lipids, NT-proBNP, hs-CRP, and blood pressure
- Nausea burden score

Overall 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.

Disclosure Statement:

This is a placebo-controlled, treatment study with 5 arms that is participant-, Investigator-, and Sponsor-blinded.

Number of Participants:

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.

Intervention Groups and Duration:

There will be four TERN-601 treatment arms and one placebo treatment arm (Figure 1-1). Each participant will be randomly assigned to one of the five treatment arms in a 1:1:1:1:1 manner. To maintain the blind, all treatments will be administered as 3 tablets from 3 different bottles contained in each weekly kit, taken orally once daily and without regard to food. Dose interruptions and/or dose reductions will be allowed for the management of adverse events (AEs); see Section 6.6 Dose Modifications/Reductions and Section 6.7 Study Drug Interruption for details on dose reductions and/or interruptions. Each participant will be on study

approximately 20 weeks, including a ≤4-week screening period, 12-week treatment period, and a 4-week follow-up period.

1.2. Schema

Figure 1-1 Treatment Arms

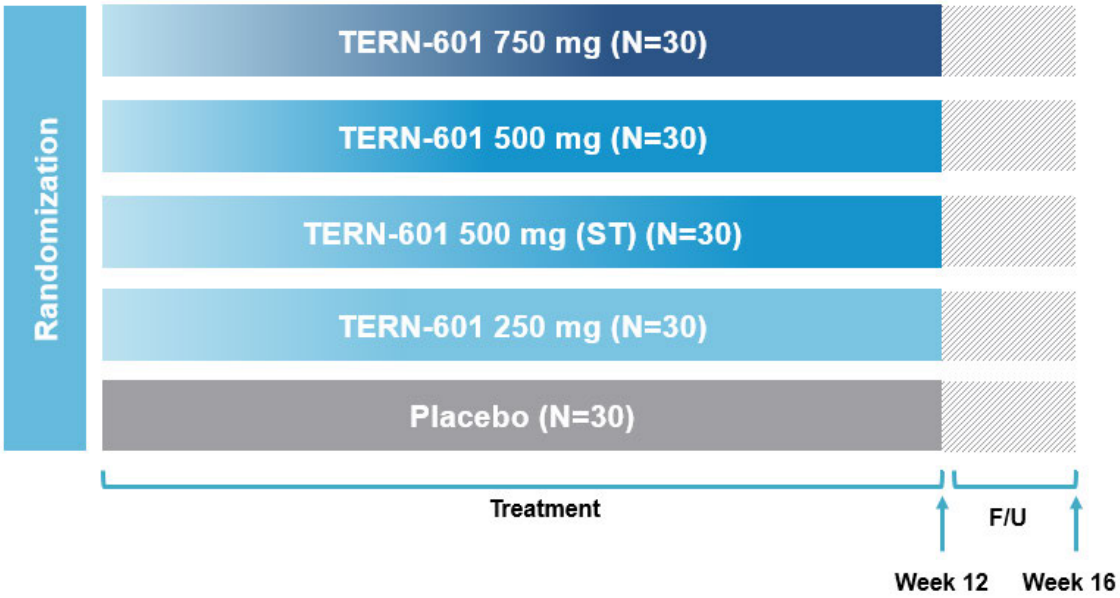
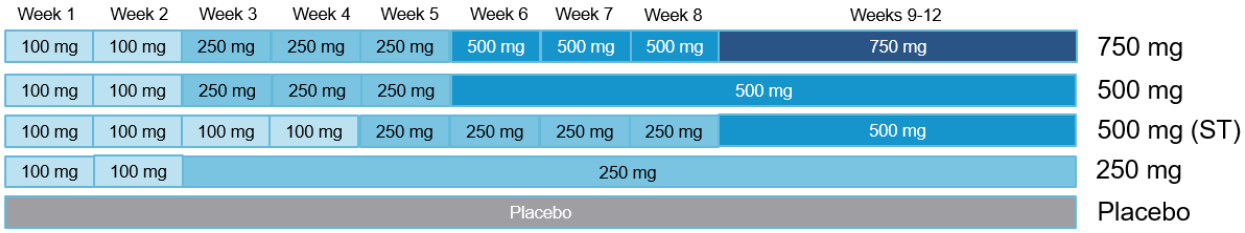


Figure 1-2 Treatment Arm Dose Titration Schedules



1.3. Schedule of Activities (SoA)

	Screening	Treatment Period						Follow-up
Visit/Week	**Screening**	**Randomization**	**2**	**4**	**5**	**8**	**12[b]/EEoT**	**16/FU[q]**
Study Day[a]	**-30 to -1**	**1**	**14**	**28**	**35**	**56**	**84**	**112**
Participant Fasting	X	X	X	X		X	X	X
Informed consent	X							
Review Inclusion and Exclusion Criteria	X	X[d]						
Medical History	X							
Randomization[c]		X						
Demographics	X							
Height	X							
Weight and BMI[e,i]	X	X[c,d]	X	X		X	X	X
Waist Circumference		X		X		X	X	X
Hip circumference and waist to hip ratio calculation		X		X		X	X	X
Physical Examination[f]	X						X	X
Vital Signs[g]	X	X[d]	X	X		X	X	X
Triplicate 12-lead ECG[h]	X	X[d]		X		X	X	X
Urinalysis	X	X[d]	X	X		X	X	X
Chemistry[i]	X	X[d]	X	X		X	X	X
Hematology	X	X[d]	X	X		X	X	X
Coagulation	X	X					X	X
Fasting Lipid Profile[i,j]	X	X[d]	X	X		X	X	X

	Screening	Treatment Period						Follow-up
Visit/Week	**Screening**	**Randomization**	**2**	**4**	**5**	**8**	**12[b]/EEoT**	**16/FU[q]**
NT-proBNP		X[d]					X	X
hs-CRP		X[d]					X	X
HbA1c	X						X	
TSH	X	X					X	X
Calcitonin	X	X[d]		X		X	X	X
Amylase/Lipase	X	X[d]		X		X	X	X
HIV/HBV/HCV Screening	X							
Serum FSH[r]	X							
Serum pregnancy test (WOCBP only)	X		X	X		X	X	X
Urine pregnancy test (WOCBP only)		X[d,k]						
Urine Drug and Alcohol Screen	X							
Urine Drug Screen		X[d,k]		X		X	X	X
Optional Intensive PK Sub-study[l]							X	
Sparse PK Sampling[m]			X	X		X	X[n]	
Exploratory biomarker sample collection[o]		X[d]		X		X	X	
Genetic buccal swab collection		X[d]						
IWQOL-Lite-CT		X[d]					X	
C-SSRS Baseline/Screening version	X							
C-SSRS Since Last Visit version		X[c,d]	X	X		X	X	X
PHQ-9	X	X[c,d]	X	X		X	X	X
Study Drug Dispensing[p]		X	X	X	X	X		

	Screening	Treatment Period						Follow-up
Visit/Week	**Screening**	**Randomization**	**2**	**4**	**5**	**8**	**12[b]/EEoT**	**16/FU[q]**
Participant returns unused study drug & study drug accountability			X	X	X	X	X	
Take Study Drug Tablets		←==========→						
Diet and Exercise Counseling		←==========→						
Adverse Events Review		←==========→						
Concomitant Medications Review		←==========→						

a. Where applicable, visits should be conducted ±3 days of Study Day, with the exception of the Week 16/Follow-Up visit which should be conducted within -7 days/+3 days of nominal Study Day.

b. Week 12 visit should occur as close as possible to the last day of Week 12 (Day 84); it should ideally correspond to the last dose of study drug. If a participant discontinues study drug administration prior to completion of the treatment period, the participant should complete the same procedures listed for Week 12 as an Early End of Treatment (EEoT) visit, as soon as feasible. If a participant also discontinues further study participation at EEOT, the participant should also return to the clinic approximately 4 weeks after the last dose of study drug for the Final Follow-up (FU) Visit.

c. Clinical status will be re-confirmed before randomization and/or 1st dose of study drug.

d. Assessments shall be performed, or sample shall be collected, prior to first dose of study drug.

e. See Section 8.1.3 for details on weight measurement. During the treatment period, a participant's height at Screening will be used to calculate BMI.

f. Targeted physical examinations can be conducted at any study visit as necessary to evaluate AEs or symptoms reported by the participant, or abnormal laboratory results per the Investigator's discretion.

g. Vital signs should be collected in the supine position after participant has been supine for ≥5 minutes; Includes BP, PR, and temperature.

h. Triplicate ECGs should be collected in the supine position after participant has been supine for ≥10 minutes. Triplicate 12-lead ECGs will be collected as 3 single ECGs acquired ≥1 minute apart, within a 5-minute window, after participant has been supine in a quiet setting without distractions for ≥10 minutes prior to 12-lead ECG collection.

i. Participant should be fasting for assessment and/or sample collection. Participants should also be instructed to hold their dose on days where fasting is required, however, lab samples or assessments that are collected or performed postdose will not be considered a protocol deviation.

j. Extended lipid panel, includes: TC, TG, HDL, non-HDL, LDL, VLDL, ApoB. See Appendix 1.

k. Negative urine pregnancy test and urine drug screen must be confirmed prior to randomization.

l. Participants choosing to participate in the PK substudy should hold their dose at the Week 12 visit until after collection of the predose PK sample. Samples will be collected at predose (0 hr) and 1, 2, 4, 6, 8, 24, and 48 hours postdose; the date, time, and prandial state of the last dose prior to the predose PK sample and the dose administered at the Week 12 visit will be recorded.

m. Sparse PK samples can be collected anytime relative to dosing; the date, time, and prandial state of the last dose prior to PK sample collection will be recorded.

n. Participants participating in the optional PK substudy will not have a Week 12 sparse PK sample collected (ie, intensive PK samples will take the place of the sparse PK sample).

o. Two dedicated serum samples will be collected at each scheduled timepoint.

p. Study drug will be dispensed in weekly kits with 3 bottles per kit. At the Randomization visit on Day 1, participants will receive two kits for a 2 week supply of study drug (ie, they will receive the kit for Week 1 (Days 1-7) and Week 2 (Days 8-14) dosing); at the Week 2 visit participants will receive two kits (2 week supply); at the Week 4 visit, participants will receive one kit (1 week supply); at the Week 5 visit, participants will receive three kits (3 week supply); at the Week 8 visit, participants will receive four kits (4 week supply).

q. FU = Follow-Up visit; For participants that complete the study as per protocol with the last dose of study drug at Week 12, the Follow-Up visit should coincide with Week 16.

   - For participants that discontinue study drug administration prior to Week 12 but agree to continue participation in the study, the EEoT visit should be completed at the time of study drug discontinuation and the Follow-Up Visit should be completed approximately 4 weeks after a participant completes the Week 12 visit or permanently discontinues from the study (e.g. the Follow-Up should coincide with Week 16 if the participant completes all remaining study visits).
   - If a participant discontinues study drug administration and simultaneously discontinues from the study prior to the Week 12 visit, the EEoT visit should be completed at the time of study drug discontinuation and the Follow-Up visit should be completed approximately 4 weeks after the last dose of study drug (i.e., visit should be completely approximately 4 weeks after the EEoT visit).

r. Serum FSH to be collected as needed to confirm postmenopausal status in women of nonchildbearing potential due to presumed menopause (as outlined in Appendix 10); surgically sterile women need not have an FSH. If postmenopausal status cannot be confirmed by FSH, the participant will be required to follow the protocol-mandated contraception guidance and pregnancy testing.

2. Introduction

TERN-601 is an orally bioavailable small molecule glucagon-like peptide-1 (GLP-1) receptor agonist that is being developed for chronic weight management in adults.

2.1. Study Rationale

Study TERN601-2003 is a 12-week Phase 2 multicenter, randomized, double-blind, placebo-controlled study designed to evaluate the efficacy and safety of four titration schedules of TERN-601 administered once daily compared with placebo in participants who have overweight or obesity. The primary objective is to demonstrate that at least one treatment arm of TERN-601 is superior to placebo in percent body weight reduction. This study is also designed to inform the dose selection and dose titration schedule for longer term studies.

2.2. Background

2.2.1. Obesity

Obesity is as a chronic, complex, relapsing disease that impacts an individual's health by increasing complications such as prediabetes and T2DM, cardiovascular disease, polycystic ovary syndrome, metabolic dysfunction-associated steatotic liver disease, cancers, and depression. The World Health Organization (WHO) classifies obesity as a global epidemic, and the prevalence of obesity is rapidly rising across the world. Approximately 1 in 3 adults is living with obesity in North America, and 8% of deaths worldwide, comprising 4.7 million deaths annually, are attributable to complications associated with obesity. Obesity is associated with decreased life expectancy of 5 to 20 years. It is increasingly recognized that obesity is not merely a risk factor for other illnesses but is a disease in its own right.

Historically, weight-loss therapies have focused on intensive lifestyle changes concurrent with medications, which often confer minimal to modest weight loss. The majority of individuals rapidly regain, and more than 50% of individuals who underwent a weight loss regimen have been shown to regain almost all of their weight after 5 years. The failure to maintain weight loss may be due to counterregulatory mechanisms that promote weight regain, including a decrease in basal metabolic rate and persistent changes in appetite regulatory hormones. These altered biological mechanisms underlie why short-term lifestyle interventions are frequently insufficient for long-term weight loss.

Bariatric surgery, which may be indicated for individuals with a BMI ≥35 (or between 30 and 35 with an obesity-related condition), generally results in a higher degree of sustained weight loss compared with intensive medical therapy. However, bariatric surgery has adverse effects, including malabsorption and micronutrient deficiency, and carries potential postoperative surgical risks of bleeding, anastomotic leaks, and infections. Moreover, bariatric surgery is contraindicated in patients with medical conditions such as severe heart failure, unstable coronary artery disease, respiratory disease, coagulopathy, mental health concerns, or drug/alcohol dependency.

2.2.2. GLP-1R Agonists

Non-surgical interventions to induce weight loss were transformed by the discovery and development of therapeutics targeting GLP-1R. Activation of GLP-1R by GLP-1 stimulates postprandial pancreatic insulin release to lower blood glucose, delays gastric emptying, and induces satiety, leading to reduced food intake. While GLP-1R agonists (GLP-1RAs) were initially developed for the treatment of T2DM given their ability to lower blood glucose, GLP-1R agonism can also induce highly significant weight-loss effects, approaching those achieved with bariatric surgery. Wegovy (2.4 mg once-weekly dose of semaglutide), an injectable, synthetic, stabilized version of GLP-1, was approved by the US FDA in 2021 for chronic weight management in adults with obesity or adults with overweight who have at least one weight-related condition (such as hypertension, T2DM, or dyslipidemia), for use in addition to a reduced-calorie diet and increased physical activity (WEGOVY 2023). Wegovy was the second GLP-1RA approved for body weight management, as Saxenda (3 mg liraglutide QD) was approved by the FDA in 2014 for treatment of adult obesity and in 2020 for obesity in adolescents aged 12 to 17 years (SAXENDA 2023). More recently, Zepbound (5, 10, and 15 mg once-weekly tirzepatide), a dual agonist for GLP-1R and glucose-dependent insulinotropic polypeptide receptor (GIPR), was approved by the FDA in 2023 for the treatment of adult obesity.

The emerging evidence of the efficacy of peptide-based GLP-1RAs in lowering weight and improving glycemic control and cardiometabolic risk in patients with or without T2DM has established this mechanism as a target for highly efficacious pharmacotherapy (Husain 2019, Lincoff 2023). While peptide-based GLP-1RAs have revolutionized obesity pharmacotherapy, currently approved medications require daily or weekly subcutaneous injection. Research suggests patients may prefer oral medications over injectables and are also more likely to adhere to oral therapies. Rybelsus, a version of semaglutide coformulated with sodium N–[8–(2 hydroxybenzoyl)amino]-caprylate, a gastric absorption enhancer, to promote oral bioavailability, was approved in 2019 to improve glycemic control in patients with T2DM; oral semaglutide is not approved as a therapy for chronic weight management. In addition, the bioavailability of semaglutide (a large peptide molecule) dosed orally is relatively low due to poor absorption, which is further impaired by the presence of food or water in the stomach. Therefore, Rybelsus must be taken QD, in a fasted state, with minimal liquid. Further, the approved daily dosage of 7 to 14 mg QD for glycemic control is substantially greater than that of the approved once-weekly injectable formulation and only results in moderate weight loss. Thus, there remains an unmet need for more effective oral treatments for chronic weight management, including convenient options which may be dosed without regard to food and water consumption.

Non-peptidic (ie, small-molecule) GLP-1RAs (such as TERN-601) can achieve good oral bioavailability with a standard formulation and may be suitable for an oral combination with other small molecule therapeutics. Orally bioavailable GLP-1RAs may have certain advantages over injectable peptides, including improved compliance, lower cost of goods, ease of coformulation with other oral medications, and reduced burden on prescribers to teach patients how to perform self-injections.

2.2.3. TERN-601

TERN-601 is an orally bioavailable small molecule GLP-1RA that is being developed for chronic weight management in adults. As described above, GLP-1R is a well validated target for the treatment of obesity and T2DM with broad physiological roles including slowing gastric emptying, stimulating glucose-dependent insulin secretion to regulate glycemia, and reducing food intake to induce body weight loss.

A brief description of results from nonclinical and clinical testing conducted to date for TERN-601 is provided below. A detailed description of the drug substance and drug product, nonclinical development program, and study design and pharmacokinetic (PK), pharmacodynamic (PD), and safety findings from initial clinical studies of TERN-601 is provided in the Investigator's Brochure.

2.2.3.1. Nonclinical Pharmacology

In vitro pharmacology studies have demonstrated TERN-601 is a potent agonist of human GLP-1R and, like other small molecule GLP-1RAs (eg, danuglipron), is relatively inactive against non-primate GLP-1R. TERN-601 is selective for GLP-1R with minimal activity against highly related G protein-coupled receptors ([GPCRs] eg, glucagon-like peptide-2 receptor [GLP-2R], gastric inhibitory polypeptide receptor [GIPR], and glucagon receptor [GCGR]) and minimal activity across a broad panel of targets (ie, receptors, ion channels, and enzymes) of potential safety concern.

In vivo, TERN-601 demonstrated potent activity in preclinical models of food intake, gastric emptying, glycemic control, and weight loss. In transgenic C57BL/6J mice expressing human GLP-1R (hGLP-1R), single oral doses of TERN-601 led to dose-dependent suppression of ad libitum food intake and slowed gastric emptying. Single oral doses of TERN-601 also significantly lowered blood glucose following intraperitoneal (IP) administration of glucose in an IP glucose tolerance test (IPGTT) in hGLP-1R mice. In diet-induced obese (DIO) hGLP-1R mice, oral dosing of TERN-601 over a 4-week period resulted in dose-dependent reductions in body weight, which was associated with improved body mass composition. In cynomolgus monkey, intravenous (IV) administration of TERN-601 increased glucose disposal and insulin secretion in an IV glucose tolerance test (IVGTT). Together these data support the expected on-target pharmacology of TERN-601 as a selective GLP-1RA. Moreover, the on-target effects of slowing of gastric emptying, suppression of ad libitum food intake, and body weight loss observed in DIO animals support the use of TERN-601 in chronic weight management.

Four Good Laboratory Practices (GLP) safety pharmacology studies have been undertaken with TERN-601 in compliance with International Conference on Harmonisation (ICH) and United States (US) Food and Drug Administration (FDA) guidelines to cover three major organ systems: central nervous system (CNS), respiratory, and cardiovascular. Overall, results from these studies indicate that the risk of adverse effects on the CNS, respiratory, and cardiovascular systems in humans is very low in the clinical development trials.

2.2.3.2. Nonclinical Drug Metabolism and Pharmacokinetics

The absorption, distribution, metabolism, and excretion (ADME) of TERN-601 was characterized in multiple in vitro and in vivo studies across mouse, rat, dog, and monkey, as well as in human tissue incubates. TERN-601 was orally bioavailable with exposure to TERN-601 increasing with dose in a greater than proportional manner in all species evaluated, suggesting saturable clearance. The oral bioavailability ranged from low in monkey (2.8 to 5.3%) to moderate or high depending on dose in mouse (45.6% to 231%), rat (57.0% to 85.2%), and dog (74.0% to 236%). Systemic clearance (CL) ranged from low to high relative to hepatic blood flow (Q_H: 14% to 103%), with low to moderate volume of distribution relative to total body water (TBW: 56% to 216%) across the nonclinical species. Human oral clearance and volume were predicted to be moderate assuming modest oral bioavailability (25%-50%) and this impression was consistent with the observed clinical PK data. TERN−601 was highly plasma protein bound (>99%) in all species evaluated, with high tissue partitioning (K_p = tissue/plasma concentration ratio) to GLP-1R relevant tissue such as the gastrointestinal (GI) tract (K_p value of 5.3-fold in small intestine and 6.5-fold in the large intestine), moderate partitioning to the pancreas (K_p <50%), and low partitioning to the CNS (K_p <10%) in the rat. TERN-601 was primarily cleared as metabolites of oxidation and direct conjugation via biliary-fecal elimination. Formation of oxidative metabolites was mediated primarily through cytochrome P450 (CYP)3A while multiple uridine 5'-diphospho-glucuronosyltransferase (UGT) isozymes were involved in the formation of the acyl-glucuronide metabolite. All metabolites formed in human hepatocytes were also formed in the nonclinical toxicology species, with many of these metabolites observed circulating in the rat and monkey plasma. TERN-601 has high apparent permeability and does not appear to be a substrate for efflux or uptake transporters. There was negligible potential for TERN-601 to inhibit or induce most CYP enzymes, with the exception of CYP2C8 and CYP2D6, where there was low to moderate inhibition potential. TERN-601 is anticipated to be a low to moderate inhibitor of the organic anion transporting polypeptide (OATP) 1B1, 1B3, and 2B1 transporters systemically, with intestinal inhibition of P-glycoprotein (P-gp), breast cancer resistance protein (BCRP) transporter, and CYP3A4 possible.

2.2.3.3. Toxicology

Nonclinical toxicology studies included dose range-finding and repeat-dose toxicity in Sprague Dawley rats and cynomolgus monkeys, with up to 13-weeks of dosing followed by up to 28 days of recovery. In non-GLP studies, administration of TERN-601 by QD oral gavage for up to 7 consecutive days in rats and up to 4 consecutive days in cynomolgus monkey was tolerated at doses up to 300 mg/kg/day and 1000 mg/kg/day, respectively. Once-daily oral administration of TERN-601 for up to 28 days was studied at doses up to 1000 and 500 mg/kg/day in male and female Sprague Dawley rats and up to 700 mg/kg/day in cynomolgus monkeys.

In the 13-week GLP study in Sprague Dawley rats, TERN-601 produced similar findings overall to the 28-day study. The combined findings in the 13-week study of increased organ weight, changes in several liver related clinical pathology parameters, and slight to moderate anatomical pathology changes in hepatocytes, without evidence of necrosis, suggested possible overall adverse effects on liver function at the high-dose level of 750 mg/kg/day. There was no indication of systemic toxicity at the mid- (350 mg/kg/day) and low- (75 mg/kg/day) dose levels when administered via daily oral gavage, QD, for 90 consecutive days to Sprague-Dawley rats of

both sexes. Therefore, under the conditions and procedures followed in this study, the NOAEL of TERN-601 is considered to be 350 mg/kg/day. The NOAEL dose of 350 mg/kg/day resulted in combined male and female steady-state exposures at the NOAEL for C_{max} and $AUC_{0\text{-}24hr}$ was 27950 ng/mL and 189000 hr.ng/mL, respectively.

The non-human primate (cynomolgus monkeys) was considered the sensitive species in the toxicology program and the most pharmacologically relevant species. Once daily oral gavage administration of TERN-601 for up to 28 days was tolerated in cynomolgus monkeys with the NOAEL dose of 100 mg/kg/day. In the 28-day study observations of loose stools, progressing to diarrhea/dehydration, and morbidity in 3 cases (one male and one female receiving 350 mg/kg/day and one male receiving 700 mg/kg/day) appeared to be related to TERN-601 on-target effects that were likely exacerbated by underlying gastrointestinal (GI) conditions or infections. This hypothesis is further supported by the results of the 13-week repeat dose study in monkeys, which resulted in a higher NOAEL.

Based on findings in the 28-day study, TERN-601 was administered at doses of 50, 100, and 300 mg/kg/day (PO, QD) in the 13-week toxicity and toxicokinetic study in cynomolgus monkey, which included a 4-week recovery period. Administration of TERN-601 QD for 13 weeks was not associated with signs of toxicity considered adverse at any dose level. The dose-proportional incidence of emesis and altered feces did not cause an impairment in the overall health of the animals and occurred with decreasing incidence over the duration of the study. Decreased body weight gained in males from the high-dose group normalized during the recovery period. There were no TERN-601-related findings during the ophthalmoscopic examination or ECG recordings performed at the end of the treatment and recovery periods. TERN-601-related findings were observed in the endocrine pancreas (ie, evidence of likely islet cell degranulation) and secondary findings in the exocrine pancreas (ie, decreased acinar cell secretion, likely decreased cytoplasmic zymogen), which were dose proportional in incidence and severity. Of note, the pancreas acinar cell findings were also seen in the 28-day cynomolgus monkey, suggesting possible on target effects of TERN-601. These findings were interpreted as non-adverse because of their minimal to slight severity, absence of concomitant lesions, and the complete reversibility during recovery. Based on available data, the NOAEL was established at 300 mg/kg/day and correlated with combined male and female Day 91 C_{max} and $AUC_{0\text{-}24hr}$ values of 2620 ng/mL and 17800 hr.ng/mL, respectively.

The combined male/female NOAEL exposures from the 13-week repeat dose studies in rats and monkeys are shown in Table 2-1, along with the exposure margins relative to observed human exposures over the clinically relevant dose range. Exposure margins range from 18× to 63× relative to the rat NOAEL exposure and 1.7× to 5.9× relative to the monkey NOAEL exposure over the dose range of 240 mg to 1000 mg QD in humans. Based on the monitorable and reversible nature of the findings in the 13-week toxicity studies in both species, these represent acceptable safety margins for continued clinical development of TERN-601 and dosing for up to 90 days in humans.

Table 2-1 Safety Margins for Human Doses Based on 13-Week Repeat-Dose Toxicity Studies in Rat and Monkeys

Species	Gender	Study Days	NOAEL Dose Level (mg/kg/day)	$AUC_{0\text{-}24hr}$ (hr.ng/mL)	Human Dose AUC Exposure Margin		
					$AUC_{0\text{-}24hr}$ Margin (240 mg)	$AUC_{0\text{-}24hr}$ Margin (500 mg)	$AUC_{0\text{-}24hr}$ Margin (1000 mg)
Rats	M/F	90	350	189000	63	36	18
Monkeys	M/F	91	300	17800	5.9	3.4	1.7

*Estimated NOAEL. Human exposure based on single dose AUC extrapolated to infinity from TER601-1013: 240 mg/day = 3000 hr.ng/mL, 500 mg/day = 5260 hr.ng/mL, and 1000 mg/day = 10400 hr.ng/mL

Abbreviations: AUC = area under the concentration curve; AUC0-24hr = area under the concentration curve from time zero to 24 hours postdose; NHP = non-human primate; NOAEL = no observed adverse effect level; M = male; F = female

Overall, the nonclinical testing conducted to date supports the further advancement of TERN-601 into clinical trials of up to 13 weeks in duration. Taken together, the nonclinical pharmacology, PK, and toxicology studies, TERN-601 is likely to show continued pharmacological efficacy, acceptable PK, and monitorable plus reversible adverse changes with low safety risks in human subjects.

2.2.3.4. Clinical Study Results

TERN-601 has been administered to humans in two Phase 1 studies. Study TERN601-1013 was a first-in-human study that used the original meglumine salt immediate-release (IR) formulation. Study TERN601-1015 evaluated both modified-release (MR) prototype formulations and the IR formulation.

In preliminary assessments of these two Phase 1 clinical studies, TERN–601 exhibited approximately dose-proportional PK across the dose range from 30 mg to 1000 mg with moderately high variability (%CV for AUC ranged from 40% to 75%). At higher doses, evidence of prolonged absorption was observed, providing sustained target coverage (concentration above GLP-1R in vitro potency [EC_{50}]) over 16 to 24 hours, despite a terminal elimination half-life of 3 to 6 hours in the SAD and MAD cohorts. There was no clinically meaningful effect of food or gastric acid reducing agents (ie, PPIs) on TERN-601 PK.

TERN-601 treatment groups exhibited steady, dose-dependent weight loss over 28 days of treatment, while body weight in the placebo group remained relatively stable. Other pharmacodynamic assessments of GLP-1RA mechanism of action, including dose-dependent decreases in patient-reported appetite and hunger scores, slowing of gastric emptying, and suppression of glucose, insulin, and C-peptide levels in a mixed-meal tolerance test (MMTT), supported the efficacy of TERN-601.

In preliminary assessments from two clinical trials (TERN601-1013 and TERN601-1015), single and multiple doses of TERN-601 (single doses up to 1000 mg and multiple doses up to 740 mg for 28 days) administered to 100 otherwise healthy participants with overweight or obesity have been generally well-tolerated. No SAEs or Grade ≥3 AEs have been reported. No participants had related TEAEs that led to dose interruption, reduction, or study drug discontinuation. The most common TEAEs were GI events (eg, mild-to-moderate nausea, vomiting, diarrhea,

constipation), consistent with the pharmacologic action of GLP-1RAs. The increase in incidence and severity of nausea and vomiting in the higher dose 28-day cohorts appeared closely associated with the rapid titration schedule. Per the TERN601-1013 study protocol, fasting glucose levels were measured 2 hours postdose to monitor and identify any instances of fasting hypoglycemia. During the 28-day MAD titration cohorts, hypoglycemia TEAEs, which were transient and mild (fasting glucose level <70 mg/dL and ≥54 mg/dL), were reported in 50.0%, 77.8%, and 88.9% of participants in the TERN-601 240 mg, 500 mg, and 740 mg groups, respectively. No incidences of hypoglycemia were observed at predose timepoints. There were no clinically meaningful changes in heart rate, blood pressure or ECG parameters.

Overall, the preliminary PK, PD, efficacy, and safety data from the first 2 clinical studies support the continued clinical development of TERN-601 for chronic weight management.

2.3. Benefit/Risk Assessment

More detailed information about the known and expected benefits and risks, and reasonably expected adverse events of TERN-601, may be found in the Investigator's Brochure. Data from the Phase 1, FIH study TERN601-1013 indicate treatment with TERN-601 may result in a decrease in body weight. These data support the working hypothesis that TERN-601 may improve weight management in participants with obesity. Based on data from the FIH study, there may also be improvement in glycemic control.

Nonclinical safety data of TERN-601 are available from 13-week repeat-dose toxicology studies in rats and monkeys. In the 13-week rat study, decreased weight gain was observed and was considered adverse at the 750 mg/kg dose. In the rat study, there were slight to moderate dose-related increases in bilirubin (total, direct, and indirect) and ALP, which in conjunction with mild microscopic findings of hepatocellular hypertrophy and vacuolation (periportal) were considered important. During the recovery period, weight gain partially recovered, and all other parameters completely recovered. The no observed adverse effect level (NOAEL) was determined to be 350 mg/kg/day (the mid-dose), which provides exposure margins of approximately 36× and 18× relative to exposures observed at TERN-601 doses of 500 mg and 1000 mg in humans (TERN601-1013). Findings from the 13-week monkey study included vomiting, changes in stool consistency, and decreased body weight gain. All parameters recovered or nearly recovered during the recovery period. The NOAEL in the monkey study was the highest dose evaluated (300 mg/kg/day PO), which provides exposure margins of approximately 3.4× and 1.7× relative to exposures observed at TERN-601 doses of 500 mg and 1000 mg in humans (TERN601-1013).

Clinical data to date with TERN-601 have shown a safety profile generally consistent with the GLP-1RA class. Common adverse events observed in the Phase 1 studies (TERN601-1013 and TERN601-1015) included nausea, vomiting, diarrhea, constipation, decreased appetite, and mild/transient fasting hypoglycemia. It is worth noting there were no clinically significant changes in liver enzymes or bilirubin. There were no clinically significant changes in heart rate, blood pressure, or ECG parameters. These safety parameters will continue to be monitored in the Phase 2 study.

The nonclinical and clinical safety findings to date for TERN-601 are considered monitorable, reversible, manageable, and similar to risks for marketed GLP-1RAs. Overall, the benefit/risk

profile is favorable and supports the continued development of TERN-601 as a once daily treatment for chronic weight management in adults with obesity.

3. Objectives and Endpoints

Objectives:

Primary Objective:

- To evaluate the effect of TERN-601 on body weight relative to placebo

Secondary Objective:

- To assess the safety and tolerability of TERN-601

Exploratory Objectives:

- To evaluate the PK of TERN-601
- To assess the effect of TERN-601 on glycemic control
- To evaluate the effect of TERN-601 on waist circumference
- To evaluate the effect of TERN-601 on quality of life
- To evaluate the effect of TERN-601 on cardiovascular risk factors
- To evaluate the effect of different titration schedules of TERN-601 on GI tolerability

Endpoints:

Primary Endpoint:

- 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

Safety Endpoint(s):

- Participant incidence of treatment-emergent adverse events
- Change from baseline in laboratory parameters
- Change from baseline in ECG parameters
- Change from baseline in vital sign parameters

Exploratory Endpoints:

- PK parameters (eg, AUC, C_{max}, C_{tau})
- Proportion of participants achieving ≥10% or ≥15% weight loss
- Change from baseline in waist circumference and waist-to-hip ratio
- Change from baseline in fasting glucose and HbA1c
- Change from baseline in IWQOL-Lite-CT
- Change from baseline in fasting lipids, NT-proBNP, hs-CRP, and blood pressure
- Nausea burden score

4. Study Design

4.1. Overall 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.

This is a placebo-controlled, treatment study with 5 arms that is participant-, Investigator-, and Sponsor-blinded. Each participant will be randomly assigned to one of the 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). For details on dose reductions and/or interruptions, see Section 6.6, Dose Modifications/Reductions and Section 6.7, Study Drug Interruption. 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.

See Section 1.2, Study Schema for more information.

4.2. Scientific Rationale for Study Design

Study TERN601-2003 is a Phase 2 study designed to examine the efficacy, safety, and tolerability of TERN-601 dosed once daily compared with placebo during the 12-week treatment period in participants who have overweight or obesity without diabetes. The primary endpoint at 12-week will allow assessment of clinically meaningful weight loss (ie, ≥5%). Additionally, the safety and tolerability of the doses and dose titration schemes will be used to inform the selection of doses and titration schedules used in longer-term clinical studies. The use of placebo comparison for efficacy and safety is aligned with FDA guidance on development of drugs for weight management.

Consistent with current weight management guidelines, all participants will receive diet and exercise counseling throughout the study.

Participants with diabetes are excluded from this study as the disease and/or concomitant medications used to treat diabetes may impact the interpretation of efficacy and/or safety data from this study.

4.3. Justification for Dose

Maintenance doses of 250 mg, 500 mg, 750 mg administered orally once daily were selected based on data from the FIH study (TERN601-1013), where this dose range demonstrated dose-dependent and clinically meaningful weight loss over 28 days as well as on-target PD effects on appetite questionnaires, gastric emptying, and glycemic parameters. Additionally, this dose range was shown to be well tolerated with no TERN-601-related discontinuations, dose interruptions, or dose reductions, despite a rapid titration schedule, with full titration occurring in ≤2 weeks in

all cohorts. The PK data over this dose range indicated a prolonged absorption profile with sustained target coverage over the dosing interval (12 to 18 hours above the protein corrected GLP-1R in vitro potency (EC_{50}) value of 67 ng/mL), despite a terminal phase half-life of 3 to 6 hours. Phase 1 study TERN601-1013 showed that the faster titration rate in the higher-dose groups likely contributed to more GI side effects compared to the 240 mg group, which had a slower weekly titration and no nausea or vomiting. Therefore, two-to-four-week titration steps were selected for evaluation in this study. The 14-day non-titration cohorts in the FIH study (TERN601-1013) demonstrated 100 mg QD was a well-tolerated dose without titration with rates of nausea similar to placebo and no AEs of vomiting. As such, 100 mg QD was selected as the starting dose for all titration schemes in this 12-week study. The dose range and dose titration schedules were selected to evaluate the effects of these parameters on efficacy, safety, and tolerability of TERN-601 and inform selection of doses and titration schemes that will be used in longer clinical studies.

4.4. End of Study Definition

The end of the study is defined as the date of the last scheduled, or if applicable, unscheduled assessment, for a participant in the study.

5. Study Population

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1. Inclusion Criteria

Participants are eligible to be included in the study only if all of the following criteria apply:

Age

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

Sex

2. Male and/or female, must be willing to follow the contraception requirements defined by the study protocol (Appendix 10)
    a. Female participants of childbearing potential, including those whose postmenopausal status cannot be confirmed, must also have negative pregnancy tests at screening and on Day 1 (prior to Randomization), not be breastfeeding, and not plan to become pregnant or donate eggs (oocytes) during the study or within 30 days after the last dose of study drug
    b. Male participants must be willing not to donate sperm from the first dose of study drug until 90 days after the last dose of study drug

Weight

3. Must have a body mass index (BMI) at Screening and on Day 1 (prior to Randomization) of:
    a. $\geq$30 kg/m^2 to <50 kg/m^2
    OR
    b. $\geq$27 kg/m^2 to <30 kg/m^2 with at least 1 of the following weight-related comorbidities:
        i. Hypertension: on BP-lowering medication or SBP $\geq$130 mmHg or DBP $\geq$80 mmHg at Screening
        ii. Dyslipidemia: on lipid-lowering medication or having LDL $\geq$160 mg/dL or TG $\geq$150 mg/dL or HDL <40 mg/dL for men or HDL <50 mg/dL for women at Screening
        iii. Cardiovascular disease: NYHA Functional Classification Class I-II heart failure
        iv. Obstructive sleep apnea (only in participants >30 years of age)
4. Must have self-reported stable body weight for at least 3 months prior to Screening and prior to Randomization (<5% body weight gain or loss)

Additional Characteristics

5. Must have an HbA1c <6.5% at Screening

Informed Consent

6. Capable of giving signed informed consent as described in Section 10.1.2, which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol

5.2. Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

Medical Conditions

Diabetes Related

1. Have any prior diagnosis of type 1 or type 2 diabetes mellitus (T1DM or T2DM) or rare forms of diabetes mellitus
   Note: Participants with gestational diabetes that resolved >3 years ago (and no current evidence of diabetes mellitus) may be enrolled in the study
2. Have any laboratory value suggestive of diabetes mellitus during Screening, including any of the following:
   - HbA1c ≥6.5% (48 mmol/mol),
   - Fasting glucose ≥126 mg/dL (7.0 mmol/L), or
   - Random glucose ≥200 mg/dL (11.1 mmol/L)

Obesity Related

3. Have had or are planning surgical treatment for obesity, including but not limited to gastric bypass or restrictive bariatric surgery (eg, Lap-Band);
   a. Prior history of liposuction or abdominoplasty are allowed, if performed >1 year prior to Screening
   b. Prior treatment with reversible gastric devices (eg, Lap-Band) are allowed if removed >1 year prior to Screening
4. Have obesity induced by other diagnosed endocrinologic disorders (eg, Cushing's Syndrome, hypogonadism, growth hormone deficiency, hypothalamic disorder, etc) or diagnosed with monogenetic or syndromic forms of obesity (eg, Melanocortin 4 Receptor deficiency or Prader-Willi Syndrome)
   Note: polycystic ovarian syndrome and/or stable/well-controlled hypothyroidism are allowed
5. Have had or are planning endoscopic and/or device-based therapy for obesity; or have had an obesity-related device removed within the last 12 months prior to Screening. Excluded endoscopic and/or device-based therapies for obesity include but not limited to:
   a. Mucosal ablation
   b. Gastric artery embolization
   c. Intragastric balloon
   d. Duodenal-jejunal endoluminal liner
6. Obesity induced by medication
7. Prior treatment with anti-obesity medications (including, but not limited to, GLP-1RAs including compounded GLP-1RAs) or participation in a medical weight loss program within 3 months prior to Screening

Other Medical

8. Have renal impairment, measured as estimated glomerular filtration rate (eGFR) <60 mL/min/1.73m^2, calculated by Chronic Kidney Disease-Epidemiology (CKD-EPI, 2021 equation) at Screening
9. Have a known clinically significant gastric emptying abnormality (eg, severe gastroparesis or gastric outlet obstruction) or regularly take drugs that directly affect GI motility
10. Have a history of acute or chronic pancreatitis
11. Have a history of significant active or unstable Major Depressive Disorder (MDD) or other severe psychiatric disorder (eg, schizophrenia, bipolar disorder, or other serious mood or anxiety disorder) within the last 2 years (MDD that is controlled and stable for >2 years, in the opinion of the Investigator, is allowed).
12. Have a lifetime history of suicide attempt
13. Have a Patient Health Questionnaire-9 (PHQ-9) score of 15 or more at Screening or prior to Randomization
14. On the C-SSRS at Screening and prior to Randomization:
    a. A 'yes' answer to Question 4 (Active Suicidal Ideation with Some Intent to Act, Without Specific Plan) on the "Suicidal Ideation" portion of the C-SSRS

    OR

    b. A "yes" answer to Question 5 (Active Suicidal Ideation with Specific Plan and Intent) on the "Suicidal Ideation" portion of the C-SSRS

    OR

    c. A "yes" answer to any of the suicide-related behaviors (actual attempt [see Exclusion Criterion #12], interrupted attempt, aborted attempt, preparatory act, or behavior) on the "Suicidal Behavior" portion of the C-SSRS

    AND

    d. The ideation or behavior occurred within the past month
15. Have poorly controlled hypertension (ie, supine systolic BP ≥160 mmHg or supine diastolic BP ≥100 mmHg) at Screening, renal artery stenosis, or evidence of labile BP including symptomatic postural hypotension. Participants on antihypertensive medications must be on a stable dose for at least 3 months prior to Screening

    Note: If a single BP measurement demonstrates an SBP ≥160 mmHg or DBP ≥100 mmHg, the BP measurement can be repeated two times more and the average of the 3 BP values used to determine eligibility at Screening
16. Have an elevated resting pulse rate (PR) (>100 bpm) at Screening. If a single PR demonstrates a value outside the normal range, the PR measurement can be repeated two times more and the average of the 3 PR values used to determine eligibility at Screening.
17. Have experienced any of the following cardiovascular conditions within 6 months prior to Screening:

a. Acute myocardial infarction
b. Cerebrovascular accident (stroke)
c. Transient ischemic attack (stroke symptoms that rapidly resolved)
d. Unstable angina
e. Congestive heart failure (CHF) requiring hospitalization

18. Ongoing or history of frequent, intermittent or chronic tachyarrhythmia syndromes (such as atrial fibrillation, supraventricular tachycardia, and positional orthostatic tachycardia syndrome [POTS]).
    Note: Participants with history of premature atrial contractions or premature ventricular contractions may be included in the study
19. Have a history of NYHA Functional Classification III or IV CHF
20. Have an electrocardiogram (ECG) with abnormalities at Screening which are considered by the Investigator to potentially interfere with the interpretation of changes in ECG intervals
21. Have a mean QTcF of >450 msec (male) or >470 msec (female) at Screening
22. Have a personal or family history of long QT syndrome, family history of sudden death in a first-degree relative (parents, siblings, or children) before the age of 40 years, or a personal history of unexplained syncope within the last year.
    Note: Chronic use of prescription or over-the-counter medications known to significantly prolong the QT or QTc interval at Screening is exclusionary
23. Have a history of clinically significant gallbladder disease and/or choledocholithiasis (gallstones)
    Note: Participants with cholecystectomy may be included in the study
24. Have signs and symptoms of any liver disease other than metabolic dysfunction-associated steatotic liver disease, or have any of the following at Screening:
    a. ALT or AST level >3.0× ULN for the reference range
    b. ALP level >1.5× ULN for the reference range
    c. TBL >1.5× ULN for the reference range (except for cases of known Gilbert's Syndrome)
    d. TBL between 1× ULN and 1.5× ULN and direct bilirubin >ULN for the reference range
25. Have evidence of hypothyroidism or hyperthyroidism based on clinical evaluation and/or an abnormal thyroid-stimulating hormone (TSH) that, in the opinion of the Investigator and Terns Medical Monitor, would pose a risk to participant safety. Participants on a stable dose of thyroid replacement therapy for at least 3 months prior to Screening who are clinically euthyroid and who are anticipated to remain on the same dose through the trial period may be eligible if they meet other criteria. No participant with an abnormal TSH value at screening may be enrolled without written authorization from the Terns Medical Monitor.
26. Have a known personal or family history (first degree relative) of multiple endocrine neoplasia type 2A or type 2B, thyroid C-cell hyperplasia, or medullary thyroid carcinoma

27. Have a serum calcitonin level at Screening of ≥20 ng/L
28. Have a history or evidence, in the opinion of the Investigator, of a significant uncontrolled endocrine abnormality (eg, thyrotoxicosis or adrenal crises)
29. Have a history of an active or untreated malignancy, or are in remission of a clinically significant malignancy (ie, malignancy other than basal or squamous cell skin cancer, in situ carcinoma of the cervix, ductal carcinoma in situ [DCIS] of the breast, or in situ prostate cancer, eg, high-grade prostatic intraepithelial neoplasia [PIN]) for less than 5 years).
30. Have evidence of human immunodeficiency virus (HIV) and/or positive HIV antibodies historically or as evidenced from laboratory results collected at Screening
31. Evidence of hepatitis B and/or positive hepatitis B surface antigen
32. Hepatitis C as defined by presence of hepatitis C virus (HCV) RNA or positive hepatitis C antibody (anti-HCV). Participants treated for hepatitis C (and diagnosed as cured) must have a negative RNA test at Screening, AND also be documented as RNA negative for at least 3 years prior to Screening to be eligible for the study
33. Have a history of any other condition (such as known drug or alcohol abuse, diagnosed eating disorder, or other serious psychiatric disorder) that, in the opinion of the Investigator, may preclude the participant from following and completing the protocol
34. Have an average weekly alcohol intake that exceeds 14 units per week (males) or 7 units per week (females) [1 unit = 12 oz or 260 mL of beer; 5 oz or 150 mL of wine; 1.5 oz or 45 mL of distilled spirits]
35. Have a history of use of illicit drugs, marijuana or tetrahydrocannabinol (THC)-containing products within 3 months of enrollment and/or unwillingness to abstain from illicit drugs, marijuana or THC-containing products during the trial
36. Have had a transplanted organ (other than corneal transplants [keratoplasty], which are allowed) or are awaiting organ transplant
37. Have had any exposure to GLP-1 analogs, GLP-1 receptor agonists (including dual GLP-1/GIP receptor agonists) or other related compounds within the prior 3 months; this includes compounded drugs

    Note: Participants who previously took GLP-1 analogs or related compounds and who discontinued those medications for intolerability or lack of efficacy should not be randomized
38. Have any prior history of hypersensitivity/allergies to GLP-1 analogs or excipients of TERN-601
39. Have given a blood donation of ≥500 mL within 8 weeks prior to Screening, or had a blood transfusion or severe blood loss within the prior 3 months, or have known autoimmune or congenital anemia (eg, hemolytic anemia, sickle cell anemia), or have a hemoglobin value <11 g/dL (males) or <10 g/dL (females)
40. Triglycerides >500 mg/dL (5.7 mmol/L); if participant is on lipid-lowering therapy, must be on stable dose(s) for ≥3 months prior to Screening
41. Have evidence of significant active gastrointestinal disease, prior gastrointestinal surgery, or gastrointestinal symptoms (eg, abdominal pain, nausea, vomiting, diarrhea,

constipation) which could alter study drug absorption and/or interpretation of key gastrointestinal safety and tolerability signals

42. Have evidence of a significant active, uncontrolled medical condition, or a history of any medical problem capable of constituting a risk when taking the study drug or interfering with the interpretation of data, as judged by the Investigator at Screening
43. Have evidence of a significant active autoimmune abnormality (eg, lupus or rheumatoid arthritis) that, in the opinion of the Investigator, is likely to require concurrent treatment with systemic glucocorticoids in the next 9 months
44. Have difficulty swallowing tablets
45. Are planning to undergo an elective surgery or procedure requiring general anesthesia or deep sedation during the study period (eg, approximately next 4 months)

Prior/Concomitant Therapy

46. Unless otherwise specified, all concomitant medications used to treat chronic conditions should be at a stable dose for ≥3 months prior to Screening and Randomization
47. Are receiving or have received within 3 months prior to Screening, chronic (>2 weeks) systemic glucocorticoid therapy (excluding topical, intraocular, intranasal, single intraarticular injection, or inhaled preparations)
48. Have current treatment with or history of treatment with (within 3 months prior to Screening) medication that may cause significant weight gain, including but not limited to, tricyclic antidepressants, atypical antipsychotics, and mood stabilizers. However, participants at a stable dose (greater than 6 months and with no expectation that the dose will change within the next 6 months) and who are weight stable for the last 6 months on these medications may be included in the study (providing they meet all other entry criteria).

    Examples of medications causing weight gain that must be at stable doses for at least 6 months and with no expectation of changing within the next 6 months include:

    i. imipramine
    ii. amitriptyline
    iii. mirtazapine
    iv. paroxetine
    v. phenelzine
    vi. chlorpromazine
    vii. thioridazine
    viii. clozapine
    ix. valproic acid and its derivatives
    x. lithium

    Note: Selective serotonin reuptake inhibitors other than paroxetine are permitted

49. Have taken within 3 months prior to Screening, medications (prescribed or over the counter) or alternative remedies (including herbal/nutritional supplements) intended to promote weight loss

    Examples include, but are not limited to:

    i. liraglutide
    ii. orlistat (prescription or OTC)
    iii. sibutramine
    iv. phenylpropanolamine
    v. mazindol
    vi. phentermine, topiramate or phentermine/topiramate combination
    vii. lorcaserin
    viii. naltrexone/bupropion
    ix. semaglutide
    x. tirzepatide
    xi. other similar body weight loss medication(s), including OTC or compounded medications

50. Have taken metformin, or any other glucose-lowering medication, regardless of reason for prescription (eg, polycystic ovarian syndrome, diabetes prevention) within 3 months of Screening
51. Are currently taking or chronic use (>2 weeks) within 3 months prior to Screening a central nervous system stimulant (eg, Ritalin-SR®), with the exception of caffeinated beverages, at Screening
52. Are taking any medications that may result in a drug-drug interaction (see Section 6.5) within 30 days prior to Randomization
53. Evidence (in the opinion of the Investigator) of regular use of known drugs of abuse

Prior Clinical Study Experience

54. Are currently enrolled in any other clinical study involving an investigational drug or any other type of medical research judged not to be scientifically or medically compatible with this study
55. Have participated within the last 3 months in a clinical study and received treatment, whether active or placebo. If the study involved an investigational drug, at least 5 elimination half-lives or 3 months (whichever is longer) should have passed.

Other Exclusions

56. Are, in the opinion of the Investigator or Sponsor, unsuitable for inclusion in the study

5.3. Lifestyle Considerations

Contraceptives and/or other means of birth control are required during study participation (see Appendix 10).

5.3.1. Lifestyle Counseling

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

5.3.2. Meals and Dietary Restrictions

Participants should follow the diet and physical activity recommendations provided by the study site or given in Appendix 9 if the study site does not have their own recommendations.

Participants should arrive at the clinic fasting for assessments as defined in the Schedule of Activities (Section 1.3). This includes at least an 8-hour fast prior to the visit, during which food and drink is restricted. Water is allowed ad libitum. Participants should also be instructed to hold their dose on days where fasting is required, however, lab samples or assessments that are collected or performed postdose will not be considered a protocol deviation.

Participants should refrain from consumption of grapefruit or grapefruit juice 2 weeks before Randomization and through the end of treatment (Section 6.5).

5.3.3. Alcohol, Cannabis, and Illicit Drug Use

Participants must agree to not consume >14 standard drinks per week for males or >7 standard drinks per week for females. A standard drink is defined as 12 oz (360 ml) beer, 1.5 oz (45 ml) liquor, or 5 oz (150 ml) wine. Participants should avoid alcohol use within 24 hours prior to study site visits.

Participants must not have used illicit drugs, marijuana (cannabis), or THC-containing products for 3 months prior to study participation and must agree to abstain from use of illicit drugs, marijuana (cannabis), and THC-containing products during study participation.

Participants must abstain from CBD ingestion during study participation. Short-term, topical CBD use (<14 days) is acceptable.

5.3.4. Physical Activity

Provided there are no medical contraindications, in the opinion of the Investigator, participants will be advised to increase their regular levels of physical activity during the study. Participants will be advised, however, to avoid strenuous physical activity (eg, long-distance running or heavy weightlifting) within 24 hours prior to each study site visit, if possible. Participants may be required to remain seated or supine for certain study procedures.

5.4. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently randomized. A minimal set of screen failure information is required and will be documented to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography,

reason(s) for screen failure, eligibility criteria, and any serious adverse event (SAE) that is reported by a screen failure participant. Screen failures shall not be re-screened.

6. 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 6-1.

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 6-1 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 tablet*	placebo*
Route of Administration	oral	oral
Use	experimental	placebo
IMP and NIMP	IMP	IMP
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

6.1. 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 6-2. Study drug may be taken with or without food.

For subjects 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 postdose will not be considered a protocol deviation.

Table 6-2 Study Drug by Dose Level

Dose Level	TERN-601 tablets	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

6.2. Preparation/Handling/Storage/Accountability

The study drug kits should be stored at room temperature between 15°C and 25°C (59°F to 77°F). Kits should be kept away from light and moisture. Each IMP bottle should be kept tightly closed with the supplied cap.

The Investigator or designee must acknowledge receipt of each shipment of study drug in good condition including documentation that appropriate temperature conditions have been maintained during transit for all study drug received. Any discrepancies must be reported and resolved in a timely manner (generally within 24 hours of receipt) and before the study drug may be dispensed.

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

The Investigator, and/or their designee, is responsible for study drug accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).

The Investigator or designee must confirm appropriate temperature conditions have been maintained during storage for all study drug received and any discrepancies are reported and resolved before use of the study drug. Further guidance and information for the study drugs are provided in the Pharmacy Manual.

6.3. Measures to Minimize Bias: Randomization and Blinding

Participants will be randomized to 1 of 4 TERN-601 arms (ie, 250 mg, 500 mg (ST), 500 mg, or 750 mg) or placebo using an Interactive Response Technology (IRT) System. Before the study is initiated, the log-in information and directions for the IRT will be provided to each site.

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 BMI (≤35, >35 kg/m^2 at Randomization) and sex 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 the IRT which will assign the kit(s) numbers to each participant at visits as defined in the SoA (Section 1.3). Each kit will be uniquely labeled with a randomized kit number. Each kit 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 a -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 (ie, 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 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, Section 1.3. Returned study drug should be quarantined for study drug accountability and should not be re-dispensed to participants.

6.3.1. Unblinding

An individual participant's treatment assignment may be unblinded if knowing the participant's treatment assignment would affect immediate medical management of the participant. The IRT will be programmed with blind-breaking instructions. In case of an emergency, the Investigator has the sole responsibility for determining if unblinding of a participant's treatment assignment is warranted. Participant safety must always be the first consideration in making such a determination. If the Investigator decides that unblinding is warranted, the Investigator should make every effort to contact the Medical Monitor/Sponsor prior to unblinding a participant's treatment assignment unless this could delay emergency care of the participant. If a participant's treatment assignment is unblinded prior to contacting the Medical Monitor/Sponsor, the Medical Monitor/Sponsor must be notified within 24 hours after breaking the blind. The date and reason that the blind was broken must be recorded in the source documentation and case report form (CRF), as applicable.

Any unblinding of Sponsor personnel for expedited reporting of suspected unexpected serious adverse reactions (SUSARs) or other reasons will be addressed in a separate plan.

An unblinded, Independent Medical Monitor (IMM) will be available to participate in safety investigations, which may be requested by the Sponsor's Medical Monitor (or designee) or triggered per criteria outlined in Section 7.1.1. The process by which the IMM will conduct safety investigations will be detailed in a separate plan.

6.3.2. Participant Enrollment and Study Drug Assignment

It is the responsibility of the Investigator to ensure that participant eligibility is confirmed prior to randomization. Documentation of the informed consent process and collection of the

personally signed and dated informed consent form (ICF) for each subject, using the study-specific ICF, is required before initiating the Screening Period.

After written informed consent has been obtained, the participant's identification number will be obtained from the IRT. Once eligibility to participate has been established, the participant's randomization will be performed in the IRT.

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

6.4. Study Drug Compliance

Participants will be dispensed study drug during their study visits and will self-administer study drug at home. Compliance will be assessed by direct questioning, counting returned tablets during the study visits, and documenting missed doses and returned tablet counts in the source documents and/or electronic case report form (eCRF). Deviation(s) from the prescribed dosage regimen should be recorded in the eCRF.

Participants will be asked to maintain records of study drug administration. A record of the number of study drug tablets dispensed to and taken by each participant must be maintained and reconciled with study drug and compliance records at the site. Study drug start and stop dates, including dates of missed doses, and dates of study drug interruption (see Section 6.7) will be recorded in the eCRF. The date, time of administration, and prandial state (fed versus fasted) for the last dose prior to each PK sample collection, will also be recorded in the eCRF.

6.5. Concomitant Therapy

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

- Reason(s) for use
- Dates of administration including start and end (unless ongoing) dates
- Dosage information including route, dose, and frequency

The Medical Monitor should be contacted if there are any questions regarding concomitant or prior therapy.

Unless otherwise specified, all concomitant medications used to treat chronic conditions should be at a stable dose for ≥3 months prior to Screening and Randomization, exceptions may be made per Sponsor's review and approval. Alcohol, illicit drugs, marijuana, THC, and CBD-containing products are restricted while on study. (See Section 5.3.3.)

Medications to treat GI AEs:

Over-the-counter and prescription medications are allowed, as needed, to treat GI symptoms (eg, dyspepsia, antiemetic, or antidiarrheal medications). If anti-emetic medication(s) are prescribed, the date, time, and dose of each administration should be recorded.

Medications prohibited from 3 months prior to Screening through End of Study due to potential effects on weight and/or glucose levels:

- Chronic (>2 weeks) systemic glucocorticoid therapy (excluding topical, intraocular, intranasal, single intraarticular injection, or inhaled preparations)
- Medications that may cause significant weight gain including, but not limited to, tricyclic antidepressants, atypical antipsychotics, and mood stabilizers. Exceptions may be made for participants at a stable dose (>6 months and with no expectation that the dose will change in the next 6 months) and who are weight stable for the last 6 months on these medications. Note: Selective serotonin reuptake inhibitors other than paroxetine are permitted.
- Medications (prescribed or over-the-counter) or alternative remedies (including herbal/nutritional supplements) intended to promote weight loss.
- Metformin or any other glucose-lowering medication, regardless of reason(s) for prescription.
- Central nervous system stimulants with the exception of caffeinated beverages
- Investigational drugs (active or placebo) in clinical trials

A noncomprehensive list of example medications prohibited from 3 months prior to Screening through the final follow-up visit is provided in Table 6-3.

Table 6-3 Prohibited Medications (3 months prior to Screening through End of Study)

Drug class	Examples	Notes
Chronic (>2 weeks) systemic glucocorticoid therapy	Prednisone, prednisolone, methylprednisolone, dexamethasone, beclomethasone, betamethasone, budesonide, cortisone, hydrocortisone	Topical, intraocular, intranasal, single intraarticular injection, or inhaled preparations of glucocorticoids are permitted
Medications that may cause significant weight gain	Imipramine, amitriptyline, mirtazapine, paroxetine, phenelzine, chlorpromazine, thioridazine, clozapine, valproic acid and its derivatives, lithium	Selective serotonin reuptake inhibitors (SSRIs) other than paroxetine are permitted
Medications or supplements intended to promote weight loss	Liraglutide, orlistat, sibutramine, phenylpropanolamine, mazindol, phentermine, topiramate, phentermine/topiramate combination, lorcaserin, naltrexone, bupropion, naltrexone/bupropion, semaglutide, tirzepatide	GLP-1 analogues and GLP-1RAs are not permitted
Metformin or other glucose lowering therapies	Metformin, dapagliflozin, sitagliptin, rosiglitazone	Disallowed, regardless of reason(s) for prescription
Central nervous system stimulants	Methylphenidate (Ritalin®), Adderall®	Caffeinated beverages are allowed
Investigational drugs		Should be discontinued ≥3 months prior to screening or ≥5 half-lives of the investigational drug, whichever is longer

Medications prohibited from 30 days prior to Randomization through last dose of study drug due to potential drug-drug interactions:

- Strong CYP3A4 inhibitors or inducers
- Drugs that are sensitive narrow-therapeutic index substrates of CYP2C8, CYP2D6, P-gp, BCRP, or OATP

A noncomprehensive list of example medications prohibited from 30 days prior to Randomization through last dose of study drug are provided in Table 6-4:

Table 6-4 Prohibited Medications (30 days prior to Randomization through last dose of study drug)

Drug Type	Examples	Notes
Strong CYP3A4 inhibitors	Ritonavir, clarithromycin, ketoconazole, itraconazole, voriconazole	If short-term use is needed during the study and an alternative medication cannot be used, the Medical Monitor should be contacted for guidance regarding TERN-601 administration
Strong CYP3A4 inducers	Rifampin, carbamazepine, enzalutamide, phenytoin, St. John's wort	
Sensitive narrow-therapeutic index substrates of CYP2C8	Repaglinide	
Sensitive narrow-therapeutic index substrates of CYP2D6	Atomoxetine, desipramine, perphenazine	
Sensitive narrow-therapeutic index substrates of P-gp	Dabigatran etexilate, digoxin	
Sensitive narrow-therapeutic index substrates of BCRP	Rosuvastatin	
Sensitive narrow-therapeutic index substrates of OATP	Rosuvastatin, pravastatin, pitavastatin	

The Medical Monitor should be contacted if there are any questions regarding concomitant therapy. Should a participant require changes to their stable concomitant medications during the study, the Medical Monitor should be notified of such changes, including dose adjustments, within 3 business days to determine the participant's continued eligibility in the study.

6.6. Dose Modifications/Reductions

If a participant does not tolerate the assigned study drug/dose (eg, due to moderate-to-severe nausea, vomiting, or diarrhea) after attempts to manage/relieve symptoms, and the Investigator does not believe that the participant will tolerate the assigned study drug/dose with further exposure, then the Investigator may request a dose reduction in IRT per the instructions below and in Appendix 12.

To maintain blinding, the IRT is set up to assign study drug kits per protocol/randomized treatment assignment to the participants. The IRT will also automatically manage any requested dose-modification kit assignments for each participant, based upon the Investigator's responses to a series of questions related to assigned study drug/dose tolerability.

A participant who does not tolerate the assigned study drug/dose in the first 2 weeks of dosing (ie, TERN-601 100 mg or Placebo) will need to permanently discontinue study drug. If a participant does not tolerate the assigned study drug/dose/escalation (ie, TERN-601 >250 mg or

Placebo) after the first 2 weeks of dosing (see Appendix 12), then dose reduction or maintenance (based upon the Investigator's assessment of the participant's AE severity and relationship to study drug per Section 6.6) may be requested in IRT. Once any symptoms attributed to study drug/dose/escalation intolerance are well managed, dose escalation per protocol/randomized treatment assignment will resume. If a dose modification previously occurred, it is recommended to maintain each dose level for at least 2 weeks before up-titrating, except in the instance when dose titration is restarted at the Week 2 dose level due to a study drug interruption (which should be maintained for at least 1 week at the Week 2 dose level). This is because, after a dose modification has occurred, the IRT system will continue dispensing the same study drug/dose level for that participant until another dose modification is entered in the system. If the dose re-escalation is not tolerated or if symptoms are not improving at the reduced dose, an additional dose reduction may be requested in IRT. IRT will automatically dispense the appropriate study drug/dose level when a dose modification of "Up-Titration" is entered in the system, allowing participants to re-challenge once at any assigned study drug/dose that caused tolerability issues (and resulted in prior dose reduction), with the goal of achieving the highest, tolerable study drug/dose (ie, less than or equal to the per-protocol/assigned study drug/dose).

Participants in the placebo group will be dispensed and remain on placebo per the automated IRT process throughout the treatment period, even if the Investigator requests a dose reduction.

Dispensing and re-starting study drug after a drug interruption is reviewed in Section 6.7.2.

6.7. Study Drug Interruption

The Investigator may interrupt study drug due to an AE (eg, nausea, vomiting, etc; see Appendix 12) or a clinically significant laboratory value. If study drug interruption is due to an AE or clinically significant laboratory value, the event should be followed and documented. The Investigator should make every effort to maintain participants on the study and to restart study drug promptly, as soon as it is deemed safe to do so. The dates of study drug interruption and restart must be documented, along with the data related to the interruption. A single missed dose which is unrelated to safety/tolerability will not be considered a dose interruption. However, more than one consecutive missed dose, for any reason, will be recorded as a dose interruption and the reason will be documented on the eCRF.

6.7.1. Missed Doses

On all non-study visit days, participants will self-administer the study drug orally once daily. If a participant forgets to self-administer study drug at their usual time on a given day, the dose can be taken on the same day (ensuring there is at least an 8-hour interval between that dose and the next dose) when the participant remembers, with the exception below:

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

If a participant forgets to self-administer study drug on a given day (or if there is <8 hours until the next dose), it will be designated a missed dose. Dosing may continue orally once daily

according to the protocol schedule after a missed dose. A single missed dose which is unrelated to safety/tolerability will be captured in the study drug compliance eCRF but will not be considered a dose interruption.

Information on dose modifications/reductions, study drug interruptions, and restarting study drug after missed doses or interruptions due to safety/tolerability is detailed in Section 6.6, Section 6.7, and Section 6.7.2, respectively.

6.7.2. Restarting Study Drug after Interruption or Missed Doses

If the number of consecutive missed doses is <5 days, study drug can be restarted at the same dose, using the same study drug bottles, provided the drug was well tolerated prior to the missed doses. If the previous dose was not well tolerated, the participant will need to return to the site so that the safety/tolerability data may be entered into EDC/IRT, and the participant may be dispensed the appropriate study drug/dose kit and restarted at the highest tolerable dose that was achieved prior to discontinuation. Participants who have missed ≥5 consecutive days of study drug will also need to return to the site so that the study drug interruption may be entered into EDC/IRT, and the participant may be dispensed the appropriate study drug/dose kit, allowing the participant to restart dose titration (ie, return to Week 2 dose level, TERN-601 100 mg or Placebo) for at least 1 week before attempting to re-escalate according to their assigned treatment group. Re-escalation after a dose modification will need to be manually managed by the Investigator (via dose modification in IRT at scheduled or unscheduled visits) because, after a dose modification has occurred, the IRT system will continue dispensing the same study drug/dose level for that participant until another dose modification is entered in the system. It is recommended to maintain each dose level for at least 2 weeks before up-titrating, except in the instance when dose titration is restarted at the Week 2 dose level due to a study drug interruption. IRT will automatically dispense the appropriate study drug/dose level upon re-escalation when a dose modification of "Up-Titration" is entered into the system, with the goal of achieving the highest, tolerable study drug/dose (ie, less than or equal to the per-protocol/assigned study drug/dose).

To maintain the study blind, the Investigator should always obtain the appropriate dispensing information and kit number assignment from the IRT after accurately responding to the series of questions related to the previous assigned study drug/dose tolerability.

Dispensing new study kids and restarting of study drug may occur at unscheduled visits.

6.8. Intervention after the End of the Study

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

7. Discontinuation of Study Drug and Participant Discontinuation/Withdrawal

7.1. Discontinuation of Study Drug

7.1.1. Study Stopping Criteria

The Sponsor may temporarily or permanently stop the study at any time it judges necessary for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and/or GCP. The Sponsor may also discontinue or reduce a dose level due to emerging data (see Section 7.1.2).

During the study, the Sponsor's Medical Monitor will regularly conduct blinded safety reviews, including but not limited to analysis of laboratory values, vital signs, ECGs, and AEs. In addition, an unblinded, Independent Medical Monitor (IMM) will be available to participate in safety investigations, which may be requested by the Sponsor's Medical Monitor (or designee) or triggered if any of the following criteria are met:

- Three or more study participants experience the same TEAE or SAE considered probably related or related to study drug that is severe; or is medically significant, but not immediately life-threatening; or requires hospitalization of prolongation of hospitalization; or is disabling; or limits self-care activities of daily living
  OR
- Two or more study participants experience any TEAE or SAE considered probably related or related to study drug that has life-threatening consequences or requires urgent intervention
  OR
- Death of any study participant that is considered probably related or related to study drug

Note: Causality of AEs will be determined by the Investigator based on the 4-category system specified in Appendix 11.

The IMM will, based upon the results of safety investigations, make recommendations to the Sponsor. Furthermore, a regulatory agency or Institutional Review Board (IRB)/Independent Ethics Committee (IEC) may temporarily or permanently stop the study at any time if it judges necessary for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and/or GCP.

7.1.2. Early Discontinuation of Study Drug

The Sponsor may also discontinue or reduce a dose level due to emerging data.

If a participant develops any exclusion criteria during the study, the Investigator should contact the Sponsor to determine whether discontinuation of study drug is necessary.

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

- Participant requests to discontinue study drug for any reason
- Investigator discretion (eg, due to participant noncompliance)
- Change in clinical status that, in the judgement of the Investigator, compromises the participant's ability to continue treatment or makes it clear that continuation is not in the participant's best interest
- Any TEAE, SAE, or clinically significant laboratory value for which the Investigator believes that permanent study drug discontinuation is the appropriate measure to be taken
- A female participant becomes pregnant during the study (refer to Appendix 10)
- Diagnosis of cirrhosis after randomization
- Diagnosis of pancreatic cancer after randomization
- Diagnosis of medullary thyroid cancer (MTC) after randomization
- Diagnosis of an active or untreated malignancy (other than basal or squamous cell skin cancer, in situ carcinomas of the cervix, or in situ prostate cancer) after randomization
- Diagnosis of T1DM or latent autoimmune diabetes after randomization
- Severe hypoglycemia (see Appendix 13)
- Diagnosis of pancreatitis (see Appendix 14)
- Diagnosis of acute gallbladder disease (see Appendix 15)
- Diagnosis of acute liver toxicity (see Appendix 16)
- Diagnosis of acute kidney injury (see Appendix 17)
- Clinically significant changes in ECG

Note: study drug may be temporarily discontinued during diagnostic work-up of the above stopping criteria based on Investigator discretion.

A participant may discontinue study drug administration at any time at his/her own request or may be discontinued from study drug administration at any time at the discretion of the Investigator for safety, behavioral, compliance, or administrative reasons. If study drug is permanently discontinued prior to the completion of the treatment period (ie, Week 12) and it is deemed safe for the participant to continue in the study, the participant may remain in the study and continue participation through the Week 12 visit and Follow-Up visit. At the time of study drug discontinuation, the Early End of Treatment visit (EEoT) visit should be completed as soon as possible. If the participant is continuing in the study, they will complete study visits as scheduled. If the participant is permanently discontinuing both study drug and the study, the Follow-Up visit should be completed approximately 4 weeks after the last dose of study drug. See the Schedule of Activities, Section 1.3, for data to be collected at the time of early discontinuation of study drug and at the Follow-Up.

7.2. Participant Discontinuation/Withdrawal from the Study

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

Participants discontinuing the study for any reason should complete the EEoT visit as soon as possible per Section 7.1 and return for a Follow-Up visit approximately 4 weeks after the last

dose of study drug. See the Schedule of Activities, Section 1.3, for data to be collected at the time of early discontinuation of study drug and at the Follow-Up visit.

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

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

7.3. Lost to Follow up

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

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

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

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

8. Study Assessments and Procedures

Study procedures and their timing are summarized in the Schedule of Activities, Section 1.3. Protocol waivers or exemptions are not allowed.

Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.

All screening and Day 1 predose evaluations must be completed and reviewed prior to randomization to confirm that potential participants meet all eligibility criteria. The Investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.

8.1. Study Assessments

Planned time points for all safety assessments are provided in the SoA (Section 1.3).

8.1.1. Demographics

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

8.1.2. Height and BMI

Height will be measured in centimeters to calculate BMI at Screening. At other study visits, a participant's height at Screening will be used to calculate BMI as specified in the SoA. Height will be measured under the following conditions at the site:

- Ask the participant to remove their footwear and any headgear (light headgear for religious reasons can remain); high hairdos may need to be pressed
- Ask the participant to stand on the calibrated height measuring board (stadiometer) or against a wall with their feet together and their knees straight with their heels against the backboard, stadiometer or wall
- Ask the participant to look straight ahead without tilting their head up
- Ask the participant to breathe in and stand tall. Measure and record the participant's height in centimeters to 1 decimal place

8.1.3. Weight

Body weight measurements will be obtained in kilograms at the visits outlined in Section 1.3, Schedule of Activities, under the following conditions at the site:

- Ensure participant is fasting. If the participant is not fasting, the participant should return for a new visit within the visit window to have fasting body weight measured.
- After a participant voids of urine;
- After the participant empties pockets and after removal of shoes, bulky layers of clothing, jackets, and headgear (light headgear for religious reasons can remain but should be worn

consistently every time weight is collected) so only light clothing remains on a participant;
- While a participant remains still during measurement.

If possible, the same scale should be used for a particular participant for all body weight measurements. For measuring weight, a calibrated scale capable of measuring weight in kilograms to 1 decimal place will be used and must be placed on a stable, flat surface. Whenever possible, body weights should be measured at approximately the same time of day each time, preferably in the morning.

8.1.4. Waist and Hip Circumference

Waist and Hip circumference measurements, and waist-to-hip ratio, will be obtained in centimeters at the visits outlined in Section 1.3, Schedule of Activities, under the following conditions at the site:

8.1.4.1. Measuring Waist Circumference:

- Waist circumference (WC) should be measured in the horizontal plane and at the midpoint between the lower margin of the last palpable rib and the top of the iliac crest.
- Measurements should be taken in centimeters at the end of a normal expiration using a non-stretchable measuring tape. The tape should lie flat against the skin without compressing the soft tissue.
- The waist circumference should be measured twice, rounded to the nearest 0.5 cm. The measuring tape should be removed between the 2 measurements. Both measurements will be recorded, and the average of both measurements will be automatically calculated in the eCRF. If the difference between the 2 measurements exceeds 1 cm, this set of measurements should be discarded and the 2 measurements repeated.
- This measurement should be taken directly over the skin. If this is not possible, a gown should be provided, and the measurement may be taken over the gown. All measurements should be taken under the same conditions (ie, over the skin or over a gown) for the duration of the study.
- Ask the participant to stand with their feet close together, arms at their side, body weight evenly distributed.
- Ask the participant to relax, inhale, exhale, and then measure the participant's waist circumference at the end of a normal expiration.

8.1.4.2. Measuring Hip Circumference:

- Hip circumference (HC) will be measured at the widest part of the hip, around the buttocks and below the iliac crest.
- Measurements should be taken in centimeters using a non-stretchable measuring tape. The tape should lie flat against the skin without compressing the soft tissue.
- The hip circumference should be measured twice, rounded to the nearest 0.5 cm. The measuring tape should be removed between the 2 measurements. Both measurements will

be recorded, and the average of both measurements will be automatically calculated in the eCRF. If the difference between the 2 measurements exceeds 1 cm, this set of measurements should be discarded and the 2 measurements repeated.

- This measurement should be taken directly over the skin. If this is not possible, a gown should be provided, and the measurement may be taken over the gown. All measurements should be taken under the same conditions (ie, over the skin or over a gown) for the duration of the study.
- Ask the participant to stand with their feet close together, arms at their side, body weight evenly distributed.
- Ask the participant to relax and measure the participant's hip circumference.

8.1.4.3. Waist-to-hip ratio (WHR)

Waist-to-hip ratio (WHR) is calculated by dividing the averaged waist circumference by the averaged hip circumference:

$$WHR = WC\ (cm)/HC\ (cm)$$

8.1.5. Medical History

Medical history, including details of illnesses and allergies, date(s) of onset, whether condition(s) is currently ongoing, and medication history, including alcohol/substance use, will be collected for all participants at Screening.

8.1.6. Physical Examinations

A complete physical examination will include assessments of general appearance, cardiovascular, respiratory, abdomen, head and neck (including ears, eyes, nose and throat), lymph nodes, thyroid, and musculoskeletal systems.

Targeted physical examinations will be conducted, as necessary, to evaluate reported current or prior AEs, symptoms reported by the participant, or abnormal laboratory readouts.

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

8.1.7. Vital Signs

Temperature, pulse rate, and blood pressure will be assessed and maintained in source documentation.

The method of obtaining body temperature will be measured per the site's standard practice; however, the method should remain consistent throughout the study across all participants at the site.

Blood pressure and pulse measurements will be assessed with a completely automated device. Manual techniques will be used only if an automated device is not available.

Blood pressure and pulse measurements will be taken with the participant in a supine position. Blood pressure and pulse measurements should be preceded by at least 5 minutes of rest (supine position) and in a quiet setting without distractions (eg, television, cell phones).

If either blood pressure or pulse is outside the normal range, as specified below, it should be repeated approximately 10 minutes later and all readings recorded in the eCRF.

- Pulse <40 beats per minute (bpm) or >100 bpm
- Systolic blood pressure <90 mmHg or >140 mmHg
- Diastolic blood pressure <45 mmHg or >90 mmHg

8.1.8. Electrocardiograms

Triplicate 12-lead ECG will be obtained as outlined in the Schedule of Activities (see Section 1.3) using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTcF intervals.

At each time point at which triplicate ECG are required, 3 individual ECG tracings should be obtained within a 5-minute window, with at least 1 minute apart, after participant has been supine in a quiet setting without distractions for at least 10 minutes prior to 12-lead ECG collection.

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

8.1.9. Clinical Safety Laboratory Assessments

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

The Investigator must review every laboratory report, document this review, and record any AEs per the guidance in Appendix 11. The laboratory reports must be filed with the source documents.

Abnormal and clinically significant laboratory abnormalities should be repeated as soon as possible and followed to resolution or until stable, in the opinion of the Investigator. Recommended management strategies for specific clinically significant laboratory abnormalities (including those that may be associated with organ-specific injury) are detailed in Appendix 13 (hypoglycemia), Appendix 14 (pancreatitis), Appendix 15 (gallbladder disease), Appendix 16 (liver disease), and Appendix 17 (acute renal events). All protocol-required laboratory assessments, as defined in Appendix 1, must be conducted in accordance with the laboratory manual and the Schedule of Activities (Section 1.3).

8.1.10. Patient Reported Outcomes

The Investigator or trained study staff should discuss with the participant the reasons for completing the below questionnaires and how to fill it out. After the participant has completed

the questionnaires, it is scored by the Investigator or trained designee, with the exception of the C-SSRS which will be administered by the Investigator or trained designee.

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

The IWQOL-Lite-CT will be completed as specified in the SoA. It is a validated, 20 item, self-report measure of obesity-specific quality of life in adults, see Appendix 8.

8.1.10.2. Patient Health Questionnaire 9 (PHQ-9)

The PHQ-9 will be completed as specified in the SoA and includes 9 direct questions related to depression, sleep issues and suicidal thoughts. See Appendix 6, Patient Health Questionnaire (PHQ-9) for more information regarding the PHQ-9.

8.1.10.2.1. Scoring Information and Guidelines

Since the questionnaire is based on a participant's self-report, all answers should be verified by the Investigator or designee that is trained to assess and manage these disorders, and a definitive diagnosis is made on clinical judgement, taking into consideration how well the participant understood the questionnaire, as well as other relevant information from the participant (Diagnoses of Major Depressive Disorder or Other Depressive Disorder also require impairment of social, occupational, or other important areas of functioning [Question #10] and ruling out normal bereavement, a history of a Manic Episode [Bipolar Disorder], and a physical disorder, medication, or other drug as the biological cause of the depressive symptoms).

If any depressive disorder is considered, based on clinical interview and responses provided by the PHQ-9, it may trigger the following clinical management options:

- Determine if the participant will be excluded or withdrawn from study participation after interview with the Investigator
- Initiate participant safety precautions
- Alert additional study team as needed
- Referral to mental health services/psychiatric consultation for severity assessment of depression, potential treatment options or potential interventions.

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

The study visit-specific C-SSRS (Baseline/Screening or Since Last Visit) will be completed as specified in the SoA and includes questions to assess suicidal thoughts and suicidal behavior, including severity and intensity. See Appendix 7 for more information regarding the C-SSRS.

8.1.10.3.1. Scoring Information and Guidelines

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).

The Investigator or trained designee will administer the C-SSRS by asking a series of questions and recording responses. 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 should be asked to report on ideation and behavior since the last scheduled C-SSRS assessment.

If a participant reports suicidal ideation of categories 4 or 5 (ie, suicidal ideation with intent, with or without a plan) or any suicidal behavior (eg, including imminent risk of self-harm or harm to others in the opinion of the Investigator), based on clinical interview and responses provided by the C-SSRS it may trigger the following clinical management:

- Determine if the participant will be excluded or withdrawn from study participation after interview with the Investigator
- Initiate participant safety precautions
- Alert additional study team as needed
- Referral to mental health services/psychiatric consultation for severity assessment of depression, potential treatment options or potential interventions.

8.2. Pharmacokinetics and Optional PK Sub-Study

Blood samples will be collected for measurement of plasma concentrations of TERN-601 at timepoints specified in Appendix 2 and as specified in the Schedule of Activities (Section 1.3).

Participants who are not participating in the PK sub-study will undergo sparse PK sampling collection only, as specified in the Schedule of Activities (Section 1.3) and Appendix 2.

Participants in the optional PK sub-study will undergo sparse PK sample collection and intensive PK sample collection as specified in the Schedule of Activities (Section 1.3) and Appendix 2. Participants in the optional PK sub-study do not need a Week 12 sparse PK sample collected (ie, only intensive PK samples at Week 12 visit). Participants may be fed or fasted at the time of dosing (ie, no food or water restrictions) for the optional PK substudy and all sample collection. However, prandial state at the time of dosing will be required to be recorded in EDC.

Instructions for the collection and handling of biological samples will be provided by the Sponsor. The actual date and time (24-hour clock time) of each sample collected will be recorded as well as the actual dosing date and time (24-hours clock time) and prandial state (eg, fed or fasted) of the last dose prior to PK sample collection. For the optional PK substudy, both the last dose prior to the Week 12 visit and the dose at the Week 12 PK substudy visit should be recorded.

Samples will be used to evaluate the PK of study drug including concentrations of TERN-601; samples may be used to evaluate protein binding and/or metabolites of TERN-601. Samples collected for analyses of study drug concentration may also be used to evaluate safety or efficacy aspects related to concerns arising during or after the study.

Drug concentration information that may unblind the study will not be reported to investigative sites or blinded personnel until the study has been unblinded. Drug concentration information may be reviewed in a blinded manner during the conduct of the study.

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

8.3. Pharmacodynamics

Blood samples and clinical assessments will be collected for measurement of PD markers associated with cardiovascular risk including fasting lipids (eg, LDL cholesterol), NT-proBNP, and inflammation (eg, hs-CRP). Collection timepoints are specified in Appendix 2 and as specified in the Schedule of Activities, Section 1.3.

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

In addition, any remaining (leftover) samples may be stored and used for optional exploratory future research to identify biomarkers that may play a role in obesity or response to weight management therapies (eg, GLP-1RAs) or to develop methods or assays related to the disease process or mechanism of action of the study drug. Participants must provide informed consent for optional exploratory future research as specified in Section 10.1.2. Samples collected for pharmacodynamic assessments and optional exploratory future research will be destroyed no later than 15 years after the end of study.

In addition to monitoring safety, blood pressure will also be obtained at the time points outlined in the SoA to monitor cardiovascular risk. Blood pressure will be collected following the methods described in Section 8.1.7.

8.4. Genetics

A buccal swab sample for DNA isolation will be collected from all participants. The sample should be collected at Day 1 (prior to first dose) if possible. However, if this is not possible, it can be collected post-dose on Day 1 or later in the study at a subsequent visit. This sample is not optional.

In the event of DNA extraction failure, a replacement DNA sample will be requested from the participant.

Genetic samples will be analyzed for variants in genes that have been used to predict response to weight-loss medications because of their association with certain obesity phenotypes (eg, Hungry Brain, Hungry Gut, etc.). These genetic factors will be explored to further understand response to TERN-601 treatment.

See Appendix 3 for Information regarding genetic research. Details on processes for collection and shipment and destruction of these samples can be found in the laboratory manual.

8.5. Biomarkers

Serum samples for exploratory biomarker analyses will be collected from all participants, as specified in the Schedule of Activities, Section 1.3, for future research, in accordance with applicable regulations.

Exploratory biomarker analyses may include proteomic, metabolomic, and/or lipidomic profiling, which may be used to advance development of TERN-601 and/or increase our knowledge and understanding of obesity and related diseases. These specimens may also be used to study the association of biomarkers with biological pathways, and treatment outcomes, including efficacy and adverse events. In addition, these specimens may be used to develop biomarkers and/or diagnostic assays and establish the performance characteristics of these assays. The collection and analysis of future research specimens may facilitate the design of new pharmaceutical agents and the development of diagnostic tests, which may allow for individualized drug therapy for patients in the future.

Participants must provide informed consent for collection and storage of these samples, The samples collected for exploratory biomarker analysis used for exploratory future research will be destroyed no later than 15 years after the end of study.

8.6. Adverse Events and Serious Adverse Events

Events meeting the definition of an AE or SAE are defined in Appendix 11, including details on recording, reporting, and follow-up of AEs and SAEs, assessment of intensity, and assessment of causality. AEs will be reported by the participant at every study visit.

The Investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following up AEs that are serious, considered related to the study drug or study procedures, or that caused the participant to discontinue the study drug (see Section 7).

8.6.1. Time Period and Frequency for Collecting AE and SAE Information

After informed consent but prior to initiation of study drug, all AEs and SAEs related to protocol-mandated procedures will be reported as AEs/SAEs on the relevant case report forms.

Medical occurrences (events considered not related to protocol-mandated procedures) that begin before the start of study drug but after obtaining informed consent will be recorded as pre-existing conditions on the Medical History/Current Medical Conditions section of the case report form (CRF), not the AE section.

After receiving study drug, all SAEs, regardless of cause or relationship, will be collected from the start of study drug administration through the Follow-Up Period, at every study visit, as specified in the Schedule of Activities (Section 1.3).

After receiving study drug, all AEs, regardless of cause or relationship, will be collected from the start of study drug administration through the Follow-Up Period, at every study visit, as specified in the Schedule of Activities (Section 1.3).

All SAEs will be recorded and reported to the Sponsor or designee immediately and under no circumstance should this exceed 24 hours, as indicated in Appendix 11. Until the SAEs have been followed to resolution, the Investigator will submit any updated SAE data to the Sponsor within 24 hours of it being available.

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

8.6.2. Method of Detecting AEs and SAEs

The methods of recording, evaluating, and assessing causality of AE and SAE and the procedures for completing and transmitting SAE reports are provided in Appendix 11.

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

8.6.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the Investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs (as defined in Appendix 11) will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3). Further information on follow-up procedures is provided in Appendix 11.

8.6.4. Regulatory Reporting Requirements for SAEs

Prompt notification by the Investigator to the Sponsor of an SAE (whether suspected or confirmed) is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety surveillance processes for a study drug under clinical investigation can be met.

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

Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and sponsor policy and forwarded to Investigators as necessary.

An Investigator who receives an Investigator safety report describing a SAE or other specific safety information (eg, summary or listing of SAEs) from the sponsor will review and then file it

along with the Investigator's Brochure and will notify the IRB/IEC, if appropriate according to local requirements.

8.6.5. Pregnancy

Details of any pregnancies in female participants will be collected from the start of study drug until 30 days following the last dose of the study drug.

Details of any pregnancies in female partners of male participants, including relevant medical history, will be collected from the start of study drug until 90 days following the last dose of the study drug.

If a pregnancy in a female participant or a female partner of a male participant is reported, the Investigator should inform the Sponsor within 24 hours of learning of the pregnancy and should follow the procedures outlined in Appendix 10 and Appendix 11.

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

8.6.6. Assessment and Management of Adverse Events

For all AEs, the Investigator will be asked to provide an assessment of the severity of the AE using the categories included in Appendix 11.

Guidance for management of GI AEs that are commonly observed with GLP-1 receptor agonists will be based upon the Investigator's assessment of AE severity and the participant's response to supportive and/or therapeutic interventions. Detailed guidance is organized by prevailing symptom(s) and/or diagnosis in the following appendices: Appendix 12 (nausea, vomiting, diarrhea, and constipation), Appendix 13 (hypoglycemia), Appendix 14 (pancreatitis), Appendix 15 (gallbladder disease), Appendix 16 (liver disease), and Appendix 17 (acute renal events).

8.6.7. Disease-Related Events and/or Disease-Related Outcomes Not Qualifying as AEs or SAEs

As weight loss is a predicted and desirable effect of treatment with TERN-601, weight loss should not be captured on the AE eCRF page. Rather, it should be documented in the EDC as described in Section 8.1.3.

8.7. Treatment of Overdose

For this study, any dose of $\geq$7 tablets within a 24-hour time period will be considered an overdose. All overdoses will be documented. An overdose itself does not constitute an AE. Any AE associated with an overdose will be documented per Appendix 11.

In the event of an overdose, the Investigator/treating physician should:

1. Contact the Medical Monitor immediately.

2. Closely monitor the participant for any AE/SAE and laboratory abnormalities for at least 48 hours. Based on the current safety profile of TERN-601 and the known profile of other GLP-1RAs, the following are possible AEs related to an overdose:
    a. Severe GI events that lead to dehydration and require medical intervention
    b. Increased HR or decreased BP
    c. Hypoglycemia
3. Implement medical intervention/monitoring according to the clinical presentation
4. Obtain a plasma sample for PK analysis as soon as possible from the date of the last dose of study drug if requested by the Medical Monitor (determined on a case-by-case basis).
5. Document the quantity of the excess dose as well as the duration of the overdose in the eCRF.

Decisions regarding dose interruptions or modifications will be made by the Investigator in consultation with the Medical Monitor based on the clinical evaluation of the participant.

8.8. Medical Resource Utilization and Health Economics

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

9. Statistical Considerations

9.1. Statistical Hypotheses

The primary statistical analysis will test whether the mean percent change from baseline in body weight is (H_1) or is not (H_0) different between placebo and TERN-601. Secondary statistical analyses will test whether the mean change from baseline in body weight (kg) is (H_1) or is not (H_0) different between placebo and TERN-601 and whether the proportion of weight loss responders (decrease of ≥5%) is (H_1) or is not (H_0) different between placebo and TERN-601.

9.2. 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.

9.3. Analysis Sets

Analysis sets are defined in Table 9-1.

Table 9-1 Definitions of Analysis Sets

Population	Description
Screened	All participants who sign the ICF
Safety	All participants who receive any amount of study drug. Treatment assignment will be based on the treatment actually received.
Intent-to-Treat (ITT)	All randomized participants who receive any amount of study drug (TERN-601 or placebo). Treatment assignment will be based on the randomized treatment.
Pharmacokinetic (PK)	All randomized participants who receive any amount of TERN-601 and have evaluable PK data. Treatment assignment will be based on the treatment actually received.
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. Treatment assignment will be based on the treatment actually received.
PK sub-study	All participants who consented to and participated in the PK sub-study and received any amount of TERN-601. Treatment assignment will be based on the treatment actually received.

Abbreviations: ICF = informed consent form; ITT = intent-to-treat; PD = pharmacodynamics; PK = pharmacokinetic(s)

9.4. Statistical Analyses

This section presents a summary of the planned statistical analyses. The statistical analysis plan (SAP) will provide the details and will be finalized prior to clinical database lock (DBL).

9.4.1. General Considerations

For continuous data, summary statistics will include the number of non-missing observations (n), arithmetic mean, arithmetic standard deviation, median, 25th percentile (Q1), 75th percentile (Q3), minimum, and maximum. For log-normal data (eg, the PK parameters: AUCs and maximum observed concentration [C_{max}]), the geometric mean and geometric coefficient of variation (CV%) will also be presented. For categorical data, frequency counts and percentages will be presented.

The baseline value for statistical analyses of quantitative laboratory parameters is defined as the mean of all available evaluations, including any unscheduled or repeat assessments, prior to the first administration of study drug. Baseline values for glycemic control and lipids will be based on fasted results only, except HbA1c, which does not need to be collected fasted. Otherwise, the baseline value is defined to be the latest assessment value prior to the first administration of study drug, unless specified in the SAP.

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

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

No adjustments for multiplicity will be made.

9.4.2. Primary Endpoint

The primary estimand is defined as:

Population: Adults with overweight or obesity and without diabetes

Treatment: TERN-601 or placebo

Intercurrent Events: Permanent treatment discontinuation (treatment policy strategy)

Variable of Interest: Percent change in body weight at Week 12

Population-level Summary: Least-squares mean difference

Analyses of body weight percent change from baseline will be based on the ITT Analysis Set. Descriptive statistics of body weight results, change from baseline, and percent change from baseline will be summarized by treatment group and visit. Analyses of percent change from baseline will be carried out using an analysis of variance (ANOVA) model at Week 12 with percent change from baseline as the dependent variable including treatment group and randomization strata as fixed effects.

The estimates of least-square (LS) means, standard errors (SE), and 95% confidence intervals (CIs) will be presented by treatment group. Estimates of the LS mean difference between each TERN-601 dose and placebo will be presented with the associated standard error of the difference, and 95% CI of the difference.

9.4.3. Secondary Endpoint(s)

The first secondary estimand is defined as:

Population: Adults with overweight or obesity and without diabetes

Treatment: TERN-601 or placebo

Intercurrent Events: Permanent treatment discontinuation (treatment policy strategy)

Variable of Interest: Change in body weight at Week 12

Population-level Summary: Least-squares mean difference

Analyses of body weight change from baseline will be based on the ITT Analysis Set. Analyses of change from baseline will be carried out using an ANCOVA model at Week 12 with change from baseline as the dependent variable including treatment group and randomization strata as fixed effects and baseline weight as a covariate.

The estimates of least-square (LS) means, standard errors (SE), and 95% confidence intervals (CIs) will be presented by treatment group. Estimates of the LS mean difference between each TERN-601 dose and placebo will be presented with the associated standard error of the difference, and 95% CI of the difference.

The second secondary estimand is defined as:

Population: Adults with overweight or obesity and without diabetes

Treatment: TERN-601 or placebo

Intercurrent Events: Permanent treatment discontinuation (treatment policy strategy)

Variable of Interest: Proportion of participants with ≥5% change in body weight

Population-level Summary: Difference in percentage of responders

Responders will be defined as any participant with a decrease of at least 5% at Week 12. Non-responders will be defined as any participant who did not have a decrease of at least 5% at Week 12. The frequency and percentage of responders along with a two-sided exact (Clopper-Pearson) 95% CI for the percentage of responders will be presented. For each pairwise comparison, the difference in percentage of responders, 95% CI, and p-values using a stratified Cochran–Mantel–Haenszel test, stratified for randomization factors, will be presented.

9.4.4. Exploratory Endpoints

9.4.4.1. Pharmacokinetic Endpoints

Individual plasma concentrations of TERN-601 will be listed by timepoint and summarized by treatment group. PK of metabolites may be explored. Individual and mean concentration-time profiles will be presented graphically in linear and semi-log scales.

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

9.4.4.2. Pharmacodynamic Endpoints

PD assessments of cardiovascular risk markers include fasting lipids (eg, LDL cholesterol), blood pressure, NT-proBNP (cardiac marker), and hs-CRP (inflammation). Descriptive statistics of cardiovascular risk marker results, change from baseline, and percent change from baseline will be summarized by treatment group and visit. Change (and separately percent change) from baseline will be analyzed at applicable time points using the same models specified for the primary and secondary endpoints of change in body weight.

9.4.4.3. Efficacy and PRO Endpoints

Other efficacy assessments include waist circumference, waist-to-hip ratio, fasting glucose, HbA1c. PRO assessments include IWQOL-Lite-CT. Descriptive statistics of efficacy and PRO results, change from baseline, and percent change from baseline will be summarized by treatment group and visit. Change (and separately percent change) from baseline will be analyzed at applicable time points using the same models specified for the primary and secondary endpoints of change in body weight.

The proportion of participants achieving ≥10% (and separately ≥15%) change in body weight will be analyzed using the same methods as for the secondary endpoint.

9.4.4.4. Nausea Burden Score

The nausea burden score is based on the number of TEAEs of nausea reported during the dosing period over 12 weeks (ie, starting from Day 1 to Week 12, inclusive). The nausea burden score is defined as the sum across all occurrences within a participant (with each occurrence being the product of the severity [mild = 1, moderate = 2, and severe = 3] and duration of nausea), normalized by the total duration of therapy. The duration related to the nausea TEAE will not be truncated to the total duration of therapy and so will be the total duration of the adverse event (ie, it may be greater than 12 weeks).

Descriptive statistics of the nausea burden score will be summarized by treatment group.

9.4.5. Safety Analyses

All safety analyses will be made on the Safety Analysis Set.

Adverse event (AE) verbatim terms on eCRFs will be mapped to preferred terms (PT) and system organ classes (SOC) using MedDRA. AE severity will be categorized per the criteria detailed in Appendix 11.

Participant incidence of treatment emergent AEs (TEAEs), defined as any AE with a start date on or after the date of first administration of study drug through 30 days after the last administration of study drug or through the Follow-Up Period (Week 16) will be summarized by treatment group. In addition, SAEs, TEAEs leading to study drug modification (reduction, interruption, or permanent discontinuation), TEAEs by maximum severity, and related TEAEs will be summarized in the same manner.

Laboratory abnormalities will be graded according to NCI CTCAE Version 5.0, where applicable. The number and percentage of participants overall and by laboratory test, with any treatment emergent laboratory abnormality, CTCAE increase of ≥2 grades, will be presented. Similarly, the number and percentage of participants overall and by laboratory test, with CTCAE increase of ≥1 grade will be presented.

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

Vital sign parameters (except BP as it is included as a PD endpoint) and ECG parameters will be summarized by treatment group using descriptive statistics at baseline and at each post-baseline visit and timepoint. The change from baseline will also be summarized. Categorical summaries for baseline, worst post-baseline, and change from baseline for the following QTcF values will be presented: >450 msec, >480 msec., >500 msec, change from baseline >30 msec, and change from baseline >60 msec.

9.5. Interim Analyses

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

10. Regulatory, Ethical, and Study Oversight Considerations

10.1. Regulatory and Ethical Considerations

This study will be conducted in accordance with the protocol and with the following:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
- Applicable International Council on Harmonisation (ICH) Good Clinical Practice (GCP) Guidelines
- Applicable laws and regulations

The protocol, protocol amendments, ICF, Investigator Brochure, and other relevant documents (eg, advertisements) must be submitted to an IRB/IEC by the Investigator and reviewed and approved by the IRB/IEC before the study is initiated.

Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.

The Investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
- Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
- Providing oversight of the conduct of the study at the site and adherence to requirements of 21 Code of Federal Regulations (CFR), ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations

10.1.1. Financial Disclosure

Investigators and sub-Investigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

10.1.2. Informed Consent Process

The Investigator or his/her representative will explain the nature of the study to the participant and answer all questions regarding the study.

Participants must be informed that their participation is voluntary. Participants will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study center.

The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.

Participants must be re-consented to the most current version of the ICF(s) during their participation in the study.

A copy of the ICF(s) must be provided to the participant.

If a potential participant is unable to provide written informed consent at an investigative site due to a pandemic or other local health regulation, the informed consent process may be conducted via telephone or secure telehealth portal with appropriate documentation of how the informed consent form was transmitted to the participant (such as via email, fax, or mail) and how signature was obtained. Screening may be initiated via telephone or secure telehealth portal to avoid an unnecessary visit to the site in the event that a participant is disqualified based on medical history.

The ICF will contain a separate section that addresses the use of remaining mandatory samples for optional exploratory research for up to 15 years after the end of the study. The Investigator or authorized designee will explain to each participant the objectives of the exploratory research. Participants will be told that they are free to refuse to participate in the optional exploratory research and may withdraw their consent at any time and for any reason during the storage period. A separate signature will be required to document a participant's agreement to allow any remaining specimens to be used for exploratory research. Participants who decline to participate in this optional research will not provide this separate signature.

10.1.3. Data Protection

Participants will be assigned a unique identifier by the sponsor. Any participant records or datasets that are transferred to the sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.

The participant must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant who will be required to give consent for their data to be used as described in the informed consent.

The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

10.1.4. Dissemination of Clinical Study Data

A clinical study report (CSR) will be prepared and provided to the regulatory agency(-ies) by Terns, Inc, as appropriate. Terns, Inc. will ensure that the report meets the standards set out in the

ICH Guideline for Structure and Content of Clinical Study Reports (ICH E3). Note that an abbreviated report may be prepared in certain cases. Public disclosure of study results will be in accordance with all applicable laws and ICH guidelines. The posting of company-sponsored study information and tabular study results on the US National Institutes of Health's website www.ClinTrials.gov and other publicly accessible sites.

10.1.5. Data Quality Assurance

All participant data relating to the study will be recorded on a printed or electronic CRF unless transmitted to the sponsor or designee electronically (eg, laboratory data). The Investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.

The Investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.

The Investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.

Monitoring details describing strategy (eg, risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are available in the Monitoring Plan and site-specific contracts.

The sponsor or designee is responsible for the data management of this study including quality checking of the data.

The sponsor is directly responsible for oversight of the actions delegated to other individuals and organizations (eg, Contract Research Organizations).

Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the Investigator until at least 2 years after the last approval of a marketing application in an ICH region (ie, United States, Europe, or Japan) and until there are no pending or contemplated marketing applications in an ICH region (ie, United States, Europe, or Japan) or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period; however, if required by the applicable regulatory requirement(s) or if needed by the sponsor. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

10.1.6. Protocol Deviations

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted. In the event of a significant deviation related to gross non-compliance from the protocol, or events that impose significant risk to participant safety, the Investigator or designee must notify the Sponsor or designee immediately. Deviations must be documented in accordance with the Sponsor's procedures, and in accordance with any site procedures or processes, and IRB/IEC and/or local regulatory requirements.

10.1.7. Source Documents

Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are stored at the Investigator's site.

Data entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The Investigator may need to request medical records, depending on the study.

The required source data should include notes containing at least the following information for each participant:

- Participant identification (name, date of birth, gender)
- Documentation that the participant meets eligibility criteria
- Documentation of the reason(s) a consented participant is not enrolled
- Participation in study (including study number)
- Documentation of Informed Consent process including study discussed and date of informed consent
- Dates of all visits
- Documentation that protocol-specific procedures were performed
- Results of efficacy parameters, as required by the protocol
- Start and end date (including dose regimen) of study drug administration, including dates of dispensation and return as applicable
- Record of all adverse events and other safety parameters (start and end date, and including causality and severity)
- Concomitant medication (including reason for use; dates of administration including start and end date; dosage information including route, dose, and frequency; and any dose changes)

- Date of study completion and reason for early discontinuation, if applicable

10.1.8. Study and Site Start and Closure

The date of the first participant screened at any investigational site is considered the first act of recruitment and will be the study start date.

The sponsor or designee reserves the right to close a study site or terminate the study at any time for any reason at the sole discretion of the sponsor. Study sites will be closed upon study termination or completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The Investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the sponsor or Investigator may include but are not limited to:

- Failure of the Investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the sponsor's procedures, or GCP guidelines
- Inadequate recruitment of participants by the Investigator
- Discontinuation of further study drug development

If the study is prematurely terminated or suspended, the sponsor shall promptly inform the Investigators, the IECs/IRBs, the regulatory authorities, and any contract research organization(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The Investigator shall promptly inform the participant and should assure appropriate follow-up care as warranted by the protocol or as medically necessary.

Appendix 1: Clinical Laboratory Tests

The tests detailed in Appendix Table 1 will be performed by the central laboratory. Local laboratory testing should only be used in the event that central laboratory results would not be available in time for necessary clinical decision making. If a local sample is required, it is important that a sample for central analysis is obtained at the same time. Additionally, if the local laboratory results are used to make either a study drug decision the results and the reference range must be entered into the eCRF.

Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5 above. Additional tests may be performed at any time during the study as determined necessary by the Investigator or required by local regulations.

Appendix Table 1 Protocol-Required Clinical Laboratory Assessments

Laboratory Assessments	Parameters	
Hematology	Hematocrit Hemoglobin Platelet Count RBC Count RBC Indices: MCV MCH % Reticulocytes	WBC count with Differential: Neutrophils Lymphocytes Monocytes Eosinophils Basophils
Clinical Chemistry[2]	Bicarbonate BUN Chloride CPK Creatinine[6] Glucose (fasting) Potassium Sodium Total Protein	Liver Function Tests: ALT Albumin AST ALP GGT Total and Direct Bilirubin[3]
Fasting Lipid Profile	HDL Non-HDL cholesterol LDL Total cholesterol Triglycerides VLDL ApoB	
Coagulation	aPTT Prothrombin Time (PT)/International Normalized Ratio (INR)	

Laboratory Assessments	Parameters
Urinalysis	Specific gravity pH, glucose, protein, blood, ketones, bilirubin, urobilinogen, nitrite, leukocyte esterase by dipstick Microscopic examination (if blood* or protein is abnormal) *Presence of blood due to menses will be documented and will not require microscopic examination.
Pregnancy	Highly sensitive serum β-hCG (WOCBP only) Urine Pregnancy test (WOCBP only)[4]
Other Tests	FSH (as needed to confirm postmenopausal status in women of nonchildbearing potential due to presumed menopause only; surgically sterile women are not required to have an FSH test)[1] TSH Urine drug and alcohol[7] screen including amphetamines, barbiturates, cocaine, opiates, cannabinoids and benzodiazepines Serology[1]: HIV antibody, HBsAg, and HCV antibody[5] high-sensitivity C-reactive protein (hs-CRP) N-terminal pro-B-type natriuretic peptide (NT-proBNP) Hemoglobin A1c (HbA1c) Calcitonin Amylase/Lipase

NOTES:
1. Only collected at Screening
2. Details of liver chemistry increased monitoring criteria are given in Appendix 16.
3. If total bilirubin is increased there should be a reflex to measure direct bilirubin, as outlined in Appendix 16.
4. Urine pregnancy test (WOCBP only) at Day 1 only
5. If HCV antibody positive, conduct HCV RNA test.
6. eGFR will be auto-calculated by the laboratory using the serum creatinine results per Appendix 5.
7. Urine alcohol screening will be done at Screening visit only.

Abbreviations: β-hCG = β-human chorionic gonadotropin; ALP = alkaline phosphatase; ALT = alanine transaminase; aPTT = activated partial thromboplastin clotting time; AST = aspartate transaminase; BUN = blood urea nitrogen; CPK = creatine phosphokinase; eGFR = estimated glomerular filtration rate; FSH = Follicle-stimulating hormone; GGT = gamma-glutamyl transpeptidase; HbA1c = hemoglobin A1c; HBsAG = hepatitis B surface antigen; HCG = human chorionic gonadotropin; HCV = hepatitis C virus; HDL = high-density lipoprotein; HIV = human immunodeficiency virus; hs-CRP = high-sensitivity C-reactive protein; LDL = low-density lipoprotein; MCH = mean corpuscular hemoglobin; MCV = mean corpuscular volume; NT-proBNP = N-terminal pro-B-type natriuretic peptide; PT/INR = Prothrombin Time/International Normalized Ratio; RBC = red blood cell; VLDL = very low-density lipoprotein; WBC = white blood cell; WOCBP = women of childbearing potential

Investigators must document their review of each laboratory safety report. Clinically significant Grade 3 or Grade 4 laboratory abnormalities or any clinically significant laboratory abnormalities considered possibly related to study drug in the opinion of the Investigator should be repeated within 48-72 hours and followed to resolution or until stable.

Appendix 2: Sample Collection for Pharmacokinetics and Pharmacodynamics

Appendix Table 2 presents a description of PK/PD sample requirements at each study visit and timepoint.

Appendix Table 2 TERN-601 PK and PD Sampling Timepoints

Week(s)	Day(s)	Timepoint(s)
0	1	• Lipid panel (All Participants) • hs-CRP (All Participants) • NT-proBNP (All Participants)
2	14 ± 3	• Sparse PK Sample[1] (All Participants) • Lipid panel (All Participants)
4	28 ± 3	• Sparse PK Sample[1] (All Participants) • Lipid panel (All Participants)
8	56 ± 3	• Sparse PK Sample[1] (All Participants) • Lipid panel (All Participants)
12	84 ± 3	• Lipid panel (All Participants) • hs-CRP (All Participants) • NT-proBNP (All Participants)
		Participants not participating in PK sub-study: • Sparse PK Sample[1]
		Participants participating in PK sub-study: • Pre-dose (within 10 minutes prior to dosing) • Post dose at the following timepoints: ○ 1 hour ± 10 minutes ○ 2 hours ± 10 minutes ○ 4 hours ± 15 minutes ○ 6 hours ± 15 minutes ○ 8 hours ± 30 minutes ○ 24 hours ± 1 hour ○ 48 hours ± 1 hour

NOTES:

[1] Sparse PK samples can be collected at any time relative to dosing

Abbreviations: hs-CRP = high-sensitivity C-reactive protein; NT-proBNP = N-terminal pro-B-type natriuretic peptide; PD = pharmacodynamic; PK = Pharmacokinetic

PD Sample Collection

The tests detailed in Appendix Table 3 will be performed by the central laboratory, as specified in the Schedule of Activities, Section 1.3. The exact times of blood sampling will be recorded in the eCRF.

Appendix Table 3 PD Laboratory Assessments

PD Assessments	Parameters
Lipid Panel (extended)	HDL Non-HDL cholesterol LDL Total cholesterol Triglycerides VLDL ApoB
Inflammation marker	hs-CRP
Other	NT-proBNP

Abbreviations: ApoB = apolipoprotein B; HDL = high-density lipoprotein; hs-CRP = high-sensitivity C-reactive protein LDL = low-density lipoprotein; NT-pro-BNP = N-terminal pro-B-type natriuretic peptide; PD = pharmacodynamic; VLDL = very low-density lipoprotein

Appendix 3: Genetics

Use/Analysis of DNA

- Genetic variation may impact a participant's response to study drug, susceptibility to, and severity and progression of disease. The MyPhenome test identifies variants at genetic loci that have been associated with disease phenotypes and response to weight loss management therapies, including GLP-1RAs. Variable response to study drug may be due to genetic determinants that impact mechanism of action of the drug; disease etiology; and/or molecular subtype of the disease being treated. Therefore, where local regulations and IRB/IEC allow, a buccal swab sample will be collected for DNA analysis from consenting participants. DNA samples isolated from buccal swab will be run in MyPhenome test for understanding response to TERN-601 treatment.
- DNA samples will be collected and extracted using standardized, validated methods, and applicable ethical guidelines. All participant data associated with these samples will be documented and managed in an ethical manner, with a primary focus on confidentiality and privacy. Data will be anonymized to the extent possible, and personal identifiers will be removed or coded to protect participant identity.
- Informed consent will be obtained from each participant, clearly stating that their genetic material will be used exclusively for research purposes within the scope of the clinical trial. All data collection and handling procedures will adhere to privacy laws, including HIPAA or any applicable local regulations, to safeguard participant information.
- Following the completion of genetic analysis and report generation, all DNA samples will be securely destroyed in compliance with ethical and regulatory standards. The retention period for DNA samples will not exceed 3 months following the conclusion of the study.
- Samples will not be stored or used for any future research or purposes beyond the scope of this trial unless further informed consent is obtained from participants and appropriate ethical approvals are secured.
- The results of genetic analyses may be reported in the CSR or in a separate study summary.

Appendix 4: Fridericia's Formula

Triplicate 12-lead ECGs will be obtained as outlined in the Schedule of Activities (see Section 1.3) using an ECG machine that automatically calculates the heart rate and measures PR, QRS, and QT intervals. QTc will be calculated using Fridericia's Formula as outlined below.

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

Fridericia's Formula:

QTc = QT/(RR^0.33)

http://www.thecalculator.co/health/QTc-Calculator-385.html

Appendix 5: 2021 Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) Formula to Estimate Glomerular Filtration Rate

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

Abbreviations / Units:
eGFR = $mL/min/1.73m^2$
S_{cr} (standardized serum creatinine) = mg/dL
κ = 0.7 (females) or 0.9 (males)
α = -0.241 (females) or -0.302 (males)
min = indicates the minimum of S_{cr}/κ or 1
max = indicates the maximum of S_{cr}/κ or 1
age = years

Appendix 6: Patient Health Questionnaire 9 (PHQ-9)

PATIENT HEALTH QUESTIONNAIRE-9 (PHQ-9)

Over the last 2 weeks, how often have you been bothered by any of the following problems? *(Use "✔" to indicate your answer)*	Not at all	Several days	More than half the days	Nearly every day
1. Little interest or pleasure in doing things	0	1	2	3
2. Feeling down, depressed, or hopeless	0	1	2	3
3. Trouble falling or staying asleep, or sleeping too much	0	1	2	3
4. Feeling tired or having little energy	0	1	2	3
5. Poor appetite or overeating	0	1	2	3
6. Feeling bad about yourself — or that you are a failure or have let yourself or your family down	0	1	2	3
7. Trouble concentrating on things, such as reading the newspaper or watching television	0	1	2	3
8. Moving or speaking so slowly that other people could have noticed? Or the opposite — being so fidgety or restless that you have been moving around a lot more than usual	0	1	2	3
9. Thoughts that you would be better off dead or of hurting yourself in some way	0	1	2	3

FOR OFFICE CODING 0 + _____ + _____ + _____

=Total Score: _____

If you checked off any problems, how difficult have these problems made it for you to do your work, take care of things at home, or get along with other people?

Not difficult at all	Somewhat difficult	Very difficult	Extremely difficult
☐	☐	☐	☐

Appendix 7: Columbia Suicide Severity Rating Scale (C-SSRS)

COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS)

Baseline/Screening Version

Version 1/14/09

Posner, K.; Brent, D.; Lucas, C.; Gould, M.; Stanley, B.; Brown, G.; Fisher, P.; Zelazny, J.; Burke, A.; Oquendo, M.; Mann, J.

Disclaimer:

This scale is intended to be used by individuals who have received training in its administration. The questions contained in the Columbia-Suicide Severity Rating Scale are suggested probes. Ultimately, the determination of the presence of suicidal ideation or behavior depends on the judgment of the individual administering the scale.

Definitions of behavioral suicidal events in this scale are based on those used in ***The Columbia Suicide History Form****, developed by John Mann, MD and Maria Oquendo, MD, Conte Center for the Neuroscience of Mental Disorders (CCNMD), New York State Psychiatric Institute, 1051 Riverside Drive, New York, NY, 10032. (Oquendo M. A., Halberstam B. & Mann J. J., Risk factors for suicidal behavior: utility and limitations of research instruments. In M.B. First [Ed.]* Standardized Evaluation in Clinical Practice*, pp. 103 -130, 2003.)*

For reprints of the C-SSRS contact Kelly Posner, Ph.D., New York State Psychiatric Institute, 1051 Riverside Drive, New York, New York, 10032; inquiries and training requirements contact posnerk@nyspi.columbia.edu

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C-SSRS Baseline Screening - United States/English - Mapi.
C-SSRS-BaselineScreening_AU5.1_eng-USori.doc

SUICIDAL IDEATION		
Ask questions 1 and 2. If both are negative, proceed to "Suicidal Behavior" section. If the answer to question 2 is "yes", ask questions 3, 4 and 5. If the answer to question 1 and/or 2 is "yes", complete "Intensity of Ideation" section below.	**Lifetime: Time He/She Felt Most Suicidal**	**Past __ Months**
1. Wish to be Dead Subject endorses thoughts about a wish to be dead or not alive anymore, or wish to fall asleep and not wake up. ***Have you wished you were dead or wished you could go to sleep and not wake up?*** If yes, describe:	**Yes** ☐ **No** ☐	**Yes** ☐ **No** ☐
2. Non-Specific Active Suicidal Thoughts General non-specific thoughts of wanting to end one's life/commit suicide (e.g., *"I've thought about killing myself"*) without thoughts of ways to kill oneself/associated methods, intent, or plan during the assessment period. ***Have you actually had any thoughts of killing yourself?*** If yes, describe:	**Yes** ☐ **No** ☐	**Yes** ☐ **No** ☐
3. Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act Subject endorses thoughts of suicide and has thought of at least one method during the assessment period. This is different than a specific plan with time, place or method details worked out (e.g., thought of method to kill self but not a specific plan). Includes person who would say, *"I thought about taking an overdose but I never made a specific plan as to when, where or how I would actually do it… and I would never go through with it."* ***Have you been thinking about how you might do this?*** If yes, describe:	**Yes** ☐ **No** ☐	**Yes** ☐ **No** ☐
4. Active Suicidal Ideation with Some Intent to Act, without Specific Plan Active suicidal thoughts of killing oneself and subject reports having some intent to act on such thoughts, as opposed to *"I have the thoughts but I definitely will not do anything about them."* ***Have you had these thoughts and had some intention of acting on them?*** If yes, describe:	**Yes** ☐ **No** ☐	**Yes** ☐ **No** ☐
5. Active Suicidal Ideation with Specific Plan and Intent Thoughts of killing oneself with details of plan fully or partially worked out and subject has some intent to carry it out. ***Have you started to work out or worked out the details of how to kill yourself? Do you intend to carry out this plan?*** If yes, describe:	**Yes** ☐ **No** ☐	**Yes** ☐ **No** ☐
INTENSITY OF IDEATION		
The following features should be rated with respect to the most severe type of ideation (i.e.,1-5 from above, with 1 being the least severe and 5 being the most severe). Ask about time he/she was feeling the most suicidal. Lifetime - ***Most Severe Ideation:*** ___ (***Type # (1-5)***) ___ (***Description of Ideation***) Past X Months - ***Most Severe Ideation:*** ___ (***Type # (1-5)***) ___ (***Description of Ideation***)	Most Severe	Most Severe
Frequency ***How many times have you had these thoughts?*** (1) Less than once a week (2) Once a week (3) 2-5 times in week (4) Daily or almost daily (5) Many times each day	____	____
Duration ***When you have the thoughts how long do they last?*** (1) Fleeting - few seconds or minutes (2) Less than 1 hour/some of the time (3) 1-4 hours/a lot of time (4) 4-8 hours/most of day (5) More than 8 hours/persistent or continuous	____	____
Controllability ***Could/can you stop thinking about killing yourself or wanting to die if you want to?*** (1) Easily able to control thoughts (2) Can control thoughts with little difficulty (3) Can control thoughts with some difficulty (4) Can control thoughts with a lot of difficulty (5) Unable to control thoughts (0) Does not attempt to control thoughts	____	____
Deterrents ***Are there things - anyone or anything (e.g., family, religion, pain of death) - that stopped you from wanting to die or acting on thoughts of committing suicide?*** (1) Deterrents definitely stopped you from attempting suicide (2) Deterrents probably stopped you (3) Uncertain that deterrents stopped you (4) Deterrents most likely did not stop you (5) Deterrents definitely did not stop you (0) Does not apply	____	____
Reasons for Ideation ***What sort of reasons did you have for thinking about wanting to die or killing yourself? Was it to end the pain or stop the way you were feeling (in other words you couldn't go on living with this pain or how you were feeling) or was it to get attention, revenge or a reaction from others? Or both?*** (1) Completely to get attention, revenge or a reaction from others (2) Mostly to get attention, revenge or a reaction from others (3) Equally to get attention, revenge or a reaction from others and to end/stop the pain (4) Mostly to end or stop the pain (you couldn't go on living with the pain or how you were feeling) (5) Completely to end or stop the pain (you couldn't go on living with the pain or how you were feeling) (0) Does not apply	____	____

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SUICIDAL BEHAVIOR *(Check all that apply, so long as these are separate events; must ask about all types)*	**Lifetime**	**Past __ Years**
Actual Attempt: A potentially self-injurious act committed with at least some wish to die, *as a result of act*. Behavior was in part thought of as method to kill oneself. Intent does not have to be 100%. If there is ***any*** intent/desire to die associated with the act, then it can be considered an actual suicide attempt. ***There does not have to be any injury or harm***, just the potential for injury or harm. If person pulls trigger while gun is in mouth but gun is broken so no injury results, this is considered an attempt. Inferring Intent: Even if an individual denies intent/wish to die, it may be inferred clinically from the behavior or circumstances. For example, a highly lethal act that is clearly not an accident so no other intent but suicide can be inferred (e.g., gunshot to head, jumping from window of a high floor/story). Also, if someone denies intent to die, but they thought that what they did could be lethal, intent may be inferred. ***Have you made a suicide attempt?*** ***Have you done anything to harm yourself?*** ***Have you done anything dangerous where you could have died?*** ***What did you do?*** ***Did you_____as a way to end your life?*** ***Did you want to die (even a little) when you_____?*** ***Were you trying to end your life when you_____?*** ***Or did you think it was possible you could have died from_____?*** ***Or did you do it purely for other reasons / without ANY intention of killing yourself (like to relieve stress, feel better, get sympathy, or get something else to happen)?*** (Self-Injurious Behavior without suicidal intent) If yes, describe:	**Yes** ☐ **No** ☐ Total # of Attempts _____	**Yes** ☐ **No** ☐ Total # of Attempts _____
Has subject engaged in Non-Suicidal Self-Injurious Behavior?	**Yes** ☐ **No** ☐	**Yes** ☐ **No** ☐
Interrupted Attempt: When the person is interrupted (by an outside circumstance) from starting the potentially self-injurious act *(if not for that, actual attempt would have occurred).* Overdose: Person has pills in hand but is stopped from ingesting. Once they ingest any pills, this becomes an attempt rather than an interrupted attempt. Shooting: Person has gun pointed toward self, gun is taken away by someone else, or is somehow prevented from pulling trigger. Once they pull the trigger, even if the gun fails to fire, it is an attempt. Jumping: Person is poised to jump, is grabbed and taken down from ledge. Hanging: Person has noose around neck but has not yet started to hang - is stopped from doing so. ***Has there been a time when you started to do something to end your life but someone or something stopped you before you actually did anything?*** If yes, describe:	**Yes** ☐ **No** ☐ Total # of interrupted _____	**Yes** ☐ **No** ☐ Total # of interrupted _____
Aborted Attempt: When person begins to take steps toward making a suicide attempt, but stops themselves before they actually have engaged in any self-destructive behavior. Examples are similar to interrupted attempts, except that the individual stops him/herself, instead of being stopped by something else. ***Has there been a time when you started to do something to try to end your life but you stopped yourself before you actually did anything?*** If yes, describe:	**Yes** ☐ **No** ☐ Total # of aborted _____	**Yes** ☐ **No** ☐ Total # of aborted _____
Preparatory Acts or Behavior: Acts or preparation towards imminently making a suicide attempt. This can include anything beyond a verbalization or thought, such as assembling a specific method (e.g., buying pills, purchasing a gun) or preparing for one's death by suicide (e.g., giving things away, writing a suicide note). ***Have you taken any steps towards making a suicide attempt or preparing to kill yourself (such as collecting pills, getting a gun, giving valuables away or writing a suicide note)?*** If yes, describe:	**Yes** ☐ **No** ☐	**Yes** ☐ **No** ☐
Suicidal Behavior: Suicidal behavior was present during the assessment period?	**Yes** ☐ **No** ☐	**Yes** ☐ **No** ☐

Answer for Actual Attempts Only	Most Recent Attempt Date:	Most Lethal Attempt Date:	Initial/First Attempt Date:
Actual Lethality/Medical Damage: 0. No physical damage or very minor physical damage (e.g., surface scratches). 1. Minor physical damage (e.g., lethargic speech; first-degree burns; mild bleeding; sprains). 2. Moderate physical damage; medical attention needed (e.g., conscious but sleepy, somewhat responsive; second-degree burns; bleeding of major vessel). 3. Moderately severe physical damage; *medical* hospitalization and likely intensive care required (e.g., comatose with reflexes intact; third-degree burns less than 20% of body; extensive blood loss but can recover; major fractures). 4. Severe physical damage; *medical* hospitalization with intensive care required (e.g., comatose without reflexes; third-degree burns over 20% of body; extensive blood loss with unstable vital signs; major damage to a vital area). 5. Death	*Enter Code* _____	*Enter Code* _____	*Enter Code* _____
Potential Lethality: Only Answer if Actual Lethality=0 Likely lethality of actual attempt if no medical damage (the following examples, while having no actual medical damage, had potential for very serious lethality: put gun in mouth and pulled the trigger but gun fails to fire so no medical damage; laying on train tracks with oncoming train but pulled away before run over). 0 = Behavior not likely to result in injury 1 = Behavior likely to result in injury but not likely to cause death 2 = Behavior likely to result in death despite available medical care	*Enter Code* _____	*Enter Code* _____	*Enter Code* _____

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COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS)

Since Last Visit

Version 1/14/09

Posner, K.; Brent, D.; Lucas, C.; Gould, M.; Stanley, B.; Brown, G.; Fisher, P.; Zelazny, J.; Burke, A.; Oquendo, M.; Mann, J.

Disclaimer:

This scale is intended to be used by individuals who have received training in its administration. The questions contained in the Columbia-Suicide Severity Rating Scale are suggested probes. Ultimately, the determination of the presence of suicidal ideation or behavior depends on the judgment of the individual administering the scale.

Definitions of behavioral suicidal events in this scale are based on those used in ***The Columbia Suicide History Form****, developed by John Mann, MD and Maria Oquendo, MD, Conte Center for the Neuroscience of Mental Disorders (CCNMD), New York State Psychiatric Institute, 1051 Riverside Drive, New York, NY, 10032. (Oquendo M. A., Halberstam B. & Mann J. J., Risk factors for suicidal behavior: utility and limitations of research instruments. In M.B. First [Ed.]* Standardized Evaluation in Clinical Practice*, pp. 103 -130, 2003.)*

For reprints of the C-SSRS contact Kelly Posner, Ph.D., New York State Psychiatric Institute, 1051 Riverside Drive, New York, New York, 10032; inquiries and training requirements contact posnerk@nyspi.columbia.edu

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C-SSRS Since Last Visit - United States/English - Mapi.
C-SSRS-SinceLastVisit_AU5.1_eng-USori.doc

SUICIDAL IDEATION

Ask questions 1 and 2. If both are negative, proceed to "Suicidal Behavior" section. If the answer to question 2 is "yes", ask questions 3, 4 and 5. If the answer to question 1 and/or 2 is "yes", complete "Intensity of Ideation" section below.

Since Last Visit

1. Wish to be Dead
Subject endorses thoughts about a wish to be dead or not alive anymore, or wish to fall asleep and not wake up.
Have you wished you were dead or wished you could go to sleep and not wake up?
If yes, describe:

Yes ☐ **No** ☐

2. Non-Specific Active Suicidal Thoughts
General non-specific thoughts of wanting to end one's life/commit suicide (e.g., *"I've thought about killing myself"*) without thoughts of ways to kill oneself/associated methods, intent, or plan during the assessment period.
Have you actually had any thoughts of killing yourself?
If yes, describe:

Yes ☐ **No** ☐

3. Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act
Subject endorses thoughts of suicide and has thought of at least one method during the assessment period. This is different than a specific plan with time, place or method details worked out (e.g., thought of method to kill self but not a specific plan). Includes person who would say, *"I thought about taking an overdose but I never made a specific plan as to when, where or how I would actually do it…..and I would never go through with it".*
Have you been thinking about how you might do this?
If yes, describe:

Yes ☐ **No** ☐

4. Active Suicidal Ideation with Some Intent to Act, without Specific Plan
Active suicidal thoughts of killing oneself and subject reports having some intent to act on such thoughts, as opposed to *"I have the thoughts but I definitely will not do anything about them".*
Have you had these thoughts and had some intention of acting on them?
If yes, describe:

Yes ☐ **No** ☐

5. Active Suicidal Ideation with Specific Plan and Intent
Thoughts of killing oneself with details of plan fully or partially worked out and subject has some intent to carry it out.
Have you started to work out or worked out the details of how to kill yourself? Do you intend to carry out this plan?
If yes, describe:

Yes ☐ **No** ☐

INTENSITY OF IDEATION

The following features should be rated with respect to the most severe type of ideation (i.e.,1-5 from above, with 1 being the least severe and 5 being the most severe).

Most Severe Ideation: _____ _____
Type # (1-5) ***Description of Ideation***

Most Severe

Frequency
How many times have you had these thoughts?
(1) Less than once a week (2) Once a week (3) 2-5 times in week (4) Daily or almost daily (5) Many times each day

____

Duration
When you have the thoughts how long do they last?
(1) Fleeting - few seconds or minutes
(2) Less than 1 hour/some of the time
(3) 1-4 hours/a lot of time
(4) 4-8 hours/most of day
(5) More than 8 hours/persistent or continuous

____

Controllability
Could/can you stop thinking about killing yourself or wanting to die if you want to?
(1) Easily able to control thoughts
(2) Can control thoughts with little difficulty
(3) Can control thoughts with some difficulty
(4) Can control thoughts with a lot of difficulty
(5) Unable to control thoughts
(0) Does not attempt to control thoughts

____

Deterrents
Are there things - anyone or anything (e.g., family, religion, pain of death) - that stopped you from wanting to die or acting on thoughts of committing suicide?
(1) Deterrents definitely stopped you from attempting suicide
(2) Deterrents probably stopped you
(3) Uncertain that deterrents stopped you
(4) Deterrents most likely did not stop you
(5) Deterrents definitely did not stop you
(0) Does not apply

____

Reasons for Ideation
What sort of reasons did you have for thinking about wanting to die or killing yourself? Was it to end the pain or stop the way you were feeling (in other words you couldn't go on living with this pain or how you were feeling) or was it to get attention, revenge or a reaction from others? Or both?
(1) Completely to get attention, revenge or a reaction from others
(2) Mostly to get attention, revenge or a reaction from others
(3) Equally to get attention, revenge or a reaction from others and to end/stop the pain
(4) Mostly to end or stop the pain (you couldn't go on living with the pain or how you were feeling)
(5) Completely to end or stop the pain (you couldn't go on living with the pain or how you were feeling)
(0) Does not apply

____

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C-SSRS—Since Last Visit (Version 1/14/09)

SUICIDAL BEHAVIOR *(Check all that apply, so long as these are separate events; must ask about all types)*	**Since Last Visit**
Actual Attempt: A potentially self-injurious act committed with at least some wish to die, *as a result of act*. Behavior was in part thought of as method to kill oneself. Intent does not have to be 100%. If there is ***any*** intent/desire to die associated with the act, then it can be considered an actual suicide attempt. ***There does not have to be any injury or harm***, just the potential for injury or harm. If person pulls trigger while gun is in mouth but gun is broken so no injury results, this is considered an attempt. Inferring Intent: Even if an individual denies intent/wish to die, it may be inferred clinically from the behavior or circumstances. For example, a highly lethal act that is clearly not an accident so no other intent but suicide can be inferred (e.g., gunshot to head, jumping from window of a high floor/story). Also, if someone denies intent to die, but they thought that what they did could be lethal, intent may be inferred. ***Have you made a suicide attempt?*** ***Have you done anything to harm yourself?*** ***Have you done anything dangerous where you could have died?*** ***What did you do?*** ***Did you_____as a way to end your life?*** ***Did you want to die (even a little) when you_____?*** ***Were you trying to end your life when you_____?*** ***Or Did you think it was possible you could have died from_____?*** ***Or did you do it purely for other reasons / without ANY intention of killing yourself (like to relieve stress, feel better, get sympathy, or get something else to happen)?*** (Self-Injurious Behavior without suicidal intent) If yes, describe: **Has subject engaged in Non-Suicidal Self-Injurious Behavior?**	**Yes** ☐ **No** ☐ Total # of Attempts _____ **Yes** ☐ **No** ☐
Interrupted Attempt: When the person is interrupted (by an outside circumstance) from starting the potentially self-injurious act *(if not for that, actual attempt would have occurred)*. Overdose: Person has pills in hand but is stopped from ingesting. Once they ingest any pills, this becomes an attempt rather than an interrupted attempt. Shooting: Person has gun pointed toward self, gun is taken away by someone else, or is somehow prevented from pulling trigger. Once they pull the trigger, even if the gun fails to fire, it is an attempt. Jumping: Person is poised to jump, is grabbed and taken down from ledge. Hanging: Person has noose around neck but has not yet started to hang - is stopped from doing so. ***Has there been a time when you started to do something to end your life but someone or something stopped you before you actually did anything?*** If yes, describe:	**Yes** ☐ **No** ☐ Total # of interrupted _____
Aborted Attempt: When person begins to take steps toward making a suicide attempt, but stops themselves before they actually have engaged in any self-destructive behavior. Examples are similar to interrupted attempts, except that the individual stops him/herself, instead of being stopped by something else. ***Has there been a time when you started to do something to try to end your life but you stopped yourself before you actually did anything?*** If yes, describe:	**Yes** ☐ **No** ☐ Total # of aborted _____
Preparatory Acts or Behavior: Acts or preparation towards imminently making a suicide attempt. This can include anything beyond a verbalization or thought, such as assembling a specific method (e.g., buying pills, purchasing a gun) or preparing for one's death by suicide (e.g., giving things away, writing a suicide note). ***Have you taken any steps towards making a suicide attempt or preparing to kill yourself (such as collecting pills, getting a gun, giving valuables away or writing a suicide note)?*** If yes, describe:	**Yes** ☐ **No** ☐
Suicidal Behavior: Suicidal behavior was present during the assessment period?	**Yes** ☐ **No** ☐
Suicide:	**Yes** ☐ **No** ☐
Answer for Actual Attempts Only	Most Lethal Attempt Date:
Actual Lethality/Medical Damage: 0. No physical damage or very minor physical damage (e.g., surface scratches). 1. Minor physical damage (e.g., lethargic speech; first-degree burns; mild bleeding; sprains). 2. Moderate physical damage; medical attention needed (e.g., conscious but sleepy, somewhat responsive; second-degree burns; bleeding of major vessel). 3. Moderately severe physical damage; *medical* hospitalization and likely intensive care required (e.g., comatose with reflexes intact; third-degree burns less than 20% of body; extensive blood loss but can recover; major fractures). 4. Severe physical damage; *medical* hospitalization with intensive care required (e.g., comatose without reflexes; third-degree burns over 20% of body; extensive blood loss with unstable vital signs; major damage to a vital area). 5. Death	*Enter Code* _____
Potential Lethality: Only Answer if Actual Lethality=0 Likely lethality of actual attempt if no medical damage (the following examples, while having no actual medical damage, had potential for very serious lethality: put gun in mouth and pulled the trigger but gun fails to fire so no medical damage; laying on train tracks with oncoming train but pulled away before run over). 0 = Behavior not likely to result in injury 1 = Behavior likely to result in injury but not likely to cause death 2 = Behavior likely to result in death despite available medical care	*Enter Code* _____

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Appendix 8: Impact of Weight on Quality of Life - Lite Clinical Trials Version (IWQOL-Lite-CT)

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

For each of the following statements, please select the response that best applies to you currently.

		Never	Rarely	Sometimes	Usually	Always
1	I have trouble bending over, for example to pick things up from the floor or tie my shoes.	☐	☐	☐	☐	☐
2	I get tired or winded walking up one flight of stairs.	☐	☐	☐	☐	☐
3	I am unable to stand comfortably for 20 to 30 minutes.	☐	☐	☐	☐	☐
4	I feel uncomfortable in small seats in public places, such as in airplanes, theaters, and sports arenas.	☐	☐	☐	☐	☐
5	I experience pain, such as pain in my knees, hips, or back.	☐	☐	☐	☐	☐
6	I feel self-conscious eating in social settings.	☐	☐	☐	☐	☐
7	I feel less confident because of my weight.	☐	☐	☐	☐	☐
8	I feel that others are judging me on the basis of my weight.	☐	☐	☐	☐	☐
9	I get frustrated shopping for clothes.	☐	☐	☐	☐	☐
10	I feel bad or upset when I see myself in pictures.	☐	☐	☐	☐	☐
11	I feel down or depressed about my weight.	☐	☐	☐	☐	☐
12	I am less interested in sexual activity than I would like to be.	☐	☐	☐	☐	☐
13	I avoid social gatherings because of my weight.	☐	☐	☐	☐	☐

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For all other correspondence contact Ronette L. Kolotkin, Ph.D., Quality of Life Consulting, at rkolotkin@qualityoflifeconsulting.com; +1 919 493-9995.

IWQOL-Lite-CT_AU1.2 – United States/English – Original version – ICON
IWQOL-Lite-CT_AU1.2_engUSori.doc

14	I am less productive than I would like to be (at work, home, and/or school) because of my weight.	☐	☐	☐	☐	☐
15	I lack the energy to do the things I would like to do.	☐	☐	☐	☐	☐

		Not at all true	**A little true**	**Moderately true**	**Mostly true**	**Completely true**
16	I am not as physically active as I would like to be.	☐	☐	☐	☐	☐
17	I am unable to walk as far or as quickly as I would like.	☐	☐	☐	☐	☐
18	I am worried about my health.	☐	☐	☐	☐	☐
19	I am self-conscious about my weight.	☐	☐	☐	☐	☐
20	I feel frustrated or upset with myself about my weight.	☐	☐	☐	☐	☐

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IWQOL-Lite-CT_AU1.2 – United States/English – Original version – ICON
IWQOL-Lite-CT_AU1.2_engUSori.doc

Appendix 9: Diet and Physical Activity Suggestions for Sites Without Specific Programs

Diet

Diet recommendations are based on the WHO guidelines (Bull [WHO] 2020) for everyone, which is based on a Mediterranean eating pattern.

The Mediterranean eating pattern for a healthy diet consists of:

- Legumes (eg, lentils and beans)
- Nuts
- Whole grains (eg, unprocessed wheat, maize, millet, oats, and brown rice)
- At least 5 portions of fruit and vegetables per day (excluding potatoes, sweet potatoes, cassava, and other starchy roots)
- Less than 10% of total energy intake from free sugars (equivalent to 50 g or 12 level teaspoons), but ideally less than 5% of total energy intake. Free sugars are sugars added to foods and drinks, as well as sugars present in honey, syrups, fruit juices, and fruit juice concentrates
- Less than 30% of total energy intake from fats. Unsaturated fats are preferred over saturated fats. Unsaturated fats are found in fish, avocado, nuts, sunflower, canola, and olive oils. Consumption of saturated fats, which are fats in fatty meat, butter, palm and coconut oil, cream cheese, ghee, and lard, should be reduced to less than 10% of total energy intake. Trans fats, which are found in industrially produced foods should be avoided.
- Salt intake should not be more than 5 g (about 1 teaspoon) per day and should be iodized.

Physical Activity

Regular physical activity can improve a participant's health. Moving more and sitting less benefits everyone, regardless of age, sex, race, ethnicity, or current fitness level. Benefits accumulate with even small amounts and start immediately.

To safely engage in physical activity, types of physical activity appropriate for the participant's current fitness should be chosen. Furthermore, the amount and duration of physical activity should be gradually increased over time. Participants with chronic conditions and symptoms should be under the care of a health provider about the types and amounts of physical activity that are appropriate for the participant.

Physical activity recommendations are based on WHO recommendations (Bull [WHO] 2020) and with the US Health and Human Services (HHS 2020) recommendations.

- Any physical activity is better than none. Adults should move more and sit less.
- Adults should do 150 minutes (2 hours and 30 minutes) to 300 minutes (5 hours) of moderate-intensity aerobic physical activity throughout the week or 75 minutes (1 hour

15 minutes) to 150 minutes (2 hours and 30 minutes) a week of vigorous-intensity aerobic physical activity, or an equivalent combination of moderate- and vigorous-intensity aerobic activity. Preferably, aerobic activity should be spread throughout the week.

- Aerobic activity should be performed in bouts of at least 10 minutes duration.
- For additional health benefits, adults should increase their moderate-intensity aerobic physical activity to 300 minutes per week or engage in 150 minutes of vigorous-intensity aerobic physical activity per week, or an equivalent combination of moderate- and vigorous-intensity aerobic physical activity. Additional health benefits are gained by engaging in physical activity beyond the equivalent of 300 minutes (5 hours) of moderate-intensity physical activity a week.
- Muscle-strengthening activities should be done involving major muscle groups on 2 or more days a week.
- Older adults, with poor mobility, should perform physical activity to enhance balance and prevent falls on 3 or more days per week, as well as aerobic and muscle-strengthening activities. They should be as physically active as their abilities and conditions allow. When older adults cannot do 150 minutes of moderate-intensity aerobic activity a week because of chronic conditions, they should be as physically active as their abilities and conditions allow.

Appendix 10: Contraceptive Guidance and Collection of Pregnancy Information

Definitions:

Woman of Childbearing Potential (WOCBP)

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

Women in the following categories are not considered WOCBP

1. Premenopausal female with surgical sterility defined as 1 of the following:
    - Documented complete hysterectomy (ie, including removal of cervix)

    Note: Given the potential for an ectopic pregnancy in a premenopausal female with a cervix-sparing hysterectomy, participants with inadequate documentation of a complete hysterectomy or documentation of a cervix-sparing hysterectomy should use an additional contraceptive method (see Appendix Table 4).

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

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

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

Contraception Guidance:

Male participants who are sexually active must use a condom with every sexual act that could expose a partner to seminal fluid. Male participants with a female partner of childbearing

potential must collaborate with their partner(s) to follow the guidance per Appendix Table 4 during the study and until 90 days following the last dose of study drug. Male participants must not donate sperm from the first dose of study drug until 90 days following the last dose of the study drug.

Female participants of childbearing potential must have negative serum pregnancy test at screening and negative urine pregnancy test at randomization, not be breastfeeding, and not plan to donate oocytes or become pregnant during study or within 30 days after dosing of study drug. Female participants of childbearing potential must either be surgically sterile (documented complete hysterectomy, bilateral salpingectomy, bilateral oophorectomy) or follow the guidance per Appendix Table 4 during the study and until 30 days following the last dose of the study drug.

Appendix Table 4 Contraceptive Methods

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

Collection of Pregnancy Information:

Male Participants with Partners Who Become Pregnant

The Investigator will attempt to collect pregnancy information including any relevant medical history on any male participant's female partner who becomes pregnant while the male participant is in this study, or if they become pregnant within 90 days following the last dose of the study drug. This applies only to male participants who receive study drug.

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

Female Participants Who Become Pregnant

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

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

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

While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication (eg, ectopic pregnancy), spontaneous termination of pregnancy (ie, miscarriage), or termination of a pregnancy for medical reasons (ie, therapeutic abortion) will be reported as an SAE.

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

Any post-study pregnancy related SAE considered reasonably related to the study drug by the Investigator will be reported to the sponsor as described in Section 8.6.5. While the Investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.

Appendix 11: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

Definition of AE

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

Events Meeting the AE Definition
• Any safety assessment (eg, ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the Investigator (ie, not related to progression of underlying disease). • A clinical condition or symptom associated with an abnormal laboratory test result (eg, hematology, clinical chemistry, or urinalysis). An abnormal laboratory test that is not accompanied with other signs or symptoms and not characterized as clinically significant should not be reported as an AE. • Exacerbation of a chronic or intermittent pre-existing condition, including either an increase in frequency and/or intensity of the condition. • New conditions detected or diagnosed after study drug administration even though it may have been present before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study drug or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.

Events NOT Meeting the AE Definition
• Abnormal laboratory findings that are not clinically significant or other abnormal safety assessments which are associated with an underlying disease present at baseline without worsening, unless judged by the Investigator to be more severe than expected for the participant's condition. • An abnormal laboratory test that is not clinically significant and is not accompanied with other signs or symptoms • The disease/disorder being studied, or signs or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition. • Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE. • Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital). • Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

Definition of SAE

An SAE is an AE that meets the following criteria:

An SAE is defined as any untoward medical occurrence that, at any dose:
a. Results in death
b. Is life-threatening The term 'life-threatening' in the definition of 'serious' refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
c. Requires inpatient hospitalization or prolongation of existing hospitalization • In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious. • Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.
d. Results in persistent disability/incapacity

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.
- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect

f. Other situations:

- Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.
- Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

If an event does not meet the AE definition, then it cannot be an SAE even if serious conditions are met (eg, hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

Recording and Follow-Up of AE and/or SAE

AE and SAE Recording

- When an AE/SAE occurs, it is the responsibility of the Investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The Investigator will then record all relevant AE/SAE information in the CRF.
- It is **not** acceptable for the Investigator to send photocopies of the participant's medical records to the Sponsor or designee in lieu of completion of the AE/SAE CRF page.
- There may be instances when copies of medical records for certain cases are requested by the Sponsor or designee. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to the Sponsor or desi>
- gnee.
- The Investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity

The Investigator will be asked to provide an assessment of the severity of the AE using the following categories:

Appendix Table 5 Adverse Event Severity Categories

Severity	Brief Description	Detailed Description
Mild	• No or minimal intervention • Self-care or OTC therapies for management	• Asymptomatic or mild symptoms • Clinical or diagnostic observations only • No professional intervention indicated • No or minimal disruption to daily activity • Supportive and/or over the counter therapies may be self-administered for the comfort of the participant, but no prescription therapy is indicated • No contact with or intervention by a medical profession is indicated
Moderate	• Minimal or non-invasive management • Prescription therapy indicated	• Minimal, local, or noninvasive professional intervention indicated • Discomfort sufficient to reduce or affect normal daily activity. • Prescription therapy may be administered • Contact with or intervention by a medical professional is indicated

Severe	• Requires urgent or emergent medical contact and/or hospitalization • Not immediately life-threatening	• Severe or medically significant but not immediately life-threatening • Hospitalization or prolongation of hospitalization indicated • Disabling • Limiting self-care activities of daily living • Urgent or emergent contact with a medical professional is indicated
Life-threatening	• Life-threatening consequences • Urgent medical intervention indicated	
Death	• AE results in death	

When/if AE severity changes before resolution, a stop date for the current AE entry should be entered and a new AE entered with the new severity and its start date.

The general guidance on grading the severity of AEs should be adhered to as outlined in Appendix Table 5. The additional guidance provided below offers examples for assessing the severity of GI AEs (Appendix Table 6). This guidance is meant to assist the Investigator and does not supersede the Investigator's judgement or final decision regarding the severity based on their assessment.

Appendix Table 6 Assessing the Severity of GI AEs

AE	Mild	Moderate	Severe
Nausea	• No or minimal intervention indicated • Self-care and/or OTC therapies for management • No/minimal disruption to daily activity	• Prescription therapy indicated • Minimal professional intervention indicated • Discomfort sufficient to reduce normal daily activity	• Requires urgent or emergent medical contact and/or hospitalization • Limits self-care activities of daily living (eg, unable/unwilling to get out of bed, unable/unwilling to bathe/groom, etc)
Vomiting	• 1 to 3 episodes in a week	• 4 to 9 episodes in a week	• >10 episodes in a week

	• Self-care and/or OTC therapies for management	• Prescription therapy indicated	**OR** • Requiring IV fluids
Diarrhea	• Increase of 2 to 3 stools per day over baseline • Occasional/intermittent use of anti-diarrheal	• Increase of 4 to 6 stools per day over baseline • Regular use of anti-diarrheal	• Increase of ≥7 stools per day over baseline • Persists despite regular use of anti-diarrheal
Constipation	• Occasional/regular use of stool softeners • Occasional/ intermittent use of laxatives or suppository/enema	• Regular use of laxatives or enemas	• Obstipation with manual evacuation indicated
Belching/ Burping	• Increase over baseline • Occasional use of OTC treatments	• Regular use of OTC treatments	--

Assessment of Causality

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

However, it is very important that the Investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the Sponsor or designee.
- The Investigator may change his/her opinion of causality in light of follow-up information and send a SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AEs and SAEs

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

Reporting of SAEs

SAE Reporting via an Electronic Data Collection Tool

- The primary mechanism for reporting an SAE will be the electronic data collection tool.
- If the electronic system is unavailable, then the site will use the paper SAE data collection tool (see next section) in order to report the event within 24 hours.
- The site will enter the SAE data into the electronic system as soon as it becomes available.
- After the study is completed at a given site, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data.
- If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the site can report this information on a paper SAE form (see next section) or to the Pharmacovigilance Team/Medical Monitor by telephone.
- Medpace Safety and Pharmacovigilance can be contacted as shown below:

    - Medpace SAE reporting line (office location: Cincinnati, Ohio, United States):
    - Telephone: +1-513-579-9911, dial 3
    - Fax: +1-513-570-5196

- Email: medpace-safetynotification@medpace.com

SAE Reporting via Paper CRF

- Facsimile transmission of the SAE paper CRF is the preferred method to transmit this information to the Pharmacovigilance Team/Medical Monitor.
- In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of the SAE data collection tool sent by overnight mail or courier service.
- Initial notification via telephone does not replace the need for the Investigator to complete and sign the SAE CRF pages within the designated reporting time frames.
- Medpace Safety and Pharmacovigilance can be contacted as shown below:

    - Medpace SAE reporting line (office location: Cincinnati, Ohio, United States):
    - Telephone: +1-513-579-9911, dial 3
    - Fax: +1-513-570-5196
    - Email: medpace-safetynotification@medpace.com

Appendix 12: Management Plan for Participants who Develop GI AEs and Other Related AEs

Nausea, emesis, and diarrhea are anticipated adverse events with this protocol. All AEs will be graded per the criteria in Appendix 11. Study drug should be interrupted or discontinued for any severe AE, per Section 6.6 and Section 6.7. Management strategies may be implemented, at the discretion of the Investigator, according to symptom- and severity-specific tables below:

Appendix Table 7 Nausea and/or Emesis Management

Adverse Event	Severity	Management	What to do with study drug
Nausea and/or Vomiting	Mild	• Small meals and snacks (eg, saltines) • Cool compress/ice pack to neck • Ginger-containing lozenges/foods/beverages • Over the counter (OTC) therapies (eg, Tums) • Acupressure Wristbands (eg, Sea-Bands) • Oral rehydration (eg, diluted juices, sports drinks; preferably ice-cold), as tolerated	• No changes to protocol-specified dosing
	Moderate	• Strategies implemented for mild symptoms **PLUS** • Prescribe an oral or sublingual anti-emetic (ondansetron preferred)[a]; adjust dose or add additional treatments, as required • Assess improvement by phone, telehealth, or in-person visit(s) every approximately 1 to 3 days until symptoms are well-managed	• Maintain current dosing (ie, do not up-titrate) • Once symptoms are well-managed (with or without continued use prescription therapy), continue with protocol specified dosing • If moderate symptoms persist, consider dose reduction

Adverse Event	Severity	Management	What to do with study drug

	Severe	• Strategies implemented for moderate symptoms **PLUS**
		• Intravenous (IV) rehydration, as required
			• Immediately interrupt study drug until symptoms resolve to at least moderate
			• Once symptoms have started resolving, and the Investigator deems it safe to restart:
			  ○ If interruption <5 days: restart at one dose level lower
			  ○ If interruption ≥5 days: restart at Week 2 of dosing schedule

Diarrhea	Mild	• Small, low-fat, low-residue/starchy meals and snacks (eg, crackers, rice, noodles) • Cool compress/ice pack to neck • OTC therapies (eg, loperamide or bismuth salicylates) • Oral rehydration (eg, diluted juices, sports drinks), as tolerated	• No changes to protocol-specified dosing
	Moderate	• Strategies implemented for mild symptoms **PLUS** • Assess improvement by phone, telehealth, or in-person visit(s) every approximately 1 to 3 days until symptoms are well-managed	• Maintain current dosing (ie, do not up-titrate) • Once symptoms are well-managed (with or without continued use prescription therapy), continue with protocol specified dosing • If moderate symptoms persist, consider dose reduction

Adverse Event	Severity	Management	What to do with study drug
	Severe	• Strategies implemented for moderate symptoms **PLUS** • Assess participant in person to implement appropriate therapy, diagnostic testing, and/or consultations • Intravenous (IV) rehydration, as required	• Immediately interrupt study drug until symptoms resolve to at least moderate • Once symptoms have started resolving, and the Investigator deems it safe to restart: ○ If interruption <5 days: restart at one dose level lower ○ If interruption ≥5 days: restart at Week 2 of dosing schedule
Constipation	Mild	• Increase water and dietary fiber, as tolerated • Increase exercise, as tolerated • OTC therapies (eg, docusate, polyethylene glycol)	• No changes to protocol-specified dosing
	Moderate	• Strategies implemented for mild symptoms **PLUS** • Adjust the dose, frequency, and/or type of OTC therapies; or prescribe therapy • Assess improvement by phone, telehealth, or in-person visit(s) every approximately 1 to 3 days until symptoms resolve to mild or better	• Maintain current dosing (ie, do not up-titrate) • Once symptoms are well-managed (with or without increased dose/frequency of OTC or prescribed therapy), continue with protocol specified dosing • If moderate symptoms persist, consider dose reduction

Adverse Event	Severity	Management	What to do with study drug
	Severe	• Strategies implemented for moderate symptoms **PLUS** • Procedures, as required	• Immediately interrupt study drug until symptoms resolve to at least moderate • Once symptoms have started resolving, and the Investigator deems it safe to restart: ○ If interruption <5 days: restart at one dose level lower ○ If interruption ≥5 days: restart at Week 2 of dosing schedule
Other Study-Drug Related[b] AEs	Mild	• Managed per Investigator's discretion	• No changes to protocol-specified dosing
	Moderate	• Managed per Investigator's discretion	• Maintain current dosing (ie, do not up-titrate) • Once symptoms are well-managed, continue with protocol specified dosing • If moderate symptoms persist, consider dose reduction
	Severe	• Managed per Investigator's discretion	• Immediately interrupt study drug until symptoms resolve to at least moderate • Once symptoms have started resolving, and the Investigator deems it safe to restart: • If interruption <5 days: restart at once dose level lower • If interruption ≥5 days: restart at Week 2 of dosing schedule

a Participants who are started on anti-emetics such as ondansetron should be counseled on strategies to prevent or relieve constipation associated with ondansetron.
b AEs deemed related or probably related to study drug are considered related for the purposes of this management plan.

Symptoms, clinical signs, or laboratory abnormalities suggestive of a specific diagnosis should be managed per the Investigator's discretion and the guidance included in Appendix 11.

Appendix 13: Management Plan for Participants who Develop Hypoglycemia

1. Hypoglycemia Monitoring

Participants will be instructed on signs and symptoms of hypoglycemia such as neuroglycopenic symptoms (palpitations, tremor, hunger, sweats) or symptoms of neuroglycopenia (confusion, lethargy, agitation, reduced level of consciousness). Participants will be advised by the study staff regarding treatment options to alleviate the symptoms.

2. Hypoglycemia Treatment

Treatment of hypoglycemia will include the ingestion of 10-15 grams of fast-acting carbohydrates (glucose; eg, juice). A rise in blood glucose and change in symptoms should occur within 15 to 20 minutes. Re-treatment may be required in certain instances. The participant will be advised to continue ingestion of carbohydrates every 15 to 20 minutes if hypoglycemia symptoms have not resolved.

Hypoglycemia Assessment

Hypoglycemia may be identified by spontaneous reporting of symptoms from participants (whether confirmed or unconfirmed by simultaneous glucose values) or by blood glucose samples collected during study visits (scheduled or unscheduled). Hypoglycemia will be assessed and recorded according to the table below:

Appendix Table 8 Severity Grading of Hypoglycemia

Level	Glycemic Criteria/Description
Level 1	Glucose <70 mg/dL and ≥54 mg/dl; participant should be treated with fast-acting carbohydrates
Level 2	Glucose <54 mg/dL; this threshold is clinically relevant regardless of the presence or absence of symptoms
Level 3 (Discontinue study drug per Stopping Criteria)	A severe event characterized by altered mental and/or physical status requiring assistance

To avoid duplicate reporting, all hypoglycemia events occurring within a 1-hour period may be considered to be a single hypoglycemic event.

Appendix 14: Management Plan for Participants who Develop Acute Pancreatitis

The occurrence of acute pancreatitis is a possible adverse event with this protocol. For any participant that reports or shows symptoms that are consistent or suspicious of an episode of acute pancreatitis, vital sign assessments and a laboratory assessment per the below table and SoA will be performed.

Diagnosis of Acute Pancreatitis

The diagnosis of acute pancreatitis requires 2 of the following 3 features (Banks and Freeman 2006; Koizumi 2006):

- abdominal pain, characteristic of acute pancreatitis (that is, epigastric pain radiating to the back, often associated with nausea and vomiting)
- serum amylase (total, pancreatic, or both) and/or lipase ≥3× ULN, and
- characteristic findings of acute pancreatitis on CT scan or MRI.

If acute pancreatitis is suspected, the Investigator should ensure that the following steps are taken:

- obtain appropriate laboratory tests, including pancreatic amylase (p-amylase) and lipase, and
- perform imaging studies, such as abdominal CT scan with or without contrast, or abdominal MRI.

  Note: Abdominal ultrasound may be used as an alternative method only if CT and MRI cannot be performed.
- evaluate for possible causes of acute pancreatitis, including alcohol use, gallstone/gall bladder disease, hypertriglyceridemia, and concomitant medications.

Discontinuation for Acute Pancreatitis

If acute pancreatitis is suspected by the Investigator, the participant must temporarily discontinue study drug. If pancreatitis is not confirmed (ie, by imaging), the Investigator should consult with the Medical Monitor regarding restarting of study drug. If pancreatitis is confirmed, study drug should be permanently discontinued; the participant may continue in the study.

Asymptomatic Elevation of Pancreatic Amylase and/or Lipase

Serial measures of pancreatic enzymes have limited clinical value for predicting episodes of acute pancreatitis in asymptomatic participants (Nauck et al. 2017; Steinberg et al. 2017a, Steinberg et al. 2017b). Therefore, further diagnostic follow-up of cases of asymptomatic elevation of pancreatic enzymes (lipase and/or p-amylase ≥3× ULN) is not mandated but may be performed based on the Investigator's clinical judgment and assessment of the participant's overall clinical condition.

Additionally, other differential diagnosis including cholelithiasis should be considered (see Appendix 15 for more information for cholelithiasis). Routine laboratory assessments of

amylase, lipase and liver function tests (ALT, AST, alkaline phosphatase, and bilirubin) will be collected as per SoA.

Appendix 15: Management Plan for Participants who Develop Acute Gallbladder Disease

Gallstones (Cholelithiasis), Biliary Cholic, or Cholecystitis

Definitions:

Cholecystitis

A disorder characterized by inflammation involving the gallbladder. It may be associated with the presence of gallstones

Asymptomatic gallstones/asymptomatic common bile duct stones

Stones that are found incidentally in imaging investigations unrelated to gallstone disease in people who have been completely symptom free for at least 12 months before diagnosis.

Symptomatic gallstones/symptomatic common bile duct stones

Stones found on gallbladder imaging, regardless of whether symptoms are being experienced currently or whether they occurred sometime in the 12 months before diagnosis.

When should symptomatic gallbladder stones be suspected?

The characteristic symptoms of gallbladder stones (ie, episodic attacks of severe pain in the right upper abdominal quadrant or epigastrium for at least 15 to 30 minutes with radiation to the right back or shoulder and a positive reaction to analgesics) should be identified by medical history and physical examination.

Diagnostic Workup for Symptoms Suggestive of Gallstone-related Disorders:

- Laboratory testing, including amylase, lipase, and liver function tests, and ultrasound for suspected gallstone disease, and for individuals with abdominal or GI symptoms that have been unresponsive to previous management.
- Consider magnetic resonance cholangiopancreatography (MRCP) if ultrasound has not detected common bile duct stones but the:
    - ✓ bile duct is dilated and/or
    - ✓ liver function test results are abnormal.
- Consider endoscopic ultrasound (EUS) if MRCP does not allow a diagnosis to be made.
- Consider consulting with a Gastroenterologist.
- Refer people for further investigations if conditions other than gallstone disease are suspected.

Appendix 16: Liver Toxicity Monitoring Guideline

The following evaluations (Appendix Table 9) should be undertaken if tests of liver health/function (ie, LFTs) increase relative to ULN or baseline value (if baseline value abnormal).

Appendix Table 9 LFT Increased Monitoring Criteria and Follow-Up

Criteria for Elevation	Actions
If lab results were normal at Baseline: • ALT and/or AST >3× ULN • ALP >2× ULN • Total Bilirubin >2× ULN If lab results were >ULN (elevated) at Baseline: • ALT and/or AST >2× Baseline • ALP >1.5× Baseline • Total Bilirubin >1.5× Baseline	• Notify Medical Monitor immediately. • Participant may continue study drug while awaiting repeat LFTs, at the discretion of the Investigator, provided none of the following *discontinuation criteria* are met: o ALT or AST >8× ULN (if normal at baseline) o ALT or AST >5× Baseline (if abnormal at baseline) o ALT or AST >3× ULN (if normal at baseline) or >2 × Baseline (if abnormal at baseline) with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%) o ALT or AST >3× ULN (if normal at baseline) or >2 × Baseline (if abnormal at baseline) **and** (total bilirubin >2× ULN or INR >1.5) o ALP >5× ULN (if normal at baseline) o ALP >3× Baseline (if abnormal at baseline) o ALP >3× ULN and total bilirubin >2× ULN • Repeat measurement of LFTs (including ALT, AST, ALP, and total bilirubin) will be performed within 48 hours to confirm the abnormalities and to determine if they are increasing or decreasing. If total bilirubin is increased above the upper limit of normal, there should be a reflex to direct bilirubin. • PT/INR and albumin will be tested when significantly abnormal liver function is observed and repeated with repeat measurement of LFTs. • Upon confirmation of elevated LFTs: o Close observation by repeating LFTs every 24 to 72 hours will be initiated immediately. o The Investigator will initiate the recommended workup (ie, Workup to be Performed if Elevated LFTs Confirmed) • Frequency of monitoring can be decreased as LFTs decrease at the Investigator's discretion. • Close observation on abnormal LFTs will last until the parameters return to baseline, or to a stable level judged by the Investigator or a consulting hepatologist.

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

Work-up to be Performed if Elevated LFTs Confirmed:

1. Consider referral to hepatology

2. Take history to evaluate for intercurrent infection/illness

3. Obtain a history of new medications, new supplements, current alcohol use, recreational drug use, or new special diet started

4. Obtain history of exposure to environmental chemical agents

5. Rule out new liver diseases or biliary disease:

    a. Acute hepatitis panel (HAV IgM, hepatitis B surface antigen, core IgM, HCV AB, or HCV RNA [better])

    b. Antinuclear antibody, anti-smooth muscle antibody

    c. Iron, ferritin

    d. Right upper quadrant ultrasound

    e. Gamma-glutamyl transferase (GGT)

    f. Alcohol level

    g. Drug screen

Appendix 17: Acute Renal Events

Renal safety will be assessed based on repeated renal functional assessments as well as assessment of AEs suggestive of acute renal failure. Consistent with other GLP-1 RAs, GI AEs have been reported with TERN-601, including nausea, vomiting, and diarrhea. These events may lead to dehydration, which could cause deterioration in renal function, including acute renal failure. Adequate hydration (oral and/or IV, as appropriate) should be encouraged for participants with reduced oral intake due to nausea, vomiting, diarrhea, and/or acute renal injury due to dehydration (or other causes). Participants should be advised to notify Investigators in case of severe nausea or diarrhea, frequent vomiting, or symptoms of dehydration so that the Investigator and/or other medical professionals can appropriately and efficiently manage symptoms and rehydration.

Appendix 18: Depression and Suicidal Ideation or Behavior Monitoring

Participants will be monitored for depression and suicidal ideation or behavior through AE collection and by using the C-SSRS and the PHQ-9 questionnaires. Scores of the questionnaires must be reviewed by the Investigator at the time of each visit, and appropriate actions should be taken.

Participants will be referred to a Mental Health Professional if, in the opinion of the Investigator, it is necessary for the safety of the participant or if the participant had any of the following:

- A PHQ-9 score ≥15
- A "yes" answer to Question 4 (Active Suicidal Ideation with Some Intent to Act, Without Specific Plan) on the "Suicidal Ideation" portion or the C-SSRS
- A "yes" answer to Question 5 (Active Suicidal Ideation with Specific Plan and Intent) on the "Suicidal Ideation" portion or the C-SSRS
- A "yes" answer to any of the suicide-related behaviors (actual attempt, interrupted attempt, aborted attempt, preparatory act, or behavior) on the "Suicidal Behavior" portion of the C-SSRS

Appendix 19: Abbreviations

Abbreviation or Special Term	Explanation
β-hCG	Human chorionic gonadotropin
ADL	Activities of Daily Living
ADME	Absorption, distribution, metabolism, and excretion
AE	Adverse event
AKI	Acute kidney injury
ALP	Alkaline phosphatase
ALT	Alanine transaminase
APAP	Acetaminophen
ApoB	Apolipoprotein B
aPTT	Activated partial thromboplastin time
AST	Aspartate transaminase
AUC	Area under the concentration-time curve
BCRP	Breast Cancer Resistance Protein
BMI	Body mass index
BP	Blood pressure
BPM	Beats per minute
BUN	Biliary urea nitrogen
CFR	Code of Federal Regulations
CIOMS	Council for International Organizations of Medical Sciences
CK	Creatine kinase
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CL/F	Apparent clearance
CL_{SS}/F	Apparent clearance at steady state
CNS	Central nervous system
C_{max}	Maximum plasma concentration
COVID-19	Coronavirus disease 2019
CPK	Creatine phosphokinase
CRA	Clinical research associate
CRF	Case report form
CRU	Clinical research unit
CSR	Clinical study report
C-SSRS	Columbia Suicide Severity Rating Scale
C_{tau}	Steady-state plasma dosing concentration at the end of the dosing interval
CT	Computerized tomography
CTCAE	Common Terminology Criteria for Adverse Events
CV	Coefficient of variation

Abbreviation or Special Term	Explanation
CYP	Cytochrome P450
DBL	Database lock
DDI	Drug-drug interaction
DIO	Diet-induced obesity
DLT	Dose limiting toxicity
eGFR	Estimated glomerular filtration rate
eCRF	Electronic case report form
EC50	Half-maximal effective concentration
ECG	Electrocardiogram
EEoT	Early End of Treatment
EUS	Endoscopic ultrasound
FDA	Food and Drug Administration
FFA	Free fatty acid
FIH	First-in-human
FPG	Fasting Plasma Glucose
FSH	Follicle-stimulating hormone
F/U	Follow-up
GCG	Glucagon
GCGR	Glucagon receptor
GCP	Good clinical practice
GFR	Glomerular filtration rate
GGT	Gamma-glutamyl transpeptidase
GI	Gastrointestinal
GIP	Gastric inhibitory polypeptide
GIPR	Gastric inhibitory polypeptide receptor
GLP	Good laboratory practice
GLP-1	Glucagon-like peptide-1
GLP-1R	Glucagon-like peptide-1 receptor
GLP-2	Glucagon-like peptide-2
GPCR	G protein-coupled receptor
GTT	Glucose tolerance test
HAV IgM	Hepatitis A virus-specific Immunoglobulin M
HbA1c	Hemoglobin A1c
HBsAg	Hepatitis B virus surface antigen
HBV	Hepatitis B virus
HCG	β-human chorionic gonadotropin
HCV	Hepatitis C virus
HDL	High-density lipoprotein

Abbreviation or Special Term	Explanation
HDPE	High density polyethylene
HED	Human equivalent dose
Hep B/C	Hepatitis B/C viruses
HIV	Human immunodeficiency virus
HIPAA	Health Insurance Portability and Accountability Act
HR	Heart rate
hs-CRP	high-sensitivity C-reactive protein
IB	Investigator's brochure
ICF	Informed consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IMP	Investigational Medicinal Product
IND	Investigational new drug
INR	International normalized ratio
IP	Investigational product
IP	Intraperitoneal
IPGTT	Intraperitoneal glucose tolerance test
IRB	Institutional Review Board
IUD	Intrauterine device
IV	Intravenous
IVIVE	In vitro-in vivo extrapolation
IWQOL-Lite-CT	Impact of Weight on Quality of Life – Lite Clinical Trials Version
K_p	Tissue/plasma concentration ratio
LAM	Lactational amenorrhea method
LDL	Low-density lipoprotein
LFT	Liver function test
MAD	Multiple ascending dose
MAO	Monoamine oxidase
MCH	Mean corpuscular hemoglobin
MCV	Mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram
mL	Milliliter
mmHg	Millimeters of Mercury
MMTT	Mixed meal tolerance test
MRCP	Magnetic resonance cholangiopancreatography
MRI	Magnetic resonance imaging
MTC	Medullary thyroid carcinoma

Abbreviation or Special Term	Explanation
MTD	Maximum tolerated dose
NCI	National Cancer Institute
NIMP	Non-Investigational Medicinal Product
NOAEL	No observed adverse effect level
NT-proBNP	N-terminal pro-B-type natriuretic peptide
OATP	Organic anion transporting polypeptide
PD	Pharmacodynamic(s)
PE	Physical examination
P-gp	P-glycoprotein
PHQ-9	Patient Health Questionnaire 9
PI	Principal Investigator
PK	Pharmacokinetic(s)
PO	*Per os* (oral); by mouth
PPG	Postprandial glucose
PPI	Proton pump inhibitor
PR	Pulse rate
PT	Prothrombin time
QD	Once daily
QH	Hepatic blood flow
QOL	Quality of life
QT	QT interval
QTc	QT-interval corrected for heart rate using Fridericia's method
RBC	Red blood cell
RNA	Ribonucleic acid
SAD	Single ascending dose
SAE	Serious adverse event
SAP	Statistical analysis plan
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2
SCr	Standardized serum creatinine
SD	Standard deviation
SDRM	Safety data review meeting
SMBG	Self-monitoring blood glucose
SMC	Safety monitoring committee
SNRI	Serotonin and norepinephrine reuptake inhibitor
SoA	Schedule of Activites
SSRI	Selective serotonin reuptake inhibitor
ST	Slow titration
SUSAR	Suspected unexpected serious adverse reactions

Abbreviation or Special Term	Explanation
$T_{1/2}$	Apparent terminal half-life
T2	Type 2 diabetes mellitus
T3	Triiodothyronine
T4	Thyroxine
TBW	Total body water
TC	Total cholesterol
TEAE	Treatment emergent adverse event
TERN-601	An investigational GLP-1R agonist
TG	Triglycerides
THC	Tetrahydrocannabinol
T_{max}	Time to maximum plasma concentration
TSH	Thyroid stimulating hormone
UGT	UDP-glucuronosyltransferase
ULN	Upper limit of normal
US	United States
VAS	Visual analogue scale
VLDL	Very low-density lipoprotein
WBC	White blood cell
WHO	World Health Organization
WOCBP	Women of childbearing potential

Appendix 20: Investigator Signature Page

Protocol Title: A Phase 2 Study to Evaluate the Efficacy, Safety, and Tolerability of TERN-601 in Adults with Obesity

Protocol Number: TERN601-2003

Protocol Version/Date: Amendment 2/04 June 2025

I confirm that I have read the above-mentioned protocol and its attachments. I agree to conduct the described trial in compliance with all stipulations of the protocol, regulations and ICH E6 Guideline for Good Clinical Practice (GCP). I will provide all study personnel under my supervision copies of the protocol and access to all information provided by Terns, Inc. I will discuss this material with them to ensure that they are fully informed about the study drug and the study.

_____ _____

Principal Investigator Name (Printed) Signature

_____

Date

Appendix 21: Protocol Amendment History

The Summary of Changes for each amendment listed below will be provided separately.

Appendix Table 10 Protocol Amendment Summary of Changes Table

DOCUMENT HISTORY		
Document	**Date**	**Key Rationale for Amendment**
Protocol Amendment 2	04-JUN-2025	Extend the visit window for the Follow-up Visit to allow more flexibility for participants' convenience, to clarify the process for dose-re-escalation after a dose modification, and to clarify that surgically sterile women do not require FSH testing. In addition, updates were incorporated per approved and implemented Protocol Clarification Letters #2-4, dated 24 March 2025, 28 April 2025, and 07 May 2025. Refer to Summary of Changes for specific details.
Protocol Amendment 1	28-JAN-2025	Remove the MyPhenome Questionnaire and add exclusion for any participant that plans to undergo an elective surgery or require general anesthesia or deep sedation.
Original Protocol	22-NOV-2024	N/A

Appendix 22: References

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