CLINICAL STUDY PROTOCOL

Protocol Number/ID:	MET097-24-201
Protocol Title:	**A PHASE 2B, MULTI-CENTER, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY OF 28 WEEKS TO INVESTIGATE THE SAFETY AND EFFICACY OF ONCE-WEEKLY MET097 IN ADULTS WITH OBESITY OR OVERWEIGHT FOLLOWED BY A 32-WEEK EXTENSION (VESPER-1)**
Investigational Product:	MET097
U.S. IND No.:	168897
EU-CTR No.:	N/A
Development Phase:	2b
Study Sponsor	Metsera, Inc. 1200 Morris Turnpike, Suite 3005 Short Hills, NJ 07078 USA
Medical Director	PPD , M.D, FACP PPD
Protocol Version	Version 6.0 – Amendment 5 (29 August 2025)

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By signing below, the Sponsor declares that this study will be conducted in accordance with the current United States Food and Drug Administration Code of Federal Regulations, International Council for Harmonization of Technical Requirements for Registration of Pharmaceuticals and Good Clinical Practice (ICH-GCP) standards, the Declaration of Helsinki (Brazil 2019), and local and legal requirements.

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INVESTIGATOR SIGNATURE PAGE

By signing below, the investigator agrees to adhere to the clinical study protocol as written and agrees that any changes to the protocol must be approved by Sponsor before seeking approval from the Institutional Review Board (IRB) / Ethics Committee (EC).

The study will be conducted in accordance with the current International Council for Harmonization of Technical Requirements for Registration of Pharmaceuticals (ICH) and Good Clinical Practice (ICH-GCP) standards, the Declaration of Helsinki (Brazil 2019), and local, ethical, and regulatory requirements.

The information contained in this clinical study protocol is proprietary and provided to me in confidence and may not be disclosed to any other party, in any form, without prior authorization from the Sponsor, except to the extent necessary for the conduct of the study at this study site.

Principal Investigator

Signature	Date

Print Name

Institution Name

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LIST OF ABBREVIATIONS

βArr2	beta-arrestin-2
ΔWT	change from baseline body weight data
Ab	antibody
ADA	anti-drug antibodies
AE	adverse event
AECI	adverse event of clinical interest
Ag	antigen
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the curve
BMI	body mass index
BP	blood pressure
BUN	blood urea nitrogen
cAMP	cyclic adenosine monophosphate
CDC	Centers for Disease Control
CFR	Code of Federal Regulations
CI	confidence interval
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
C_{max}	maximum observed concentration
C_{min}	minimum observed concentration
CRF	case report form
C-SSRS	Columbia-Suicide Severity Rating Scale
CT	computed tomography
DIO	diet-induced obese
ECG	electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
eGFR	estimated glomerular filtration rate
EOS	end of study
EOT	end of treatment
ER	exposure-response
ES	exposure-safety
ET	early termination
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GI	gastrointestinal
GLP	Good Laboratory Practice
GLP-1	Glucagon-like peptide-1
GLP-1RA	Glucagon-like peptide-1 receptor agonist

HbA1c	glycated hemoglobin A1c
HCG	human chorionic gonadotropin
hGLP-1	human glucagon-like peptide-1
HDL-C	high-density lipoprotein-cholesterol
HED	human equivalent dose
HIV	human immunodeficiency virus
IB	investigator's brochure
ICE	intercurrent event
ICF	informed consent form
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals
IEC	Independent Ethics Committee
INR	international normalized ratio
IRB	Institutional Review Board
IUD	intrauterine device
LDL-C	low-density lipoprotein-cholesterol
MACE	major adverse cardiovascular events
MAD	multiple ascending dose
MAR	missing at random
MCH	mean corpuscular hemoglobin
MCV	mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
mFAS	modified full analysis set
MMRM	Mixed-effects Model for Repeated Measures
MRI	magnetic resonance imaging
NOAEL	no-observed-adverse effect level
NuSH	nutrient-stimulated hormone
PD	pharmacodynamic
PHQ-9	Patient Health Questionnaire 9
PK	pharmacokinetic
PT	prothrombin time
PTT	partial thromboplastin time
QTc	QT interval corrected
QW	once weekly
RBC	red blood cell
SAD	single ascending dose
SAE	serious adverse event
SAP	Statistical Analysis Plan
SC	subcutaneous
SoA	Schedule of Activities
SOP	standard operating procedure

SUSAR	suspected unexpected serious adverse reaction
$t_{1/2}$	elimination half-life
T2DM	Type 2 diabetes mellitus
T3	triiodothyronine
T4	thyroxine
TEAE	treatment emergent adverse event
T_{max}	time to maximum concentration
TSH	Thyroid-stimulating hormone
ULN	upper limit of normal
US	United States
WBC	white blood cell
WHO	World Health Organization

PROTOCOL SYNOPSIS

Short Title: A Phase 2b, 28-Week, Randomized, Double-blind, Study of Once-Weekly MET097 Compared with Placebo in Participants with Obesity or Overweight Followed by a 32-Week Extension

Rationale

Obesity is a serious and complex chronic medical condition and is recognized as a multifactorial disease that presents a risk to human health [Bray et al, 2017]. Excess body weight is a growing global health problem; worldwide obesity rates have almost tripled in recent decades [World Health Organization (WHO), 2021]. Excess body weight and obesity are important health concerns as they are linked to many chronic diseases that impact health and well-being [Del Prato et al, 2022] such as cardiovascular disease, Type 2 diabetes mellitus (T2DM), respiratory disorders (eg, sleep apnea, and asthma), musculoskeletal disorders including increased risk for osteoarthritis and other joint issues, selected cancers [WHO, 2021; Centers for Disease Control (CDC) 2022], non-alcoholic fatty liver disease [Li et al, 2016], and psychiatric disorders (eg, depression and anxiety) [Luppino et al, 2010].

Several Food and Drug Administration (FDA)-approved non-incretin pharmacological options are available for weight management for overweight and obese patients. However, their clinical use is limited due to modest weight loss outcomes (approximately 5%), the likelihood of weight regain after discontinuation, and notable side effects [Khera et al, 2016]. In contrast, glucagon-like peptide-1 receptor agonists (GLP-1RAs) have been approved for chronic weight management when combined with diet and exercise. These agents not only facilitate weight loss but also significantly reduce the risks associated with weight-related comorbidities, such as T2DM and cardiovascular complications.

MET097 is an analog of human GLP-1 being evaluated as an adjunct treatment for body weight loss in addition to a reduced calorie diet and increased physical activity for chronic weight management in adults. MET097 may offer enhanced efficacy and tolerability aiming to provide better value and health outcomes with less burden for people with obesity. GLP-1RAs typically have a short half-life and have to be dose escalated to increase tolerability. The longer half-life of MET097 relative to other GLP-1RAs may also allow for a gradual increase in plasma exposure over a time period of CCI weeks while remaining on the same dose, thus mimicking the effect of dose escalation protocols used for other GLP-1RAs.

Part A

Part A is double-blinded (sponsor-, investigator- and participant-blinded) from randomization until the primary reporting milestone at Week 28 (Day 197). Investigators, participants, and Sponsor personnel directly involved in the conduct of the study will remain blinded to participant-level treatment allocation for the entire duration of the Part A of the study. Participants that elect not to continue in the study extension (Part B) will complete the Part A Post-Treatment Follow-up Period as specified in Table 2.

Part B

Part B is double-blinded (sponsor-, investigator- and participant-blinded) from the dosing at Week 28 (Day 197) until the first participant reaches Week 40 (Day 281). Investigators, participants, and Sponsor personnel directly involved in the conduct of the study will remain

blinded to participant-level treatment allocation in Part B from the dosing at Week 28 (Day 197) until the first participant reaches Week 40 (Day 281).

The Study will also include an optional study extension consisting of a total of 12 weeks of double-blind treatment, which includes a switch from MET097 once-weekly (QW) to either biweekly (Q2W) or once-monthly (QM) MET097 dosing regimens and switching of QW placebo arm into MET097 QW. The study extension will only be available to participants who complete the primary endpoint at Week 28, do not meet any protocol-specified discontinuation criteria, and sign informed consent for continued treatment.

Objectives and Endpoints

The table below provides the objectives and endpoints for Part A (from Study Week 0 [Day 1] through pre-dose Study Week 28 [Day 197]).

Part A	
Objectives	**Endpoints**
Primary	
1) To evaluate the efficacy of once-weekly MET097 on body weight in participants with obesity or overweight, after 28 once-weekly doses of 0.4 mg, 0.6 mg, 0.9 mg or 1.2 mg, compared to placebo	• Percent change from baseline in body weight at Week 28 (Day 197)
Secondary	
1) To evaluate the efficacy of MET097 on body weight and additional weight-related parameters at all weekly timepoints in participants with obesity or overweight, with 28 once-weekly doses (0.4 mg, 0.6 mg, 0.9 mg and 1.2 mg) compared to placebo	• Percent change from baseline in body weight at all weekly post-baseline weight measurements prior to Week 28 (Day 197). • Occurrence of body weight reduction (weight loss) from baseline at Week 28 (Day 197) that is: ≥ 5%, ≥ 10%, ≥ 15% • Change from baseline (at all protocol-specified weekly post-baseline measurements in Part A) in: o Body weight (kg) o Body Mass Index (BMI) (kg/m²) o Waist circumference (cm)
2) To assess the safety and tolerability of MET097 compared to placebo in Part A	The following safety and tolerability endpoints will be measured in Part A: • Occurrence, severity and relatedness of treatment emergent adverse events (TEAEs) AEs of clinical interest: gastrointestinal adverse events (AEs) of Nausea, Vomiting and Diarrhea. • Occurrence, severity, and relatedness of other TEAEs • Occurrence of abnormal clinically significant physical examination • 12-lead electrocardiogram (ECG) measurements • Laboratory measurements • Columbia-Suicide Severity Rating Scale (C-SSRS) • Patient Health Questionnaire (PHQ-9) • Occurrence of anti-drug antibodies (ADAs)
3) To characterize the pharmacokinetic (PK) profile of MET097 in participants with obesity or overweight, with 28 once-weekly doses.	The following endpoints measured for the duration of the weekly dosing in Part A for all participants: • Minimum observed concentration (C_{min}) The following endpoints measured for the duration of the weekly dosing in Part A for subset of [redacted] participants of each arm: • Area under the concentration versus time curve during the dosing interval ($AUC_{(0-t)}$) • Maximum observed concentration (C_{max}) • Time to maximum concentration (T_{max}) • Other PK parameters may be evaluated

Part A	
Objectives	**Endpoints**
	• MET097 concentrations will be summarized
Exploratory	
1) To evaluate glucose metabolism parameters and lipid levels of MET097 in participants with obesity or overweight, with 28 once-weekly doses compared to placebo	• Change from baseline (at all protocol-specified post-baseline measurements in Part A) in the following glucose metabolism parameters: fasting insulin, glycated hemoglobin A1c [HbA1c], fasting glucose and fasting glucagon • Change from baseline (at all protocol-specified post-baseline measurements in Part A) in lipid levels (triglycerides, high-density lipoprotein-cholesterol [HDL-C] and low-density lipoprotein-cholesterol [LDL-C])

The last available measurement prior to first dose received in Part A will be used as baseline for both Part A and Part B.

The table below provides the objectives and endpoints for Part B (from dosing at Study Week 28 [Day 197] through the End of Study). All objectives and endpoints for Part B are exploratory.

Part B	
Objectives	**Endpoints**
Exploratory	

1) To evaluate the effects of all dose-regimens of MET097 in body weight reduction and other weight-related parameters in Part B	• Percent change from baseline in body weight at all Part B protocol-specified post-baseline measurements.
	• Occurrence of body weight reduction (weight loss) at all Part B protocol-specified measurements that is: ≥5%, ≥10%, ≥15%, ≥20%
	• Change from baseline (at all Part B protocol-specified measurements) in:
	  ○ Body weight (kg)
	  ○ Body Mass Index (kg/m^2)
	  ○ Waist circumference (cm)

2) To evaluate the safety and tolerability of all dose-regimens of MET097 in Part B	The following safety and tolerability endpoints will be measured in Part B: • Occurrence and severity of treatment-emergent adverse events (TEAEs) • Occurrence of abnormal clinically significant physical examination • Occurrence of abnormal clinically significant 12-lead electrocardiogram (ECG) measurements • Occurrence of abnormal clinically significant clinical laboratory measurements • Columbia-Suicide Severity Rating Scale (C-SSRS) • Patient Health Questionnaire (PHQ-9) • Occurrence of anti-drug antibodies (ADAs)
3) To evaluate the pharmacokinetics of all dose-regimens of MET097 in Part B	The following endpoints will be measured in Part B for all participants: • Minimum observed concentration (C_{min}) • Other PK parameters may be evaluated • MET097 concentrations will be summarized

The last available measurement prior to first dose received in Part A will be used as baseline for both Part A and Part B.

Overall Study Design

Part A

This is a Phase 2b, multi-center, randomized, double-blind, placebo-controlled study to investigate the efficacy and safety of four different dose levels of MET097 vs. placebo for body weight loss in adult participants (aged 18 to 70) with obesity or overweight (body mass index [BMI] 27 to 50 kg/m^2,) after 28 weeks of once weekly dosing.

Approximately 225 participants will be randomized in a 1:1:1:1:1 ratio to one of 5 treatment arms (n=45 per treatment arm) as shown in the study schematic (Figure 2). Randomization will be stratified by CCI and the accrual of CCI will be capped at CCI to ensure at least CCI. Each treatment arm will be comprised of a subset of CCI participants that will undergo intensive pharmacokinetic (PK) draws during inpatient visits at the first, Week 16 (post steady-state), and last doses in addition to limited trough samplings. The remaining CCI participants per treatment arm will be outpatient visits and undergo limited PK sampling only. The intensive PK sampling subset (ie, CCI participants per treatment regimen) will not be stratified by CCI.

No interim analyses (for potential modification of the ongoing trial) are planned. The primary reporting milestone (ie, the first unblinded analysis) for the primary analysis (Part A, Day 197) will occur when all (ie, N=~225) participants have completed their Day 197 visit (or permanently discontinued from the study prior to Day 197). Specifically, this reporting milestone will occur when all participants have completed their dosing period but before all participants have completed their safety follow-up period. Complete details will be documented in the study statistical analysis plan (SAP) which will be finalized prior to unblinding for this planned reporting milestone.

Part B

Enrollment in Part B is optional and available only to participants who have completed Week 28 assessments and procedures for the primary reporting milestone, shown good compliance throughout Part A (as determined by PI), do not meet any study discontinuation criteria and sign an informed consent. Investigators, participants, and Sponsor personnel directly involved in the conduct of the study will remain blinded to participant-level treatment allocation in Part B from the dosing at Week 28 (Day 197) until the first participant reaches Week 40 (Day 281).

Part B participants will receive an additional 8 weeks of QW MET097 treatment followed by the switch to a QW, Q2W, or QM dose for an additional 24 weeks as described in the table below. Additional visits will occur to maintain the double-blind of Part A and the double-blind phase of Part B. All participants will be followed for an additional 12 weeks (covering >5 half-lives of MET097) after administration of the last dose of study medication for safety and efficacy assessments.

Summary of Dosing and Blinding Status for Part A and Part B

Treatment Arm	Part A Double-Blind Phase	Part B		
		Double-Blind Phase		Open-Label Phase
	*From Study Week 0 through pre-dose Study Week 28**	*From the dosing of Study Week 28 through pre-dose Study Week 36*	*From the dosing Study Week 36 through pre-dose Study Week 40*	*From the dosing Study Weeks 40 through End of Study*
Treatment Arm 1	0.4 mg	0.8 mg QW	1.6 mg Q2W	1.6 mg Q2W
Treatment Arm 2	0.6 mg	0.6 mg QW	2.4 mg QM	2.4 mg QM
Treatment Arm 3	0.9 mg	0.9 mg QW	3.2 mg QM	3.2 mg QM
Treatment Arm 4	1.2 mg	1.2 mg QW	4.8 mg QM	4.8 mg QM
Treatment Arm 5	Placebo	0.4mg/0.8 mg QW	1.6 mg QW	1.6 mg QW (Arm 5A) 2.4 mg QW (Arm 5B)**

*For participants who opt out of Part B, the double-blind phase continues through the safety follow-up until End-of-Study
** The first participants in Treatment Arm 5 (n=~24) will continue on the 1.6 mg QW regimen for the remainder of the study (Arm 5A) while the second half of participants in this treatment arm will be given 2.4 mg QW (n=up to 24; Arm 5B) starting at Week 40 for the remainer of the study. Participants in Arm 5B have may have an additional 4-week window during which they may start the 2.4 mg QW regimen (eg, may start 2.4 mg up to Week 44), due to operational considerations.

The final study database lock and final study analysis (for inclusion in the clinical study report), will occur after all participants have completed both Part A and Part B dosing periods as well as the subsequent safety follow-up period.

Key Inclusion Criteria

1. Provision of signed and dated informed consent form (ICF).
2. Adult (≥18 to ≤70 years) male and female participants
3. Have a BMI at Screening of
    - BMI ≥30 kg/m^2 and ≤50.0 kg/m^2 (may have the weight-related co-morbidities listed below)
    - BMI ≥27.0 kg/m^2 to <30.0 kg/m^2 must have at least one of the following weight-related co-morbidities:
        1. Hypertension: on blood pressure (BP)-lowering medication or having systolic BP ≥130 mmHg or diastolic BP ≥80 mmHg at Screening
        2. Dyslipidemia: on lipid-lowering medication or having low-density lipoprotein-cholesterol (LDL-C) ≥160 mg/dL (4.1 mmol/L) or triglycerides ≥150 mg/dL (1.7 mmol/L), or high-density lipoprotein-cholesterol (HDL-C) <40 mg/dL (1.0 mmol/L) for men or HDL-C <50 mg/dL (1.3 mmol/L) for women at Screening
4. Participant has stable body weight (defined as a self-reported change [increase or decrease] in body weight ≤5 kg) within 3 months prior to Screening.

Key Inclusion Criteria – Part B Study Extension

1. Completion of the Week 28 (Day 197) assessments and procedures for evaluation of the primary reporting milestone in Part A and demonstrated compliance with all protocol requirements throughout the duration of the primary study as designated by PI.
2. Provision of signed and dated ICF for Part B (Study Extension).
3. Willingness and ability to comply with scheduled visits, treatment plan, laboratory tests, and other protocol-specified assessments and procedures for Part B.

Key Exclusion Criteria

1. Female who is lactating or who is pregnant according to the pregnancy test at Screening or on Day 1 or Day -1 for subset of intensive PK participants
2. Unwilling or unable to follow contraceptive requirements detailed in Appendix 1.
3. Diagnosis of diabetes (Type 1 or T2DM) or glycated hemoglobin A1c (HbA1c) ≥ 6.5% or fasting plasma glucose >125 mg/dL at the Screening visit or history of taking any medications to lower glucose.
4. Uncontrolled hyperlipidemia: LDL-C ≥ 5.2 mmol/L (≥200 mg/dL), or fasting triglycerides ≥ 5.6 mmol/L (≥500 mg/dL) at the Screening visit, whether on lipid lowering therapies or not.
5. Poorly controlled hypertension at, defined as any of the following:
   - Mean seated systolic BP ≥160 mm Hg or mean seated diastolic BP ≥95 mm Hg at Screening visit
   - A change in antihypertensive medications within 30 days of Screening visit
   - Renal artery stenosis, or evidence of labile blood pressure including symptomatic postural hypotension at Screening
6. Thyroid-stimulating hormone (TSH) level lower than 0.4 mIU/L or higher than 6.0 mIU/L at the Screening visit. Note: participants receiving treatment for hypothyroidism may be included, provided their thyroid hormone replacement dose has been stable for at least 6 months.
7. An estimated glomerular filtration rate (eGFR) of <75 mL/min/1.73 m^2, as determined by the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) at the Screening visit.

Participant Eligibility

For Part A, participant eligibility for participation in the treatment phase of the study will be determined following the assessments at the Screening and Baseline visits. Participants that meet the inclusion criteria and do not meet the exclusion criteria will be randomized.
After completion of Part A, with participants meeting all Part B study eligibility criteria, and having signed a Part B ICF will receive treatments in the study extension.

Number of Participants

Approximately 225 participants will be randomized in a 1:1:1:1:1 ratio into one of 5 treatment regimens (n=45/arm).

Treatments and Duration

For Part A, the total study duration for an individual participant will be approximately 42 weeks, including the screening period (up to 4 weeks), the 28-week treatment period, and an approximately 11-week (~5 half-lives) post-treatment follow-up period.

For participants that roll over into Part B, the total study duration (Part A and Part B) for an individual participant will be approximately 75 weeks (including up to a 4-week Screening Period).

Sample Size Determination & Statistical Analysis Methods

Sample-size:

For the Part A primary efficacy analysis comparing each of the MET097 doses to placebo with respect to the primary efficacy endpoint at Week 28, the following assumptions were made in the power calculation: total study sample size is approximately 225 participants with ~45 participants per arm, true common standard deviation is CCI the overall study dropout rate is CCI%, the overall Type 1 error rate for the primary efficacy analysis will be controlled at 5% using the Hochberg procedure to adjust for multiplicity for the four pairwise statistical comparisons of MET097 dose arms to placebo. With these assumptions, the power is CCI% for each MET097 dose-comparison to placebo, if the assumed true placebo-corrected mean percent change from baseline at Week 28 for 0.4 mg, 0.6 mg, 0.9 mg and 1.2 mg is CCI [redacted]% respectively.

With a more conservative dropout rate of CCI%, if the assumed true placebo-corrected mean percent change from baseline at Week 28 for 0.4 mg, 0.6 mg, 0.9 mg and 1.2 mg is CCI [redacted]% respectively, the power will be CCI [redacted]% respectively, for the 0.4 mg, 0.6 mg, 0.9 mg and 1.2 mg statistical comparisons to placebo.

These power calculations are based on simulating 5000 studies for each treatment difference scenario and dropout rate and analyzing percent change from baseline at Day 197 using the ANOVA model along with Hochberg's adjustment for multiple comparisons to placebo.

Part A Statistical Analysis Methods:
Primary Efficacy Analysis: A mixed effects repeated measures model (MMRM) will be used to analyze the primary efficacy endpoint of percent change from baseline at Week 28 (Day 197). The appropriate contrasts will be constructed for comparing each of the four MET097 dose arms to placebo at Week 28 (Day 197). Least square means for the treatment differences from placebo will be reported along with p-values and two-sided 95% confidence intervals (CIs). P-values associated with 2-sided tests (for each statistical comparison of a MET097 dose-arm to placebo) will be used for assessing statistical significance, using the Hochberg procedure for multiplicity adjustment. The primary efficacy estimand is the mean treatment difference in percent change from baseline body weight following 28 weeks of MET097 doses relative to placebo, among adults aged 18 to 70 years with obesity or overweight (BMI of 27 to 50 kg/m^2) under the hypothetical scenario that they remained on treatment for the entire duration of the treatment period, without changes to lifestyle that could impact weight loss (ie, use of other weight loss interventions such as weight-loss medication or bariatric surgery or commercial weight-loss programs) [Wharton et al, 2021; Jastreboff et al, 2022]. Missing data will be assumed to be missing at random (MAR). A supplementary efficacy estimand will include participant outcomes without regard to treatment adherence or lifestyle changes.

Summary statistics will be reported for each visit and treatment arm, including the sample size, arithmetic mean, standard deviation, median, interquartile range and range.

Secondary Efficacy and Exploratory Analysis: The secondary and exploratory endpoints that are continuous and longitudinal will be analyzed using the same MMRM methodology and same adherence to study dataset for treatment comparisons as used for the primary efficacy analysis, with the same descriptive statistics used for summarization. A logistic regression model will be used for making treatment comparisons in binary endpoints, with p-values, and 2-sided 95% CIs. Binary and other categorical endpoints will be summarized using sample size, frequencies and percentages. There will be no multiplicity adjustment for any of the secondary or exploratory analyses.

Safety and tolerability endpoints will be summarized using descriptive statistics (number of participants, frequencies, and percentages for categorical endpoints) and will be based on the Safety Analysis Set.

Complete details on the statistical analyses will be described in the study SAP (including any additional sensitivity, supplementary or exploratory analyses), which will be finalized prior to the unblinding for the first planned study reporting milestone at Week 28 (Day 197).

Safety Monitoring

There will be ongoing review of AEs, clinical laboratory measures, vital sign parameters, electrocardiograms (ECGs), physical examinations, and questionnaires. There will not be any independent data monitoring committee for this study.

SCHEDULE OF ACTIVITIES (SoA)

Table 1: MET097-24-201 Once-Weekly Dosing SoA – Part A Outpatient Visits (Screening through Week 16)

Study Period	Screening Period	Part A Treatment Period																
Study Visit	**Screening [a]**	V1 [a]	V2 [a]	V3 [a]	V4 [a]	V5 [a]	V6 [a]	V7 [a]	V8 [a]	V9 [a]	V10 [a]	V11 [a]	V12 [a]	V13 [a]	V14 [a]	V15 [a]	V16 [a]	V17 [a]
Study Day	-28 to -1	1	8	15	22	29	36	43	50	57	64	71	78	85	92	99	106	113
Study Week		0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
Visit Window (Days)	0	±1	±1	±1	±1	±1	±1	±1	±1	±1	±1	±1	±1	±1	±1	±1	±1	±1
Dosing Days – SC Administration		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Informed Consent [b]	X																	
Eligibility Criteria Review	X	X [c]																
Medical History	X	X [d]																
Demographics/ Height	X																	
C-SSRS [e]	X				X				X				X				X	
PHQ-9 [f]	X				X				X				X				X	
Pregnancy Test (serum beta-HCG) [g o]	X																	
Pregnancy Test (urine beta-HCG) [h o]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Serology [i o]	X																	
Lipids [j o]	X				X				X				X				X	X
Drugs of Abuse Screening (urine) [k o]	X																	
Alcohol Abuse Screening (urine) [l o]	X																	
Biochemistry, Hematology [m o]	X	X	X		X				X				X				X	
Coagulation [n o]	X	X	X		X				X				X				X	
Urinalysis [p o]	X	X	X		X				X				X				X	
Endocrinology (TSH, T3, free T4) [o]	X																	
Amylase, Lipase [o]	X	X			X				X				X				X	
Insulin and Glucagon [o]		X																X
HbA1c [o]	X																	X
Calcitonin [o]	X																	
Full Physical Examination [q]	X	X																
Brief Physical Examination [r]			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Body Weight and Waist Circumference [s]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
12-lead ECG [t]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Blood Sampling for PK [t]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Vital signs [u]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Randomization		X																
Capillary Blood Glucose Testing [v]		X	X		X				X				X				X	X
Injection Site Inspection/Assessment [w]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Study Period	Screening Period	Part A Treatment Period																
Study Visit	**Screening [a]**	V1 [a]	V2 [a]	V3 [a]	V4 [a]	V5 [a]	V6 [a]	V7 [a]	V8 [a]	V9 [a]	V10 [a]	V11 [a]	V12 [a]	V13 [a]	V14 [a]	V15 [a]	V16 [a]	V17 [a]
Study Day	-28 to -1	1	8	15	22	29	36	43	50	57	64	71	78	85	92	99	106	113
Study Week		0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
Visit Window (Days)	0	±1	±1	±1	±1	±1	±1	±1	±1	±1	±1	±1	±1	±1	±1	±1	±1	±1
Dosing Days – SC Administration		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
ADA Blood collection [x]		X				X				X								X
Diet & Physical Activity Guidance [y]	X	X			X				X				X				X	
Concomitant Medication Monitoring	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
AE/SAE Monitoring and Review [z]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Ab=antibody; ADA=anti-drug antibody; AE=adverse event; Ag=antigen; ALT=alanine aminotransferase; AST=aspartate aminotransferase; BUN=blood urea nitrogen; CKD-EPI = Chronic Kidney Disease Epidemiology Collaboration; C-SSRS=Columbia Suicide Severity Rating Scale; ECG = electrocardiogram; eGFR=estimated glomerular filtration rate; HbA1c=glycated hemoglobin; HCG= human chorionic gonadotropin; HDL-C=high density lipoprotein-cholesterol; HIV=human immunodeficiency virus; INR=international normalized ratio; LDL-C=low density lipoprotein-cholesterol; MCH= mean corpuscular hemoglobin; MCV= mean corpuscular volume; PHQ-9=Patient Health Questionnaire-9; PK=Pharmacokinetic; PT = prothrombin time; PTT = partial thromboplastin time; RBC=red blood cell; SAE=serious adverse event; SC = subcutaneous; T3=triiodothyronine; T4=thyroxine; TSH = thyroid-stimulating hormone; WBC = white blood cell

Note: The intensive PK subsets will be inpatient visits at Visit 1, Visit 16, and Visit 28 (see Table 3).

a. Participants will have to fast for at least 8 hours prior to visit.
b. The current IRB approved version of the consent form must be signed prior to participant's inclusion (prior to any study activities).
c. Participant eligibility will be reconfirmed for study inclusion on Day 1, unless the inclusion/exclusion criteria state that assessment is only being reviewed for eligibility at Screening Visit.
d. On Day 1, participants will be questioned concerning changes to their health status, compliance with the protocol, and/or ICF requirements since the Screening Visit to confirm participant is still eligible for inclusion.
e. Questionnaires must be administered by investigator or other individual that is suitably qualified by education or training.
Screening - If a participant answers "yes" to Question 4 or 5 in "Suicidal Ideation" section and/or "yes" to any of the suicide-related behaviors in the "Suicidal Behavior" section of the C-SSRS the participant should be excluded from study. Also, if the participant scores ≥ 10 on the patient health questionnaire (PHQ-9), the participant should be excluded from the study.
f. **Any other visit**- If a participant answers "yes" to Question 4 or 5 in "Suicidal Ideation" section and/or if a participant answers "yes" to any of the suicide-related behaviors in the "Suicidal Behavior" section of the C-SSRS on the "Since Last Visit Version", the study drug will be discontinued. If a participant scores ≥ 10 on the patient health questionnaire (PHQ-9), the participant should be evaluated by investigator or medically qualified sub-investigator for continuation of study drug.
g. Serum pregnancy is to be performed for women of childbearing potential (WOCBP). If positive, the participant will be excluded from the study
h. Urine pregnancy only WOCBP. If positive, confirm with a serum pregnancy test. If positive result occurs on Day 1 prior to dose, the participant will be excluded from the study.
i. Serology tests are HIV Ag/Ab, Hepatitis B surface antigen, and Hepatitis C virus. If the participant tests results are positive, they will be excluded from the study.
j. Lipids tests are total cholesterol, LDL-C, HDL-C, triglycerides.
k. Drugs of abuse screening will test for amphetamines, barbiturates, benzodiazepines, cocaine, MDMA, methadone, methamphetamines, opiates (including fentanyl and oxycodone), opioids, phencyclidine, propoxyphene. If the participant's drug screen is positive, the participant will be excluded from the study.
l. If the participant' alcohol screening is positive, the participant will be excluded from the study.
m. Biochemistry testing will measure ALT, albumin, alkaline phosphate, AST, bicarbonate, bilirubin (total/direct/indirect), BUN, calcium total, chloride, creatinine, glucose, magnesium, potassium, and sodium. **The creatinine value will be used to calculate eGFR throughout the study using the CKD-EPI or similar equation. The eGFR result at the screening visit will be used for study eligibility.** Hematology testing will measure WBC w/differential, RBC, hemoglobin, hematocrit, MCH, MCV, platelets.
n. Coagulation testing will measure PT/INR and PTT.
o. All labs will be collected after an 8 hour fast and prior to dose administration on dosing days. ***Day 1 collection will be considered baseline.
p. Urinalysis testing will measure color, clarity, specific gravity, pH, leukocyte, protein, glucose, ketones, bilirubin, blood, nitrite, urobilinogen. Microscopic examination will only be performed if the dipstick test is outside of the reference range for leukocyte, blood, nitrite or protein.
q. The full physical examination will include examination of the following body systems (at minimum): head and neck (including complete thyroid exam), cardiovascular, respiratory, gastrointestinal, brief neurological, and general appearance.
r. Brief physical exam – will be limited systems review including cardiovascular, respiratory, gastrointestinal systems, as well as general appearance and/or other systems as needed.
s. Body weight and waist circumference will be collected under fasting condition. BMI will be calculated at each body weight measurement. See Appendix 2 and Section 6.4.1.

t. Predose ECGs assessments will be performed as per Section 6.3.6 after being in a supine position for at least 5 minutes. When ECG collection timepoints align with PK collection timepoints, PK collection is to be done within ≤ 1hr of ECG. All [redacted] intensive PK participants per cohort will have their ECGs done in triplicate at all timepoints. The participants not undergoing intensive PK will have a single ECG recorded at all applicable timepoints. All screening ECG assessments will be a single reading. PK sample collection will be performed per Section 6.5. When PK sample collection timepoints align with ECG collection timepoints, PK collection is to be done within ≤ 1hr of ECG.
u. Vital signs assessments will include heart rate, blood pressure, and body temperature. Vital signs will be performed per Section 6.3.5. Blood pressure & heart rate will be taken after being seated with feet on the floor for 5 minutes and collected in triplicate with a mean value calculated.
v. Capillary glucose samples are to be collected predose. Also, ad hoc samples can be collected if symptoms suggest the potential for hypoglycemia.
w. The injection site inspection should be performed weekly prior to drug administration. The inspection of abdomen should include determination of the acceptable quadrant to administer the current injection and also an inspection of the previous injection site. The previous injection site should be checked for a post dose inspection reaction which may include pain, tenderness, erythema, and/or swelling See Section 7.2.1 and Table 15.
x. ADA samples should be collected predose.
y. Monthly reminder for participants that their exercise and diet practices need to remain the same throughout the study.
z. AE/SAE collection begins with participant signature of IRB approved informed consent.

Study participants that elect to continue in Part B (Extension Study) will complete all Week 28 (Day 197) assessments and procedures as specified in Table 2 prior to receiving their first dose of study treatment which is covered in Table 4 (8-Week QW MET097 Extension Period SoA). Participants that elect not to participate in Part B will complete the Part A Post-Treatment Follow-Up visits as specified below.

Table 2: MET097-24-201 Once-Weekly Dosing SoA – Part A Outpatient Visits (Week 17 - Part A End of Study)

Study Period	Part A Treatment Period (continued)													Post-Treatment Follow-Up Period	
Study Visit	V18	V19	V20	V21 [a]	V22	V23	V24	V25 [a]	V26	V27	V28	V29 [a] / EOT	ET [b]	V30 [a]	V31/EOS
Study Day	120	127	134	141	148	155	162	169	176	183	190	197		220	274
Study Week	17	18	19	20	21	22	23	24	25	26	27	28		31	39
Visit Window (Days)	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2		±5	±5
Dosing Days – SC Administration	X	X	X	X	X	X	X	X	X	X	X				Phone call [u]
C-SSRS [c]				X				X				X	X	X	
PHQ-9 [c]				X				X				X	X	X	
Pregnancy Test (serum beta-HCG) [d]															X [u]
Pregnancy Test (urine beta-HCG) [d]				X				X				X	X	X	
Lipids [e, f]				X				X				X	X	X	
Biochemistry, Hematology [e, g]				X				X				X	X	X	
Coagulation [e, h]				X				X				X	X	X	
Urinalysis [e, i]				X				X				X	X	X	
Amylase, Lipase [e]				X				X				X	X	X	
Insulin and Glucagon [e]												X	X		
HbA1c [e]												X	X	X	
Calcitonin [e, j]												X	X	X	
Full Physical examination [k]												X	X	X	
Brief Physical Examination [l]				X				X							
Body Weight and Waist Circumference [m]				X				X				X	X	X	
12-lead ECG [n]				X				X				X	X	X	
Blood Sampling for PK [n]				X				X			X	X	X	X	
Vital signs [o]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Capillary Blood Glucose Testing [p]				X				X				X	X	X	
Injection Site Inspection/Assessment [q]				X				X				X	X	X	
ADA Blood collection [r]				X				X				X	X	X	
Diet & Physical Activity Guidance [s]				X				X			X				
Concomitant Medication Monitoring	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
AE/SAE Monitoring and Review [t]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Ab=antibody; ADA=anti-drug antibody; AE=adverse event; Ag=antigen; ALT=alanine aminotransferase; AST=aspartate aminotransferase; BUN=blood urea nitrogen; CKD-EPI = Chronic Kidney Disease Epidemiology Collaboration; C-SSRS=Columbia Suicide Severity Rating Scale; ECG = electrocardiogram; eGFR=estimated glomerular filtration rate; EOS = end of study; EOT = end of treatment; ET = early termination; HbA1c=glycated hemoglobin; HCG=

human chorionic gonadotropin; HDL-C=high density lipoprotein-cholesterol; HIV=human immunodeficiency virus; INR=international normalized ratio; LDL-C=low density lipoprotein-cholesterol; MCH= mean corpuscular hemoglobin; MCV = mean corpuscular volume; PHQ-9 = Patient Health Questionnaire-9; PK=Pharmacokinetic; PT = prothrombin time; PTT = partial thromboplastin time; RBC=red blood cell; SAE=serious adverse event; SC = subcutaneous; T3=triiodothyronine; T4=thyroxine; TSH = thyroid-stimulating hormone; WBC = white blood cell

Note: The intensive PK subsets will be inpatient visits at Visit 1, Visit 16, and Visit 28 (see Table 3).

a. Participants will have to fast for at least 8 hours prior to visit
b. Participants who choose to withdraw consent or withdraw from the study and are unable or unwilling to continue attending visits for data collection for any reason will have an ET visit performed. The ET visit may align with scheduled visit timing or may need to be performed during an unscheduled time point. See electronic case report form (eCRF) guidelines on how to document an ET visit.
c. If a participant answers "yes" to Question 4 or 5 in "Suicidal Ideation" section and/or if a participant answers "yes" to any of the suicide-related behaviors in the "Suicidal Behavior" section of the C-SSRS on the "Since Last Visit Version", the study drug will be discontinued. If a participant scores ≥ 10 on the patient health questionnaire (PHQ-9), the participant should be evaluated by investigator or medically qualified sub-investigator for continuation of study drug.
d. Serum pregnancy is to be performed for women of childbearing potential (WOCBP). If positive, the participant will be excluded from the study. Urine pregnancy is to be performed for women of childbearing potential (WOCBP). If positive, confirm with a serum pregnancy test. If confirmed positive, the participant will be excluded from the study
e. All labs will be collected after an 8 hour fast and prior to dose administration on dosing days.
f. Lipids tests are total cholesterol, LDL-C, HDL-C, triglycerides.
g. Biochemistry testing will measure ALT, albumin, alkaline phosphate, AST, bicarbonate, bilirubin (total/direct/indirect), BUN, calcium total, chloride, creatinine, glucose, magnesium, potassium, and sodium. The creatinine value will be used to calculate eGFR throughout the study using the CKD-EPI or similar equation. The eGFR result at the screening visit will be used for study eligibility. Hematology testing will measure WBC w/differential, RBC, hemoglobin, hematocrit, MCH, MCV, platelets.
h. Coagulation testing will measure PT/INR and PTT.
i. Urinalysis testing will measure color, clarity, specific gravity, pH, leukocyte, protein, glucose, ketones, bilirubin, blood, nitrite, urobilinogen. Microscopic examination will only be performed if the dipstick test is outside of the reference range for leukocyte, blood, nitrite or protein
j. Calcitonin testing at Week 31 will only occur if a participant has a serum calcitonin that increases 50% of the mean of the Screening visit values AND an absolute value ≥20 pg/mL and <35 pg/mL at Week 28 visit
k. The full physical examination will include examination of the following body systems (at minimum): head and neck (including complete thyroid exam), cardiovascular, respiratory, gastrointestinal, brief neurological, and general appearance.
l. Brief physical exam – will be limited systems review including cardiovascular, respiratory, gastrointestinal systems, as well as general appearance and/or other systems as needed.
m. Body weight and waist circumference will be collected under fasting condition. BMI will be calculated at each body weight measurement. See Appendix 2 and Section 6.4.1.
n. Predose ECGs assessments will be performed as per Section 6.3.6 after being in a supine position for at least 5 minutes. When ECG collection timepoints align with PK collection timepoints, PK collection is to be done within ≤ 1hr of ECG. All[redacted] intensive PK participants per cohort will have their ECGs done in triplicate at all timepoints. The participants not undergoing intensive PK will have a single ECG recorded at all applicable timepoints. All screening ECG assessments will be a single reading.PK sample collection will be performed per Section 6.5. When PK sample collection timepoints align with ECG collection timepoints, PK collection is to be done within ≤ 1hr of ECG.
o. Vital signs assessments will include heart rate, blood pressure, and body temperature. Vital signs will be performed per Section 6.3.5. Blood pressure & heart rate will be taken after being seated with feet on the floor for 5 minutes and collected in triplicate with a mean value calculated.
p. Capillary glucose samples are to be collected predose. Also, ad hoc samples can be collected if symptoms suggest the potential for hypoglycemia.
q. The injection site inspection should be performed weekly prior to drug administration. The inspection of abdomen should include determination of the acceptable quadrant to administer the current injection and also an inspection of the previous injection site. The previous injection site should be checked for a post dose inspection reaction which may include pain, tenderness, erythema, and/or swelling See Section 7.2.1 and Table 15.
r. ADA samples should be collected predose.
s. Monthly reminder for participants that their exercise and diet practices need to remain the same throughout the study.
t. AE/SAE collection begins with participant signature of IRB approved informed consent.
u. During the EOS phone call all participants that are WOCBP will be requested to come in for an unscheduled visit to have a serum pregnancy test performed.

Table 3: MET097-24-201 Once-Weekly Dosing SoA – Part A Inpatient Visits for Intensive PK Sampling Subset

Study Visit	Admission	V1				Admission	V16				Admission	V28			
Study Day	-1	1 [a]	2	3	4	105	106 [a]	107	108	109	189	190 [a]	191	192	193
Study Week		0					15					27			
Visit Window (Days)	±1	NA	NA	NA	NA	±1	NA	NA	NA	NA	±1	NA	NA	NA	NA
Dosing Days – SC Administration		X					X					X			
Pregnancy (urine beta-HCG)	X					X					X				
Medical History	X [b]														
Blood Sampling for PK		X [c]	X [d]	X [e]	X [f]		X [c]	X [d]	X [e]	X [f]		X [c]	X [d]	X [e]	X [f]
12-lead ECG (triplicate) [g]		X	X	X	X		X	X	X	X		X	X	X	X
Concomitant Medication Monitoring	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
AE/SAE Monitoring and Review [h]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

E=adverse event; ECG = electrocardiogram; HCG= human chorionic gonadotropin; PK=Pharmacokinetic; SAE=serious adverse event; SC = subcutaneous.
Note: complete PK collection is in Section 6.5.

a. All Day 1, Day 106, and Day 190 assessments from Table 1 and Table 2 (except for assessments that move to Day -1, Day 105, or Day 189 which may include pregnancy test, and medical history re-check) need to be done in addition to the assessments shown in Table 3.
b. On Day -1, participants will be questioned concerning changes to their health status, compliance with the protocol, and/or ICF requirements since the Screening Visit to confirm participant is still eligible for inclusion.
c. Draws at the following timepoints: predose, 2, 4, 8, and 16 hours post dose
d. Draws at the following timepoints: 24 and 36 hours post dose
e. Draw at the following timepoints: 48 hours post dose.
f. Draw at the following timepoints: 72 hours post dose
g. ECGs assessments will be performed as per Section 6.3.6 after being in a supine position for at least 5 minutes. All screening ECG assessments will be a single reading. There is no need to wait in between ECG assessments. ECGs for the PK sampling subset of participants will all be collected in triplicate including all ECGs listed in Table 1 and Table 2. When ECG collection timepoints align with PK collection timepoints, PK collection is to be done within ≤ 1hr of ECG.
h. AE/SAE collection begins with participant signature of IRB approved informed consent.

Table 4: MET097-24-201 Part B – 8-Week QW MET097 Extension Period (Week 28 dosing - Week 35)

Study Period	**Part B – Double Blind Treatment Extension**							
Study Visit	DBEV1	DBEV2	DBEV3	DBEV4	DBEV5	DBEV6	DBEV7	DBEV8
Study Day	197	204	211	218	225	232	239	246
Study Week	28	29	30	31	32	33	34	35
Visit Window (Days)	±2	±2	±2	±2	±2	±2	±2	±2
Fasted Visit	X				X			
Dosing Days – SC Administration	X*	X	X	X	X	X	X	X
Diet & Physical Activity Guidance [r]					X			
Clinical Assessments								
Vital signs [n]	*All assessments/ procedures for study Week 28 performed for Part A are as specified in SoA Table 2 Part B DBEV1 – dosing	X	X	X	X	X	X	X
Body Weight and Waist Circumference [l]					X			
Full Physical examination [j]								
Targeted Physical Examination [k]								
12-lead ECG [m]								
C-SSRS [a]					X			
PHQ-9 [a]					X			
Injection Site Inspection/Assessment [p]	X	X	X	X	X	X	X	X
AE/SAE Monitoring and Review [s]	← Monitored Throughout Study →							
Concomitant Medication Monitoring		X	X	X	X	X	X	X
Laboratory Assessments								
Pregnancy Test (serum beta-HCG)[c]	*All assessments/procedures for study Week 28 performed for Part A are as specified in SoA Table 2 Part B DBEV1 – dosing							
Pregnancy Test (urine beta-HCG) [b]					X			
Urinalysis [d h]					X			
Biochemistry, Hematology [d f]					X			
Lipids [d e]					X			
Coagulation [d g]								
Calcitonin [d i]								
Amylase, Lipase [d]					X			
hsCRP, Albumin, Pre-albumin [d]								
Fasting Plasma Glucose (FPG), Fasting Serum Insulin (FSI) and Glucagon [d]					X			
HbA1c [d]								
Capillary Blood Glucose Testing [o]		X					X	

Study Period	Part B – Double Blind Treatment Extension							
Study Visit	DBEV1	DBEV2	DBEV3	DBEV4	DBEV5	DBEV6	DBEV7	DBEV8
Study Day	197	204	211	218	225	232	239	246
Study Week	28	29	30	31	32	33	34	35
Visit Window (Days)	±2	±2	±2	±2	±2	±2	±2	±2
Fasted Visit	X				X			
Dosing Days – SC Administration	X*	X	X	X	X	X	X	X
Blood Sampling for PK [m]					X			
ADA Blood collection [q]					X			

Ab=antibody; ADA=anti-drug antibody; AE=adverse event; Ag=antigen; ALT=alanine aminotransferase; AST=aspartate aminotransferase; BUN=blood urea nitrogen; CKD-EPI = Chronic Kidney Disease Epidemiology Collaboration; C-SSRS=Columbia Suicide Severity Rating Scale; ECG = electrocardiogram; eGFR=estimated glomerular filtration rate; EOS = end of study; EOT = end of treatment; ET = early termination; HbA1c=glycated hemoglobin; HCG= human chorionic gonadotropin; HDL-C=high density lipoprotein-cholesterol; HIV=human immunodeficiency virus; INR=international normalized ratio; LDL-C=low density lipoprotein-cholesterol; MCH= mean corpuscular hemoglobin; MCV = mean corpuscular volume; PHQ-9 = Patient Health Questionnaire-9; PK=Pharmacokinetic; PT = prothrombin time; PTT = partial thromboplastin time; RBC=red blood cell; SAE=serious adverse event; SC = subcutaneous; T3=triiodothyronine; T4=thyroxine; TSH = thyroid-stimulating hormone; WBC = white blood cell

a. If a participant answers "yes" to Question 4 or 5 in "Suicidal Ideation" section and/or if a participant answers "yes" to any of the suicide-related behaviors in the "Suicidal Behavior" section of the C-SSRS on the "Since Last Visit Version", the study drug will be discontinued. If a participant scores ≥ 10 on the patient health questionnaire (PHQ-9), the participant should be evaluated by investigator or medically qualified sub-investigator for continuation of study drug.
b Urine pregnancy test only for WOCBP. If there is a positive or inconclusive test, confirm with a serum pregnancy test. If positive result occurs on Day 1 prior to dose, the participant will be excluded from the study. Additional pregnancy tests (beyond those required per the SoA) should be performed at any time during the study if a menstrual period is missed or there is clinical suspicion of pregnancy.
c. Serum pregnancy test is to be performed for women of childbearing potential (WOCBP). If positive, the participant will be excluded from the study
d. All labs will be collected after an 8 hour fast and prior to dose administration on dosing days.
e. Lipids tests are total cholesterol, LDL-C, HDL-C, triglycerides.
f. Biochemistry testing will measure ALT, albumin, alkaline phosphate, AST, bicarbonate, bilirubin (total/direct/indirect), BUN, calcium total, chloride, creatinine, glucose, magnesium, potassium, and sodium. The creatinine value will be used to calculate eGFR throughout the study using the CKD-EPI or similar equation. The eGFR result at the screening visit will be used for study eligibility. Hematology testing will measure WBC w/differential, RBC, hemoglobin, hematocrit, MCH, MCV, platelets.
g. Coagulation testing will measure PT/INR and PTT.
h. Urinalysis testing will measure color, clarity, specific gravity, pH, leukocyte, protein, glucose, ketones, bilirubin, blood, nitrite, urobilinogen. Microscopic examination will only be performed if the dipstick test is outside of the reference range for leukocyte, blood, nitrite or protein
i. Calcitonin testing at Week 31 will only occur if a participant has a serum calcitonin that increases 50% of the mean of the Screening visit values AND an absolute value ≥20 pg/mL and <35 pg/mL at Week 28 visit
j. The full physical examination will include examination of the following body systems (at minimum): head and neck (including complete thyroid exam), cardiovascular, respiratory, gastrointestinal, brief neurological, and general appearance.
k. The targeted physical exam will be a limited systems review based on any clinical signs, symptoms, and/or AEs reported by participants, including cardiovascular, respiratory, gastrointestinal systems, as well as general appearance and/or other systems as needed.
l. Body weight and waist circumference will be collected under fasting condition. BMI will be calculated at each body weight measurement. See Appendix 2 and Section 6.4.1.
m. Predose ECGs assessments will be performed as per Section 6.3.6 after being in a supine position for at least 5 minutes. When ECG collection timepoints align with PK collection timepoints, PK collection is to be done within ≤ 1hr of ECG. All participants will have a single ECG recorded at all applicable timepoints. All screening ECG assessments will be a single reading.PK sample collection will be performed per Section 6.5. When PK sample collection timepoints align with ECG collection timepoints, PK collection is to be done within ≤ 1hr of ECG.
n. Vital signs assessments will include heart rate, blood pressure, and body temperature. Vital signs will be performed per Section 6.3.5. Blood pressure & heart rate will be taken after being seated with feet on the floor for 5 minutes and collected in triplicate with a mean value calculated.
o. Capillary glucose samples are to be collected predose. Also, ad hoc samples can be collected if symptoms suggest the potential for hypoglycemia
p. The injection site inspection should be performed weekly prior to drug administration. The inspection of abdomen should include determination of the acceptable quadrant to administer the current injection and also an inspection of the previous injection site. The previous injection site should be checked for a post dose inspection reaction which may include pain, tenderness, erythema, and/or swelling See Section 7.2.1 and Table 15.
q. ADA samples should be collected predose.
r. Monthly reminder for participants that their exercise and diet practices need to remain the same throughout the study.
s. AE/SAE collection begins with participant signature of IRB approved informed consent.

Table 5: MET097-24-201 Part B – 24-Week Extension Period: Q2W Arm Only (Week 36 - End of Study)

Study Period	Part B 4-Week Double Blind – 1.6 mg Q2W Arm [a]				Part B 20-Week Open-Label Extension Period – 1.6 mg Q2W Arm											12-Week Post-Dose Follow-Up Period
Study Visit	BWEV 1	BWEV 2	BWEV 3	BWEV 4	BWEV 5	BWEV 6	BWEV 7	BWEV 8	BWEV 9	BWEV 10	BWEV 11	BWEV 12	BWEV 13	BWEV 14	BWEV15 / Part B EOT	Part B ET [b]	BWEV16 / Part B EOS
Study Day	253	260	267	274	281	295	309	323	337	351	365	379	393	407	421	-	491
Study Week	36	37	38	39	40	42	44	46	48	50	52	54	56	58	60	-	70
Visit Window (Days)	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	-	±5
Fasted Visit	X				X		X		X		X		X		X	X	X
Dosing Days – SC Administration	X	***PBO*** [a]	X	***PBO*** [a]	X	X	X	X	X	X	X	X	X	X			
Diet & Physical Activity Guidance [s]	X				X		X		X		X		X		X	X	X
Clinical Assessments																	
Vital signs [o]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Body Weight and Waist Circumference [m]	X				X		X		X		X		X		X	X	X
Full Physical examination [k]															X	X	X
Targeted Physical Examination [l]	X				X		X		X		X		X				
12-lead ECG [n]	X	X	X						X						X	X	X
C-SSRS [c]	X				X		X		X		X		X		X	X	X
PHQ-9 [c]	X				X		X		X		X		X		X	X	X
Injection Site Inspection/ Assessment [q]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
AE/SAE Monitoring and Review [t]	← Monitored Throughout Study →																
Concomitant Medication Monitoring	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Laboratory Assessments																	
Pregnancy Test (serum beta-HCG) [e]															X	X	X
Pregnancy Test (urine beta-HCG) [d]	X				X		X		X		X		X				
Urinalysis [fj]	X				X		X		X		X		X		X	X	X
Biochemistry, Hematology [fh]	X				X		X		X		X		X		X	X	X
Lipids [fg]	X								X						X	X	X
Coagulation [fi]	X														X	X	X
Calcitonin [f]	X														X	X	X
Amylase, Lipase [f]	X				X		X		X		X		X		X	X	X

Study Period	Part B 4-Week Double Blind – 1.6 mg Q2W Arm [a]				Part B 20-Week Open-Label Extension Period – 1.6 mg Q2W Arm												12-Week Post-Dose Follow-Up Period
Study Visit	BWEV 1	BWEV 2	BWEV 3	BWEV 4	BWEV 5	BWEV 6	BWEV 7	BWEV 8	BWEV 9	BWEV 10	BWEV 11	BWEV 12	BWEV 13	BWEV 14	BWEV15 / Part B EOT	Part B ET [b]	BWEV16 / Part B EOS
Study Day	253	260	267	274	281	295	309	323	337	351	365	379	393	407	421	-	491
Study Week	36	37	38	39	40	42	44	46	48	50	52	54	56	58	60	-	70
Visit Window (Days)	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	-	±5
Fasted Visit	X				X		X		X		X		X		X	X	X
Dosing Days – SC Administration	X	***PBO*** [a]	X	***PBO*** [a]	X	X	X	X	X	X	X	X	X	X			
hsCRP, Albumin, Pre-albumin [f]	X								X						X	X	X
Fasting Plasma Glucose (FPG), Fasting Serum Insulin (FSI) and Glucagon [f]									X						X	X	X
HbA1c [f]									X						X	X	X
Capillary Blood Glucose Testing [p]		X	X		X		X				X		X			X	X
Blood Sampling for PK [n]	X	X	X		X		X		X		X		X		X	X	X
ADA Blood collection [r]	X								X						X	X	X

Ab=antibody; ADA=anti-drug antibody; AE=adverse event; Ag=antigen; ALT=alanine aminotransferase; AST=aspartate aminotransferase; BUN=blood urea nitrogen; CKD-EPI = Chronic Kidney Disease Epidemiology Collaboration; C-SSRS=Columbia Suicide Severity Rating Scale; ECG = electrocardiogram; eGFR=estimated glomerular filtration rate; EOS = end of study; EOT = end of treatment; ET = early termination; HbA1c=glycated hemoglobin; HCG= human chorionic gonadotropin; HDL-C=high density lipoprotein-cholesterol; HIV=human immunodeficiency virus; INR=international normalized ratio; LDL-C=low density lipoprotein-cholesterol; MCH= mean corpuscular hemoglobin; MCV = mean corpuscular volume; PHQ-9 = Patient Health Questionnaire-9; PK=Pharmacokinetic; PT = prothrombin time; PTT = partial thromboplastin time; RBC=red blood cell; SAE=serious adverse event; SC = subcutaneous; T3=triiodothyronine; T4=thyroxine; TSH = thyroid-stimulating hormone; WBC = white blood cell

a. This 4-week period is still double blinded but the split of dosing regimens (Q2W, QM, and QW) begins at Week 36. Therefore, the weeks that the participant is not scheduled to receive study drug there will be a "dummy dose" of 0.9% NSS (placebo) given to maintain the blind until Week 40. Only the unblinded pharmacy team will know if the participant receives placebo or active drug
b. Participants who choose to withdraw consent or withdraw from the study and are unable or unwilling to continue attending visits for data collection for any reason will have an ET visit performed. The ET visit may align with scheduled visit timing or may need to be performed during an unscheduled time point. See electronic case report form (eCRF) guidelines on how to document an ET visit.
c. If a participant answers "yes" to Question 4 or 5 in "Suicidal Ideation" section and/or if a participant answers "yes" to any of the suicide-related behaviors in the "Suicidal Behavior" section of the C-SSRS on the "Since Last Visit Version", the study drug will be discontinued. If a participant scores ≥ 10 on the patient health questionnaire (PHQ-9), the participant should be evaluated by investigator or medically qualified sub-investigator for continuation of study drug.
d. Urine pregnancy test only for WOCBP. If there is a positive or inconclusive test, confirm with a serum pregnancy test. If positive result occurs on Day 1 prior to dose, the participant will be excluded from the study. Additional pregnancy tests (beyond those required per the SoA) should be performed at any time during the study if a menstrual period is missed or there is clinical suspicion of pregnancy.
e. Serum pregnancy test is to be performed for women of childbearing potential (WOCBP). If positive, the participant will be excluded from the study
f. All labs will be collected after an 8 hour fast and prior to dose administration on dosing days.
g. Lipids tests are total cholesterol, LDL-C, HDL-C, triglycerides.
h. Biochemistry testing will measure ALT, albumin, alkaline phosphate, AST, bicarbonate, bilirubin (total/direct/indirect), BUN, calcium total, chloride, creatinine, glucose, magnesium, potassium, and sodium. The creatinine value will be used to calculate eGFR throughout the study using the CKD-EPI or similar equation. The eGFR result at the screening visit will be used for study eligibility. Hematology testing will measure WBC w/differential, RBC, hemoglobin, hematocrit, MCH, MCV, platelets.
i. Coagulation testing will measure PT/INR and PTT.
j. Urinalysis testing will measure color, clarity, specific gravity, pH, leukocyte, protein, glucose, ketones, bilirubin, blood, nitrite, urobilinogen. Microscopic examination will only be performed if the dipstick test is outside of the reference range for leukocyte, blood, nitrite or protein
k. The full physical examination will include examination of the following body systems (at minimum): head and neck (including complete thyroid exam), cardiovascular, respiratory, gastrointestinal, brief neurological, and general appearance
l. The targeted physical exam will be a limited systems review based on any clinical signs, symptoms, and/or AEs reported by participants, including cardiovascular, respiratory, gastrointestinal systems, as well as general appearance and/or

other systems as needed.

m. Body weight and waist circumference will be collected under fasting condition. BMI will be calculated at each body weight measurement. See Appendix 2 and Section 6.4.1.

n. Predose ECGs assessments will be performed as per Section 6.3.6 after being in a supine position for at least 5 minutes. When ECG collection timepoints align with PK collection timepoints, PK collection is to be done within ≤ 1hr of ECG. All participants will have a single ECG recorded at all applicable timepoints.PK sample collection will be performed per Section 6.5. When PK sample collection timepoints align with ECG collection timepoints, PK collection is to be done within ≤ 1hr of ECG.

o. Vital signs assessments will include heart rate, blood pressure, and body temperature. Vital signs will be performed per Section 6.3.5. Blood pressure & heart rate will be taken after being seated with feet on the floor for 5 minutes and collected in triplicate with a mean value calculated.

p Capillary glucose samples are to be collected predose. Also, ad hoc samples can be collected if symptoms suggest the potential for hypoglycemia.

q. The injection site inspection should be performed weekly prior to drug administration. The inspection of abdomen should include determination of the acceptable quadrant to administer the current injection and also an inspection of the previous injection site. The previous injection site should be checked for a post dose inspection reaction which may include pain, tenderness, erythema, and/or swelling See Section 7.2.1 and Table 15.

r. ADA samples should be collected predose.

s. Monthly reminder for participants that their exercise and diet practices need to remain the same throughout the study.

t. AE/SAE collection begins with participant signature of IRB approved informed consent.

Table 6: MET097-24-201 Part B – 24-Week Extension Period: QM MET097 Treatment Arms (Week 36 - End of Study)

Study Period	Part B 4-week Double Blind – QM Arms [a]				Part B 20-Week Open-Label Extension Period – QM Arms							12-Week Post-Dose Follow-Up Period
Study Visit	QMEV1	QMEV2	QMEV3	QMEV4	QMEV5	QMEV6	QMEV7	QMEV8	QMEV9	QMEV10 / Part B EOT	Part B ET [b]	QMEV11 / Part B EOS
Study Day	253	260	267	274	281	309	337	365	393	421	-	477
Study Week	36	37	38	39	40	44	48	52	56	60		68
Visit Window (Days)	±3	±5	±5	±5	±5	±5	±5	±5	±5	±5		±7
Fasted Visit	X				X	X	X	X	X	X	X	X
Dosing Days – SC Administration	X	*PBO*[a]	*PBO*[a]	*PBO*[a]	X	X	X	X	X			
Diet & Physical Activity Guidance [s]	X				X	X	X	X	X	X	X	X
Clinical Assessments												
Vital signs [o]	X	X	X	X	X	X	X	X	X	X	X	X
Body Weight and Waist Circumference [m]	X				X	X	X	X	X	X	X	X
Full Physical examination [k]										X	X	X
Targeted Physical Examination [l]	X				X	X	X	X	X			
12-lead ECG [n]	X	X	X				X			X	X	X
C-SSRS [c]	X				X	X	X	X	X	X	X	X
PHQ-9 [c]	X				X	X	X	X	X	X	X	X
Injection Site Inspection/Assessment [q]	X	X	X	X	X	X	X	X	X	X	X	X
AE/SAE Monitoring and Review [t]	← Monitored Throughout Study →											
Concomitant Medication Monitoring	X	X	X	X	X	X	X	X	X	X	X	X
Laboratory Assessments												
Pregnancy Test (serum beta-HCG) [e]										X	X	X
Pregnancy Test (urine beta-HCG) [d]	X				X	X	X	X	X			
Urinalysis [f j]	X				X	X	X	X	X	X	X	X
Biochemistry, Hematology [f h]	X				X	X	X	X	X	X	X	X
Lipids [f g]	X						X			X	X	X
Coagulation [f i]	X									X	X	X
Calcitonin [f]	X									X	X	X
Amylase, Lipase [f]	X				X	X	X	X	X	X	X	X
hsCRP, Albumin, Pre-albumin [f]	X						X			X	X	X

Study Period	Part B 4-week Double Blind – QM Arms [a]				Part B 20-Week Open-Label Extension Period – QM Arms							12-Week Post-Dose Follow-Up Period
Study Visit	QMEV1	QMEV2	QMEV3	QMEV4	QMEV5	QMEV6	QMEV7	QMEV8	QMEV9	QMEV10 / Part B EOT	Part B ET [b]	QMEV11 / Part B EOS
Study Day	253	260	267	274	281	309	337	365	393	421	-	477
Study Week	36	37	38	39	40	44	48	52	56	60		68
Visit Window (Days)	±3	±5	±5	±5	±5	±5	±5	±5	±5	±5		±7
Fasted Visit	X				X	X	X	X	X	X	X	X
Dosing Days – SC Administration	X	***PBO*** [a]	***PBO*** [a]	***PBO*** [a]	X	X	X	X	X			
Fasting Plasma Glucose (FPG), Fasting Serum Insulin (FSI) and Glucagon [f]					X	X	X	X	X	X	X	X
HbA1c [f]							X			X	X	X
Capillary Blood Glucose Testing [p]		X	X				X			X	X	X
Blood Sampling for PK [n]	X	X	X		X	X	X	X	X	X	X	X
ADA Blood collection [r]	X						X			X	X	X

Note: See footnotes under Table 8

Table 7: MET097-24-201 Part B – 24-Week Extension Period: Placebo Switch to QW MET097 Arm (Week 36 - Week 52)

Study Period	Part B 4-Week Double Blind – Placebo to QW MET097 Arm [a]				Part B 20-Week Open-Label Extension Period – Placebo to QW MET097 Arm												
Study Visit	QW EV1	QW EV2	QW EV3	QW EV4	QW EV5	QW EV6	QW EV7	QW EV8	QW EV9	QW EV10	QW EV11	QW EV12	QW EV13	QW EV14	QW EV15	QW EV16	QW EV17
Study Day	253	260	267	274	281	288	295	302	309	316	323	330	337	344	351	358	365
Study Week	36	37	38	39	40	41	42	43	44	45	46	47	48	49	50	51	52
Visit Window (Days)	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3
Fasted Visit	X				X				X				X				X
Dosing Days – SC Administration	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Diet & Physical Activity Guidance [s]	X				X				X				X				X
Clinical Assessments																	
Vital signs [o]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Body Weight and Waist Circumference [m]	X				X				X				X				X
Full Physical examination [k]																	
Targeted Physical Examination [l]	X				X				X				X				X
12-lead ECG [n]	X	X	X		X												X
C-SSRS [c]	X				X				X				X				X
PHQ-9 [c]	X				X				X				X				X
Injection Site Inspection/Assessment [q]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
AE/SAE Monitoring and Review [t]	← Monitored Throughout Study →																
Concomitant Medication Monitoring	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Laboratory Assessments																	
Pregnancy Test (serum beta-HCG) [e]																	
Pregnancy Test (urine beta-HCG) [d]	X				X				X				X				X
Urinalysis [fj]	X				X				X				X				X
Biochemistry, Hematology [fh]	X				X				X				X				X
Lipids [fg]	X												X				
Coagulation [fi]	X																
Calcitonin [f]	X																
Amylase, Lipase [f]	X				X				X				X				X

Study Period	Part B 4-Week Double Blind – Placebo to QW MET097 Arm [a]				Part B 20-Week Open-Label Extension Period – Placebo to QW MET097 Arm												
Study Visit	QW EV1	QW EV2	QW EV3	QW EV4	QW EV5	QW EV6	QW EV7	QW EV8	QW EV9	QW EV10	QW EV11	QW EV12	QW EV13	QW EV14	QW EV15	QW EV16	QW EV17
Study Day	253	260	267	274	281	288	295	302	309	316	323	330	337	344	351	358	365
Study Week	36	37	38	39	40	41	42	43	44	45	46	47	48	49	50	51	52
Visit Window (Days)	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3
Fasted Visit	X				X				X				X				X
Dosing Days – SC Administration	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
hsCRP, Albumin, Pre-albumin [f]	X												X				
Fasting Plasma Glucose (FPG), Fasting Serum Insulin (FSI) and Glucagon [f]					X				X				X				X
HbA1c [f]													X				
Capillary Blood Glucose Testing [p]		X	X		X				X				X				X
Blood Sampling for PK [n]	X	X	X		X				X				X				X
ADA Blood collection [r]	X								X								X

Note: See footnotes under Table 8

Table 8: MET097-24-201 Part B – 24-Week Extension Period: Placebo Switch to QW MET097 Arm (Week 53 - End Study)

Study Period	Part B 20-Week Open-Label Extension Period (continued) – Placebo to QW MET097 Arm									12-Week Post-Dose Follow-Up Period
Study Visit	QWV18	QWEV19	QWEV20	QWEV21	QWEV22	QWEV23	QWEV24	QWEV25 / Part B EOT	Part B ET [b]	QWEV26 / Part B EOS
Study Day	372	379	386	393	400	407	414	421	-	498
Study Week	53	54	55	56	57	58	59	60		71
Visit Window (Days)	±3	±3	±3	±3	±3	±3	±3	±3		±7
Fasted Visit				X				X	X	X
Dosing Days – SC Administration	X	X	X	X	X	X	X			
Diet & Physical Activity Guidance [s]				X				X	X	X
Clinical Assessments										
Vital signs [o]	X	X	X	X	X	X	X	X	X	X
Body Weight and Waist Circumference [m]				X				X	X	X
Full Physical examination [k]								X	X	X
Targeted Physical Examination [l]				X						
12-lead ECG [n]								X	X	X
C-SSRS [c]				X				X	X	X
PHQ-9 [c]				X				X	X	X
Injection Site Inspection/Assessment [q]	X	X	X	X	X	X	X	X	X	X
AE/SAE Monitoring and Review [t]	← Monitored Throughout Study →									
Concomitant Medication Monitoring	X	X	X	X	X	X	X	X	X	X
Laboratory Assessments										
Pregnancy Test (serum beta-HCG) [e]								X	X	X
Pregnancy Test (urine beta-HCG) [d]				X						
Urinalysis [fj]				X				X	X	X
Biochemistry, Hematology [fh]				X				X	X	X
Lipids [fg]								X	X	X
Coagulation [fi]								X	X	X
Calcitonin [f]								X	X	X
Amylase, Lipase [f]				X				X	X	X
hsCRP, Albumin, Pre-albumin [f]								X	X	
Fasting Plasma Glucose (FPG), Fasting Serum Insulin (FSI) and Glucagon [f]				X				X	X	

Study Period	Part B 20-Week Open-Label Extension Period (continued) – Placebo to QW MET097 Arm									12-Week Post-Dose Follow-Up Period
Study Visit	QWV18	QWEV19	QWEV20	QWEV21	QWEV22	QWEV23	QWEV24	QWEV25 / Part B EOT	Part B ET [b]	QWEV26 / Part B EOS
Study Day	372	379	386	393	400	407	414	421	-	498
Study Week	53	54	55	56	57	58	59	60		71
Visit Window (Days)	±3	±3	±3	±3	±3	±3	±3	±3		±7
Fasted Visit				X				X	X	X
Dosing Days – SC Administration	X	X	X	X	X	X	X			
HbA1c [f]								X	X	X
Capillary Blood Glucose Testing [p]				X				X	X	X
Blood Sampling for PK [n]				X				X	X	X
ADA Blood collection [r]								X	X	X

Ab=antibody; ADA=anti-drug antibody; AE=adverse event; Ag=antigen; ALT=alanine aminotransferase; AST=aspartate aminotransferase; BUN=blood urea nitrogen; CKD-EPI = Chronic Kidney Disease Epidemiology Collaboration; C-SSRS=Columbia Suicide Severity Rating Scale; ECG = electrocardiogram; eGFR=estimated glomerular filtration rate; EOS = end of study; EOT = end of treatment; ET = early termination; HbA1c=glycated hemoglobin; HCG= human chorionic gonadotropin; HDL-C=high density lipoprotein-cholesterol; HIV=human immunodeficiency virus; INR=international normalized ratio; LDL-C=low density lipoprotein-cholesterol; MCH= mean corpuscular hemoglobin; MCV = mean corpuscular volume; PHQ-9 = Patient Health Questionnaire-9; PK=Pharmacokinetic; PT = prothrombin time; PTT = partial thromboplastin time; RBC=red blood cell; SAE=serious adverse event; SC = subcutaneous; T3=triiodothyronine; T4=thyroxine; TSH = thyroid-stimulating hormone; WBC = white blood cell

NOTE: These footnotes are applicable to Tables 6, 7, 8

a. This 4-week period is still double blinded but the split of dosing regimens (Q2W, QM, and QW) begins at Week 36. Therefore, the weeks that the participant is not scheduled to receive study drug there will be a "dummy dose" of 0.9% NSS (placebo) given to maintain the blind until Week 40. **(Only applicable to Table 6 & 7)**

b. Participants who choose to withdraw consent or withdraw from the study and are unable or unwilling to continue attending visits for data collection for any reason will have an ET visit performed. The ET visit may align with scheduled visit timing or may need to be performed during an unscheduled time point. See electronic case report form (eCRF) guidelines on how to document an ET visit.

c. If a participant answers "yes" to Question 4 or 5 in "Suicidal Ideation" section and/or if a participant answers "yes" to any of the suicide-related behaviors in the "Suicidal Behavior" section of the C-SSRS on the "Since Last Visit Version", the study drug will be discontinued. If a participant scores ≥ 10 on the patient health questionnaire (PHQ-9), the participant should be evaluated by investigator or medically qualified sub-investigator for continuation of study drug.

d. Urine pregnancy test only for WOCBP. If there is a positive or inconclusive test, confirm with a serum pregnancy test. If positive result occurs on Day 1 prior to dose, the participant will be excluded from the study. Additional pregnancy tests (beyond those required per the SoA) should be performed at any time during the study if a menstrual period is missed or there is clinical suspicion of pregnancy.

e. Serum pregnancy test is to be performed for women of childbearing potential (WOCBP). If positive, the participant will be excluded from the study

f. All labs will be collected after an 8 hour fast and prior to dose administration on dosing days.

g. Lipids tests are total cholesterol, LDL-C, HDL-C, triglycerides.

h. Biochemistry testing will measure ALT, albumin, alkaline phosphate, AST, bicarbonate, bilirubin (total/direct/indirect), BUN, calcium total, chloride, creatinine, glucose, magnesium, potassium, and sodium. The creatinine value will be used to calculate eGFR throughout the study using the CKD-EPI or similar equation. The eGFR result at the screening visit will be used for study eligibility. Hematology testing will measure WBC w/differential, RBC, hemoglobin, hematocrit, MCH, MCV, platelets.

i. Coagulation testing will measure PT/INR and PTT.

j. Urinalysis testing will measure color, clarity, specific gravity, pH, leukocyte, protein, glucose, ketones, bilirubin, blood, nitrite, urobilinogen. Microscopic examination will only be performed if the dipstick test is outside of the reference range for leukocyte, blood, nitrite or protein

k. The full physical examination will include examination of the following body systems (at minimum): head and neck (including complete thyroid exam), cardiovascular, respiratory, gastrointestinal, brief neurological, and general appearance

l. The targeted physical exam will be a limited systems review based on any clinical signs, symptoms, and/or AEs reported by participants, including cardiovascular, respiratory, gastrointestinal systems, as well as general appearance and/or other systems as needed.

m. Body weight and waist circumference will be collected under fasting condition. BMI will be calculated at each body weight measurement. See Appendix 2 and Section 6.4.1.

n. ECGs assessments will be performed as per Section 6.3.6 after being in a supine position for at least 5 minutes. When ECG collection timepoints align with PK collection timepoints, PK collection is to be done within ≤ 1hr of ECG. All participants will have a single ECG recorded at all applicable timepoints.PK sample collection will be performed per Section 6.5. When PK sample collection timepoints align with ECG collection timepoints, PK collection is to be done within ≤ 1hr of ECG.

o. Vital signs assessments will include heart rate, blood pressure, and body temperature. Vital signs will be performed per Section 6.3.5. Blood pressure & heart rate will be taken after being seated with feet on the floor for 5 minutes and

collected in triplicate with a mean value calculated.
p Capillary glucose samples are to be collected predose. Also, ad hoc samples can be collected if symptoms suggest the potential for hypoglycemia.
q. The injection site inspection should be performed weekly prior to drug administration. The inspection of abdomen should include determination of the acceptable quadrant to administer the current injection and also an inspection of the previous injection site. The previous injection site should be checked for a post dose inspection reaction which may include pain, tenderness, erythema, and/or swelling See Section 7.2.1 and Table 15.
r. ADA samples should be collected predose.
s. Monthly reminder for participants that their exercise and diet practices need to remain the same throughout the study.
t. AE/SAE collection begins with participant signature of IRB approved informed consent.

1. INTRODUCTION

1.1. Background

Obesity is a serious and complex chronic medical condition and is recognized as a multifactorial disease that presents a risk to human health [Bray et al, 2017]. Excess body weight is a growing global health problem; worldwide obesity rates have almost tripled in recent decades [World Health Organization (WHO) Obesity and overweight, 2021]. The WHO reports 1.9 billion persons are overweight (body mass index [BMI] ≥25 kg/m^2) of which 650 million are obese (BMI of ≥30 kg/m^2) [Obesity and overweight, 2021]. The prevalence of obesity in the United States (US) is also increasing, currently affecting nearly 42% of adults, or about 100 million people. [Centers for Disease Control (CDC), 2023]. Projections indicate that this number will rise to almost 50% by 2030 [Ward et al, 2019]. Excess body weight and obesity are important health concerns as they are linked to many chronic diseases that impact health and well-being [Del Prato et al, 2022] such as cardiovascular disease, Type 2 diabetes mellitus (T2DM), respiratory disorders (eg, sleep apnea, and asthma), increased risk for osteoarthritis and other joint issues, selected cancers [Obesity and overweight, 2021; CDC 2022], non-alcoholic fatty liver disease [Li et al, 2016], and psychiatric disorders (eg, depression and anxiety) [Luppino et al, 2010].

Chronic weight management is a healthcare priority that includes many treatment options ranging from noninvasive to invasive. Intensive behavioral therapy involves regular sessions with healthcare providers to monitor diet and exercise [Wadden et al, 2020]. It is moderately effective for short-term weight loss but less so for severe obesity, and it requires high participant engagement. Weight loss surgery offers significant, durable weight loss but is limited by availability, cost, and potential for both immediate and long-term complications including nutritional deficiencies [Arterburn et al, 2020].

Several Food and Drug Administration (FDA)-approved non-incretin pharmacological options are available for weight management for patients with obesity or overweight. However, their clinical use is limited due to modest weight loss outcomes (approximately 5%), the likelihood of weight regain after discontinuation, and notable side effects [Khera et al, 2016]. In contrast, glucagon-like peptide-1 receptor agonists (GLP-1RAs) have been approved for chronic weight management when combined with diet and exercise. These agents not only facilitate weight loss but also significantly reduce the risks associated with weight-related comorbidities, such as T2DM and cardiovascular complications.

GLP-1RAs leverage the known physiology of native GLP-1. Native GLP-1 is a 30 or 31 amino acid peptide hormone produced and secreted by intestinal enteroendocrine L cells, brainstem neurons and a subpopulation of alpha cells in human pancreatic islet cells [Mojsov et al, 1990; Campbell and Drucker, 2013; Müller et al, 2019]. The basal secretion of GLP-1 from enteroendocrine cells is augmented by the ingestion of luminal nutrients, including carbohydrates and fats [Diakogiannaki et al, 2012]. GLP-1 is a multifunctional hormone with many biological actions [Campbell and Drucker, 2013]. GLP-1 lowers glucose via stimulation of glucose-sensitive insulin secretion from pancreatic islets in response to oral carbohydrate, known as the incretin effect [Vilsbøll et al, 2003]. GLP-1 also lowers glucose by suppressing glucagon

secretion from α cells [Ramracheya et al, 2018] and by slowing gastric emptying through the inhibition of stomach peristalsis and increased contraction of the pyloric region [Nakatani et al, 2017]. While important in the regulation of glycemic control, GLP-1RAs also decrease appetite and are thought to lower weight primarily by this mechanism [Drucker, 2022].

Several GLP-1RAs (and a dual GLP-1/gastric inhibitory polypeptide agonist) are approved for T2DM treatment [Nauck et al, 2021]. Semaglutide (WEGOVY®), liraglutide (SAXENDA®), and recently tirzepatide (ZEPBOUND™) are also approved for chronic weight management when combined with diet and exercise [WEGOVY US Package Insert (USPI), 2022; SAXENDA USPI, 2022; ZEPBOUND USPI, 2023]. All these agents have led to clinically significant weight loss, with semaglutide also showing improved cardiovascular outcomes in the SELECT trial [Lincoff et al, 2023]. The currently approved agents are associated with meaningful percentage body weight loss, but weight regain upon discontinuation. Tolerability, such as nausea, vomiting, and diarrhea, are common during therapy initiation [WEGOVY USPI, 2022; SAXENDA USPI, 2022; ZEPBOUND USPI, 2023], and access to these medications remains limited.

MET097 has been shown to be a Gs protein-biased GLP-1RA which preferentially recruits the Gs protein over beta-arrestin-2 (βArr2), contrasting native human GLP-1 (hGLP-1) and semaglutide, which are comparatively balanced, recruiting both effectors maximally (see Section 1.3.1.1). This biased agonism has been correlated with prolonged residence of the GLP-1 receptor at the cell surface following MET097 stimulation when compared with hGLP-1 and semaglutide.

MET097 has been profiled preclinically and appears more potent in vivo than semaglutide (dose-to-dose comparison) and better tolerated than semaglutide in preclinical studies (see Section 1.3.1.1).

MET097 has high solubility (20 mg/mL) across a pH range from 3 to 9 and an extended half-life in preclinical species (see Section 1.3.1.2).

MET097 was studied in 4-, 13-, and 26-week Good Laboratory Practice (GLP) toxicology studies in rats and minipigs (see Section 1.3.2 and the investigator's brochure [IB]). The observations from the toxicology studies are in-line with the expected pharmacology for this class of compounds with weight loss being the prevalent finding.

1.2. Study Rationale

MET097-24-201 is a 28-week Phase 2b study designed to examine the safety and efficacy of four weekly MET097 dose levels (vs placebo) administered subcutaneously for 28 weeks in participants with obesity or overweight. The primary objective will be the effect of MET097 on percent change in body weight at Week 28. This data will support the dose selection for the Phase 3 clinical studies and allow for sufficient time to observe maximal, or near maximal, weight loss effects at each dose level.

The ultra long-half life and the biased pharmacology of MET097 at the GLP-1 receptor have the potential to provide patients with multiple flexible dosing options (eg, titration or titration-free QW dosing, intermittent (eg, Q2W) dosing, or once-monthly dosing). Therefore, the study extension aims to investigate the safety, tolerability and efficacy of switching to corresponding

biweekly (Q2W) or once-monthly (QM) dose. Preliminary findings from Study MET097-23-101 Part C suggest that switching from a QW dose to up to a 4x multiple of the QW dose (QM dose) MET097 is safe, well-tolerated, and merits further investigation.

The totality of data from the double-blind and extension phases of the study is expected to better inform not only the optimal therapeutic dose but also the monthly dosing regimen option at each of the therapeutic dose levels to investigate further in late-stage confirmatory trials. Further, a biweekly (Q2W) dose regimen will also be explored. All together, they will also inform the potential of MET097 to provide better value and health outcomes with lesser burden of injection frequency and complexity for optimal weight loss and chronic treatment of obesity. For further details please see the current edition of the IB for MET097.

Part A

Part A is double-blinded (sponsor-, investigator- and participant-blinded) from randomization until the primary reporting milestone at Week 28 (Day 197). Investigators, participants, and Sponsor personnel directly involved in the conduct of the study will remain blinded to participant-level treatment allocation for the entire duration of the Part A of the study. Participants that elect not to continue in the study extension (Part B) will complete the Part A Post-Treatment Follow-up Period as specified in Table 2.

Part B

Part B is double-blinded (sponsor-, investigator- and participant-blinded) from the dosing at Week 28 (Day 197) until the first participant reaches Week 40 (Day 281). Investigators, participants, and Sponsor personnel directly involved in the conduct of the study will remain blinded to participant-level treatment allocation in Part B from the dosing at Week 28 (Day 197) until the first participant reaches Week 40 (Day 281).

The study will also include an optional study extension consisting of a total of 12 weeks of double-blind treatment, which includes a switch from MET097 once-weekly (QW) to either biweekly (Q2W) or once-monthly (QM) MET097 dosing regimens and switching of QW placebo arm into MET097 QW. The study extension will only be available to participants who complete the primary endpoint at Week 28, do not meet any protocol-specified discontinuation criteria, and sign informed consent for continued treatment.

For more information on the scientific rationale for the study, please see Section 3.3.

1.3. Nonclinical Studies

1.3.1. Pharmacology

1.3.1.1. In Vitro Efficacy of MET097

MET097 is a potent fully efficacious GLP-1RA. In vitro studies assessing cyclic adenosine monophosphate (cAMP) accumulation responses in human GLP-1 receptor-overexpressing Chinese hamster ovary cells indicate that MET097 has over 2-fold greater potency as a GLP-1RA compared to semaglutide. Semaglutide has an 8.3-fold lower potency than the reference hGLP-1 [Ozempic (semaglutide) Nonclinical Review, FDA, 2017], MET097's potency

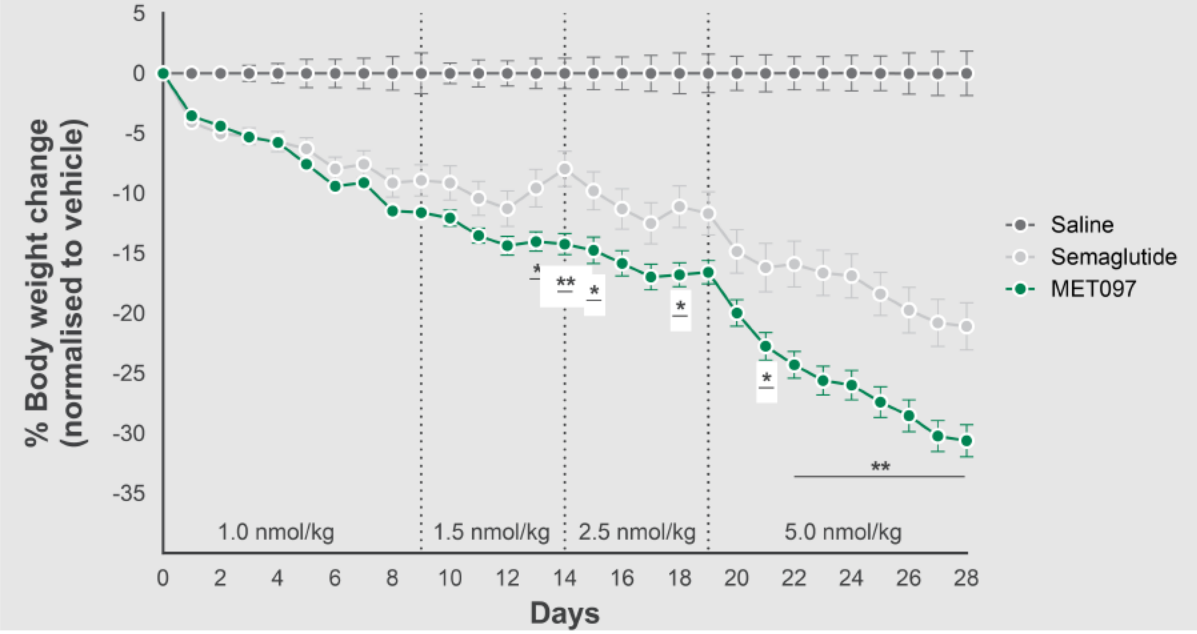
is only 3.7-fold lower than the reference hGLP-1 (GLP-1 half maximal effective concentration (EC_{50}) of 5.77 nM versus MET097 EC_{50} of 21.5 nM) (Study ICL-23-9; see the IB).

MET097 is a Gs protein-biased GLP-1RA which maximally activates the cAMP pathway with no βArr2 recruitment thus protracting the time that GLP-1 receptor remains at the cellular surface following stimulation.

1.3.1.2. In Vivo Efficacy of MET097

In a placebo (saline) controlled study (Study 230224; see the IB), MET097 significantly reduced body weight and food intake when compared to semaglutide at equivalent doses, over 28 days in a diet-induced obese (DIO) mouse model, at the specific timepoints for weight as marked with an asterisk in Figure 1.

Figure 1: Chronic Effect of MET097 on Body Weight in Male DIO Mice from Study 230224



Subcutaneous injections of vehicle (n=7), semaglutide (n=11), or MET097 (n=11) were administered to high fat diet-induced obese (DIO) male mice daily from Days 0 to 27. Treatments were initiated at 1.0 nmol/kg and escalated on Days 9, 14, and 19, to 1.5, 2.5, and 5.0 nmol/kg, respectively. Body weight was measured at time of injection and plotted as a percentage change from baseline (Day 0) as mean ± standard error of the mean. Data was analyzed by a mixed-effects model with Sidak's multiple comparison test (MET097 vs semaglutide): *p<0.05, **p<0.01. Mice were treated with a high fat diet for 77 days prior to initiation of treatment. Baseline body weight was 44.2 in the three groups.

Cumulative food intake (the amount of food eaten measured and summed over the entire study) was also assessed and was significantly lower in MET097 treated DIO mice than in mice treated with saline or semaglutide. There was an association between reduction in food intake and reduction in body weight observed with the MET097 group; MET097 had 38% reduction in food intake compared to placebo ($p < 0.0001$) and a 18% reduction in food intake compared to semaglutide ($p=0.0111$).

1.3.2. Toxicology

The toxicology and safety pharmacology of the synthetic peptide MET097 was evaluated in nonclinical studies, consistent with the principles outlined in the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals (ICH) S6 and ICH S6 (R1) Addendum and ICH M3(R2) guidelines [ICH S6, 1997; ICH M3 (R2), 2010; ICH S6 (R1) Addendum, 2012].

GLP toxicity studies of 4-weeks with a 2-week recovery period, 13-week and 26-week duration were conducted in rat (GTI0005, 701725, 701815 and 701707) and Göttingen minipig (GTI0007, 64063, 64137P and 64010P); see MET097 IB for additional details. MET097 was administered by SC injection three times weekly in rats (except in Study GTI0005 where it was administered twice weekly) and twice weekly in minipigs. The dose ranges explored in both species produced the expected body weight and food consumption decreases associated with GLP-1 receptor agonism. In rat, histologic changes were limited to the 26-week study and included atrophy of the adipocytes in the skin/subcutis and at dosing site/s (CCI µg/kg/dose), which correlated with decreased food consumption and body weight. In minipig, fully reversible increased lymphocyte cellularity of the white pulp of spleen/periarteriolar lymphoid sheath (CCI µg/kg/dose) and injection site observations (CCI µg/kg/dose) were noted in the 4-week study. No microscopic findings were seen in the 13-week minipig study. The incidence and severity of macroscopic and microscopic changes noted at the dosing site/s in control and MET097-dosed minipigs in the 26-week study was suggestive of slightly exacerbated procedure-related changes. Additional microscopic changes in the 26-week studies included thyroid c-cell hyperplasia in a small number of rats from all MET097-dosed groups (CCI µg/kg/dose-human equivalent dose [HED] of CCI mg/week) and one female minipig (concurrent with follicular cell hypertrophy/hyperplasia) from the high dose group (CCI µg/kg/dose-HED of CCI mg/week). However, due to low incidence and severity the relationship of these findings to dosing was uncertain.

While thyroid C-cell tumors have been observed in animal studies with other GLP-1RAs, the relevance of these class findings to humans has not been identified. In 2023, the European Medicines Agency (EMA) pharmacovigilance risk assessment committee (PRAC) reviewed evidence from published literature and cumulative data from nonclinical, clinical, and post-marketing data, and concluded that the available evidence does not support a causal association between GLP-1RAs and thyroid cancer [EMA, 2023; Hu et al, 2022]; see IB for additional details.

In the safety pharmacology assessments, no respiratory changes or central nervous system effects were seen in rat 4-week study. Additionally, no effects were observed on any cardiovascular parameter in minipig studies (additional details are available in the IB).

An in vivo micronucleus assay was assessed from rat whole blood in the 4-week study (and 701725; see the IB) was negative for activity.

1.4. Clinical Studies

As previously described, the clinical development program for once-weekly MET097 has been designed to evaluate the safety, tolerability, and efficacy of a broad range of MET097 doses as

adjunct to a reduced calorie diet and increased physical activity for chronic weight management in adults with BMI ≥30 kg/m^2 (obesity) or BMI ≥27 kg/m^2 (overweight) with at least one weight-related comorbidity (e.g., hypertension, dyslipidemia, obstructive sleep apnea, cardiovascular disease, or T2DM). To date, the clinical development program includes the following studies:

- The IND-opening study for MET097 (MET097-23-101), is a Phase 1/2, randomized, double-blind, placebo-controlled study to evaluate the safety, tolerability, pharmacokinetics (PK), and pharmacodynamics (PD) of SC doses of MET097 in healthy adult participants with a BMI of 27 to 38 kg/m^2. The Phase 1 portion of the study has been completed and included two parts: Part A with single-ascending-dose (SAD) cohorts and Part B with multiple-ascending-dose (MAD) cohorts (5 once weekly doses over a 4-week period on study Days 1, 8, 15, 22, and 29).
- The Phase 2a portion of the MET097-23-101 study (Part C), was designed to describe the dose-range, safety, tolerability, and PK/PD relationships over 12 once weekly (QW) SC injections of MET097 in five cohorts (titration-free MET097 dose cohorts of 0.6 mg, 0.8 mg, 1.0 mg, and 1.2 mg; MET097 dose-titration cohort of 0.4 mg/0.8 mg/1.2 mg, each received for 4 weeks). All five cohorts also included a 13th dose that explored the tolerability of a potential monthly dose regimen with a single 2-fold (1.2 mg, 1.6 mg, 2.0 mg, 2.4 mg) or 4-fold (2.4 mg, 3.2 mg, 4.0 mg, 4.8 mg) dose increase over the weekly dose (ie, after steady state MET097 exposure) to assess the tolerability of switching to a pharmacologically matched, dose at monthly intervals. After subcutaneous administration of the 13th dose, all participants were to be followed for an additional 75 days (Day 160) for assessments of safety, tolerability, PK and efficacy parameters.
- An ongoing Phase 2b study (MET097-25-202) is a multi-center, randomized, double-blind, placebo-controlled study of n=125 participants with Type 2 diabetes mellitus and obesity or overweight to investigate the efficacy, safety, PK, and tolerability of four different MET097 dosing regimens will be evaluated vs placebo: two titration-free dose groups (0.4 mg and 0.8 mg MET097) and two dose-titration groups (0.4 mg/0.8 mg/1.2 mg and 0.4 mg/0.8 mg/1.6 mg) with 28 subcutaneous injection of once-weekly dosing.
- Two additional clinical pharmacology studies are ongoing: a single dose study to evaluate the PK of MET097 in adults with normal and impaired renal function (MET097-24-103) and a drug-drug interaction study to evaluate the effect of a single dose of MET097 on the PK of a combination oral contraceptive in healthy female adults (MET097-24-104).
- The first in human study for MET097 (2022/GLP-06/01), was a Phase 1, randomized, double-blind, placebo-controlled study to evaluate the safety, tolerability, PK, and PD of SC doses of MET097 in adult participants. This study was permanently stopped on January 15, 2024, as the MET097 IND-opening study was initiated in the US; the study was not stopped for safety reasons.

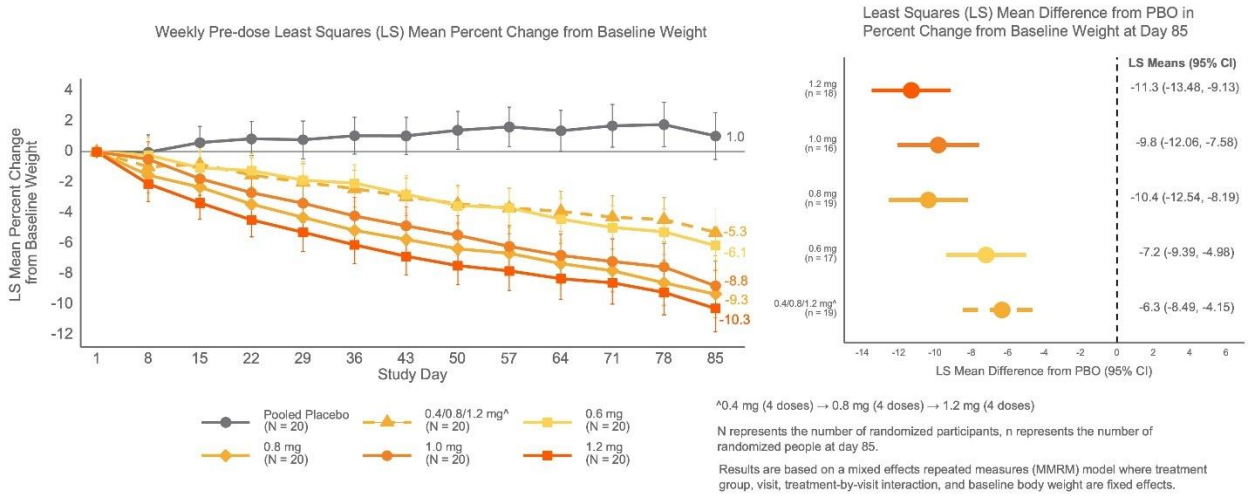
To date, approximately 260 participants have received at least 1 dose of study treatment in studies 2022/GLP-06/01 and MET097-23-101 Part A, Part B, and Part C, including 120 participants in MET097-23-101 Part C that received up to 12 weeks of study treatment with once-weekly MET097 as well as a 13th dose that explores the tolerability of a potential monthly dose regimen with a single 2- or 4-fold dose increase over the weekly dose. An additional 239

participants have received at least one dose of study treatment in an ongoing Phase 2b study in adults with obesity of overweight (Study MET097-24-201); no data are currently available for this study.

Based on available preliminary findings from planned unblinded reviews of MET097-23-101, once-weekly MET097 results in clinically meaningful weight loss and is generally well-tolerated in a titration-free or dose-titration regimen. Additional details on the clinical study designs and preliminary results through 12 weeks (Day 85) are available in the IB. A summary of key preliminary results through Week 16 (Day 115), including the 13th dose are provided below. These preliminary findings suggest that switching from QW to QM MET097 is safe and well-tolerated and merits further investigation.

- Once-weekly MET097 resulted in clinically meaningful, dose-dependent weight loss through 12 weeks across all titration-free and dose-titration groups evaluated (Figure 2). At approximately one month after the single 2-fold or 4-fold dose, the single 4-fold monthly doses resulted in continued weight loss that was consistent with expected weight loss if given as four once-weekly injections.
- With once-weekly MET097, gastrointestinal (GI) disorders (nausea, vomiting, constipation, diarrhea), headache, and decreased appetite/appetite lost were the most frequently reported treatment emergent adverse events (TEAEs), with nausea the most frequently reported AE among titration-free MET097 dose groups. The percentage of participants reporting nausea generally increased with increasing MET097 dose. Most events of nausea were mild and occurred during the first few weeks following administration of study drug. In the once-weekly MET097 dose titration group (0.4 mg/0.8 mg/1.2 mg) through 12 weeks, rates of nausea and vomiting were similar to placebo.
- Single 2-fold or 4-fold 13th doses were also well-tolerated when preceded by 12 weeks with QW MET097 (ie, steady state MET097 exposure). Gastrointestinal disorders were the most frequently reported TEAEs, with rates of nausea and vomiting ranging from CCI [redacted]% and CCI [redacted]%, respectively, following a single dose of 3.2 mg MET097 or 4.8 mg MET097 (ie, the QM MET097 doses that are planned to be evaluated in this study.
- A modest increase in heart rate from baseline was observed with once-weekly as well as after the single 2-fold and 4-fold doses of MET097. The general trend was not consistently dose dependent with once-weekly dosing. These increases in heart rate were not sustained after the last dose of study treatment.
- The mean apparent elimination half-life ($t_{1/2}$) estimate across all MET097 doses is approximately CCI [redacted] hrs.

Figure 2: MMRM Analysis of Percent Change from Baseline Weight: Least Squared Means over Time and Adjusted Mean Treatment Difference (95% CI) at Day 85



Source: IB
Data used to generate tables is interim/pre-database lock and subject to change with data-management processes progress. Based on raw data extract of 03JAN2025.
Participants in the 0.4/0.8 mg/1.2 mg QW group received 4 doses of 0.4 mg followed by 4 doses of 0.8 mg followed by 4 doses of 1.2 mg MET097.
CFB=change from baseline; CI=confidence interval; LS=least squares; MMRM=mixed model for repeated measures; PBO=placebo; QW=once weekly

Further information regarding this ongoing clinical study of MET097 can be found in the IB.

1.5. Risk/Benefit Assessment

MET097 is an analog of human GLP-1 being evaluated as an adjunct treatment for body weight loss to a reduced calorie diet and increased physical activity for chronic weight management in adults. MET097 has been administered in clinical studies in participants with obesity or overweight and was generally well tolerated.

All dosing regimens in this study are anticipated to be better than or equal to the weight management the participants receive at the time of entry into the study or continuing onto the extension phase. It is expected that all participants will benefit from continued close contact with the study site and counselling by a dietician or a similar qualified healthcare professional, all of which will most likely result in intensified weight management. Results from the MET097-23-101 Part C study demonstrated that MET097 once weekly as an adjunct to a reduced-calorie diet and increased physical activity was effective for weight loss and comparable in magnitude to those observed with approved therapies at 12 weeks.

Participants randomized to active treatment arms will be treated with doses up to 1.2 mg once weekly in Part A for 28 weeks. Participants agreeing to continue to Part B will receive up to 2.4 mg weekly or up to 4.8 mg monthly for an additional 32 weeks maximum. Participants randomized to the placebo treatment arm in Part A will be rolled over in Part B to active doses of up to 1.6 mg (Arm 5A) or 2.4 mg (Arm 5B) once weekly following a titration period. These

specific dosing levels are within the range of doses that were investigated in Study MET097-23-101 (eg, weekly doses of up to 1.6 mg and a single monthly administration of up to 4.8 mg). Dosing levels and regimens are being further studied in two additional ongoing Phase 2 studies in participants with overweight or obesity and type 2 diabetes (Study MET097 -24-202; doses up to 1.6 mg QW) and overweight or obesity without T2DM (Study MET-24-203; doses up to 4.8 mg QM).

Consistent with findings from other GLP-1 RAs, the most frequently reported adverse events (AE) in previous clinical trials with MET097 were gastrointestinal AEs.- GI tolerability, however, was improved relative to titration-free regimens when MET097 was titrated (initiated at 0.4 mg once-weekly and up-titrated to 1.2 mg once-weekly over 12 weeks), with rates of nausea and vomiting similar to placebo. Based on the clinical experience to date, the planned once-weekly and once-monthly MET097 doses and dosing regimens in this study are anticipated to be well-tolerated and have potential to provide clinically meaningful weight loss through 64 weeks of treatment.

More detailed information about the known and expected benefits and risks and reasonably expected AEs of MET097 may be found in the IB. Information on AEs expected to be related to the investigational product may be found in IB. Information on SAEs that are expected in the study population independent of drug exposure will be assessed by the Sponsor in aggregate, periodically during the course of the study, and may be found in Reference Safety Information (Section 7) of the IB.

Taking into account the measures taken to minimize risk to participants participating in this study, and based on the known safety profile of MET097, the benefit-risk balance of participation in this clinical study including in the extension phase is favorable for participants with obesity or overweight.

2. STUDY OBJECTIVES AND ENDPOINTS AND ESTIMANDS

Table 9 provides the objectives and endpoints for Part A (from Study Week 0 [Day 1] through pre-dose Study Week 28 [Day 197]).

Table 9: Study Objectives and Endpoints – Part A

Part A	
Objectives	**Endpoints**
Primary	
1) To evaluate the efficacy of once-weekly MET097 on body weight in participants with obesity or overweight, after 28 once-weekly doses of 0.4 mg, 0.6 mg, 0.9 mg or 1.2 mg, compared to placebo	• Percent change from baseline in body weight at Week 28 (Day 197)
Secondary	
1) To evaluate the efficacy of MET097 on body weight and additional weight-related parameters at all weekly timepoints in participants with obesity or overweight, with 28 once-weekly doses (0.4 mg, 0.6 mg, 0.9 mg and 1.2 mg) compared to placebo	• Percent change from baseline in body weight at all weekly post-baseline weight measurements prior to Week 28 (Day 197). • Occurrence of body weight reduction (weight loss) from baseline at Week 28 (Day 197) that is: ≥ 5%, ≥ 10%, ≥ 15% • Change from baseline (at all protocol-specified weekly post-baseline measurements in Part A) in: o Body weight (kg) o Body Mass Index (BMI) (kg/m²) o Waist circumference (cm)
2) To assess the safety and tolerability of MET097 compared to placebo in Part A	The following safety and tolerability endpoints will be measured in Part A: • Occurrence, severity and relatedness of treatment emergent adverse events (TEAEs) AEs of clinical interest: gastrointestinal adverse events (AEs) of Nausea, Vomiting and Diarrhea. • Occurrence, severity, and relatedness of other TEAEs • Occurrence of abnormal clinically significant physical examination • 12-lead electrocardiogram (ECG) measurements • Laboratory measurements • Columbia-Suicide Severity Rating Scale (C-SSRS) • Patient Health Questionnaire (PHQ-9) • Occurrence of anti-drug antibodies (ADAs)
3) To characterize the pharmacokinetic (PK) profile of MET097 in participants with obesity or overweight, with 28 once-weekly doses.	The following endpoints measured for the duration of the weekly dosing in Part A for all participants: • Minimum observed concentration (C_{min}) The following endpoints measured for the duration of the weekly dosing in Part A for subset of CCI participants of each arm: • Area under the concentration versus time curve during the dosing interval ($AUC_{(0-t)}$)

Part A	
Objectives	**Endpoints**
	• Maximum observed concentration (C_{max}) • Time to maximum concentration (T_{max}) • Other PK parameters may be evaluated • MET097 concentrations will be summarized
Exploratory	
1) To evaluate glucose metabolism parameters and lipid levels of MET097 in participants with obesity or overweight, with 28 once-weekly doses compared to placebo	• Change from baseline (at all protocol-specified post-baseline measurements in Part A) in the following glucose metabolism parameters: fasting insulin, glycated hemoglobin A1c [HbA1c], fasting glucose and fasting glucagon • Change from baseline (at all protocol-specified post-baseline measurements in Part A) in lipid levels (triglycerides, high-density lipoprotein-cholesterol [HDL-C] and low-density lipoprotein-cholesterol [LDL-C])

The last available measurement prior to first dose received in Part A will be used as baseline for both Part A and Part B.

Table 10 provides the objectives and endpoints for Part B (from dosing at Study Week 28 [Day 197] through the End of Study). All objectives and endpoints for Part B are exploratory.

Table 10: Study Objectives and Endpoints – Part B

Part B	
Objectives	**Endpoints**
Exploratory	

1) To evaluate the effects of all dose-regimens of MET097 in body weight reduction and other weight-related parameters in Part B	• Percent change from baseline in body weight at all Part B protocol-specified post-baseline measurements.
	• Occurrence of body weight reduction (weight loss) at all Part B protocol-specified measurements that is: ≥5%, ≥10%, ≥15%, ≥20%
	• Change from baseline (at all Part B protocol-specified measurements) in:
	  ○ Body weight (kg)
	  ○ Body Mass Index (kg/m²)
	  ○ Waist circumference (cm)

2) To evaluate the safety and tolerability of all dose-regimens of MET097 in Part B	The following safety and tolerability endpoints will be measured in Part B: • Occurrence and severity of treatment-emergent adverse events (TEAEs) • Occurrence of abnormal clinically significant physical examination • Occurrence of abnormal clinically significant 12-lead electrocardiogram (ECG) measurements • Occurrence of abnormal clinically significant clinical laboratory measurements • Columbia-Suicide Severity Rating Scale (C-SSRS) • Patient Health Questionnaire (PHQ-9) • Occurrence of anti-drug antibodies (ADAs)

3) To evaluate the pharmacokinetics of all dose-regimens of MET097 in Part B	The following endpoints will be measured in Part B for all participants: • Minimum observed concentration (C_{min}) • Other PK parameters may be evaluated • MET097 concentrations will be summarized

The last available measurement prior to first dose received in Part A will be used as baseline for both Part A and Part B.

Part A Estimand(s)

Primary Efficacy Estimand (for the primary endpoint): The attributes of the primary efficacy estimand are described below:

1) Target Population: All overweight and obese adults aged 18 to 70 years, with a BMI of 27 to 50 kg/m^2
2) Variable: Percent change from baseline in body weight at Week 28 (Day 197), calculated as follows:
   $100 \times \left(\frac{\text{body weight at Day 197 } - \text{body weight at baseline}}{\text{body weight at baseline}}\right)$
   where baseline is defined as the last available pre-dose body weight measurement.
3) Population Level Summary: Mean difference in percent change from baseline at Week 28 (Day 197) between MET097 and Placebo
4) Treatment: MET097 doses of 0.4 mg, 0.6 mg, 0.9 mg and 1.2 mg or Placebo
5) Intercurrent Event (ICE): The ICEs for the primary efficacy estimand are:
   (i) Premature discontinuation of treatment
   (ii) Non-adherence to the following additional protocol-specified study treatment compliance requirements (as per Section 5.7.3):
      a) 2 or more consecutive missed doses
      b) >3 of first 8 doses missed (Study Week 7)
      c) Single missed dose between dose 8 and dose 16 (between Study Week 7 and Study Week 15)
      d) 2 nonconsecutive missed doses after dose 16 (Study Week 15)
   (iii) Lifestyle changes that could impact weight loss (ie, use of other weight loss interventions such as weight-loss medications or bariatric surgery or commercial weight loss programs)

Part A Primary Efficacy Estimand:

The mean treatment difference in percent change from baseline body weight (kg) at Day 197, following 28 weeks of study treatment) for MET097 SC doses relative to placebo, among participants with obesity or overweight, aged 18 to 70 years, with BMI of 27 to 50 kg/m^2, under the hypothetical scenario that they remained on treatment for the entire duration of the treatment period, without any changes to lifestyle that could impact weight loss (ie, use of other weight loss interventions such as weight-loss medications or bariatric surgery or commercial weight-loss programs) [Wharton et al, 2021; Jastreboff et al, 2022].

Part A Supplementary Efficacy Estimand (for the primary endpoint):

The mean treatment difference in percent change from baseline body weight (kg) at Day 197 (following 28 weeks of study treatment) for MET097 SC doses relative to placebo, among participants with obesity or overweight, aged 18 to 70 years, with BMI of 27 to 50 kg/m^2, regardless of adherence to study treatment or lifestyle changes.

3. STUDY DESIGN

3.1. Overall Study Design

Part A

This is a Phase 2b, multi-center, randomized, double-blind, placebo-controlled study to investigate the efficacy and safety of four different dose levels of MET097 vs. placebo for body weight loss in adult participants (aged 18 to 70) with obesity or overweight (body mass index [BMI] 27 to 50 kg/m^2,) after 28 weeks of once-weekly dosing.

Approximately 225 participants will be randomized in a 1:1:1:1:1 ratio to one of 5 treatment arms (n=45 per treatment arm) as shown in the study schematic (Figure 3). Randomization will be stratified by CCI and the accrual of CCI will be capped at CCI to ensure at least CCI. Each treatment arm will be comprised of a subset of CCI participants that will undergo intensive pharmacokinetic (PK) draws during inpatient visits at the first, Week 16 (post steady-state), and last doses in addition to limited trough samplings. The remaining CCI participants per treatment arm will be outpatient visits and undergo limited PK sampling only. The intensive PK sampling subset (ie, CCI participants per treatment regimen) will not be stratified by CCI

No interim analyses (for potential modification of the ongoing trial) are planned. The primary reporting milestone (ie, the first unblinded analysis) for the primary analysis (Part A, Day 197) will occur when all (ie, N=~225) participants have completed their Day 197 visit (or permanently discontinued from the study prior to Day 197). Specifically, this reporting milestone will occur when all participants have completed their dosing period but before all participants have completed their safety follow-up period. Complete details will be documented in the study statistical analysis plan (SAP) which will be finalized prior to unblinding for this planned reporting milestone.

Part B

Enrollment in Part B is optional and available only to participants who have completed Week 28 (Day 197) assessments and procedures for the primary reporting milestone, shown good compliance throughout Part A (as determined by PI), do not meet any study discontinuation criteria and sign an informed consent. For participants who elect to continue to Part B, additional double-blind visits will occur in Part B to maintain the double-blind in Part A. Investigators, participants, and Sponsor personnel directly involved in the conduct of the study will remain blinded to participant-level treatment allocation in Part B from the dosing at Week 28 (Day 197) until the first participant reaches Week 40 (Day 281).

Part B participants will receive an additional 8 weeks of QW MET097 treatment followed by 24 weeks of either a QW, Q2W, or QM dose regimen as described in Table 11. All participants will be followed for an additional 12 weeks (covering >5 half-lives of MET097) after administration of the last dose of study medication for safety and efficacy assessments for a total duration of up to 75 weeks (including up to a 4-week Screening Period).

Table 11: Summary of Dosing and Blinding Status for Part A and Part B

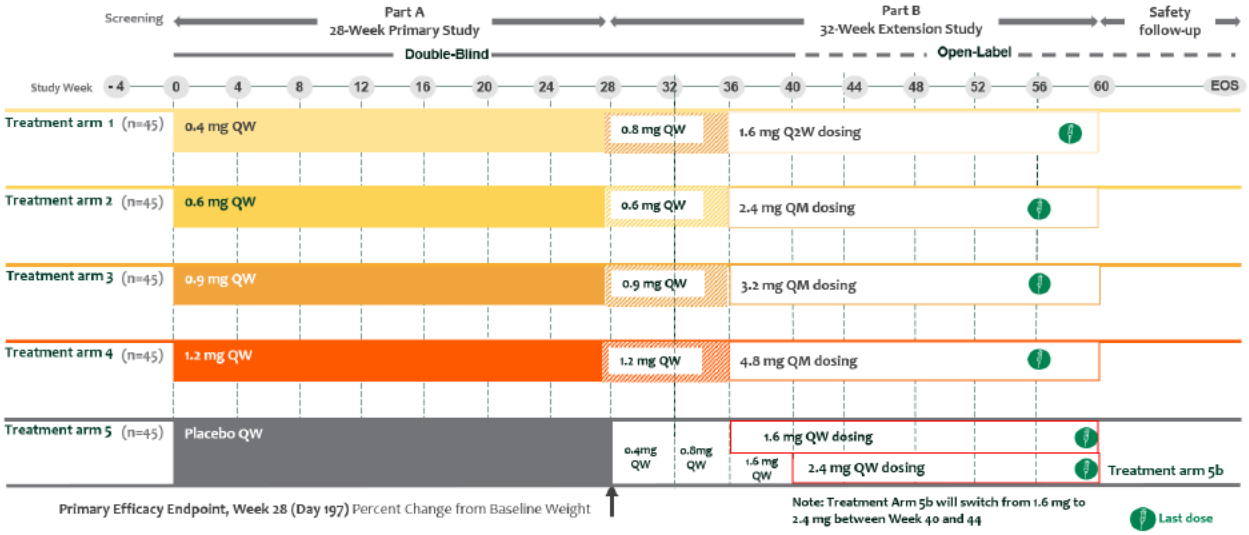
Treatment Arm	Part A Double-Blind Phase	Part B*		
		Double-Blind Phase		Open-Label Phase
	*From Study Week 0 through pre-dose Study Week 28**	*From the dosing of Study Week 28 through pre-dose Study Week 36*	*From the dosing Study Week 36 through pre-dose Study Week 40*	*From the dosing Study Weeks 40 through End of Study*
Treatment Arm 1	0.4 mg	0.8 mg QW	1.6 mg Q2W	1.6 mg Q2W
Treatment Arm 2	0.6 mg	0.6 mg QW	2.4 mg QM	2.4 mg QM
Treatment Arm 3	0.9 mg	0.9 mg QW	3.2 mg QM	3.2 mg QM
Treatment Arm 4	1.2 mg	1.2 mg QW	4.8 mg QM	4.8 mg QM
Treatment Arm 5	Placebo	0.4mg/0.8 mg QW	1.6 mg QW	1.6 mg QW (Arm 5A) 2.4 mg QW (Arm 5B)**

*For participants who opt out of Part B, the double-blind phase continues through the safety follow-up until End-of-Study

**The first half of participants in Treatment Arm 5 (n=~24) will continue on the 1.6 mg QW regimen for the remainder of the study (Arm 5A) while the second half of participants in this treatment arm will be given 2.4 mg QW (n=up to 24; Arm 5B) starting at Week 40 for the remainer of the study. Participants in Arm 5B have an additional 4-week window during which they may start the 2.4 mg QW regimen (eg, may start 2.4 mg up to Week 44), for operational purposes.

The final study database lock and final study analysis (for inclusion in the clinical study report), will occur after all participants have completed both Part A and Part B dosing periods as well as the subsequent safety follow-up period.

Figure 3: MET097-24-201 Study Design Schema



EOS = end of study.

Note: The final On Treatment Assessment visit occurs at Week 60 for all participants. The Safety Follow-up Period is 12 weeks following the last dose (green icons) administered in each specific treatment arm. As the timing of the final dose administered differs across the 5 treatment arms, the Safety Follow-up Visit occurs at different times (Week 70 for arm 1, Week 68 for arms 2, 3, and 4, and Week 71 for arm 5).

3.2. Randomization

Approximately 225 participants will be randomized in a 1:1:1:1:1 ratio to one of 5 treatment regimens as shown in the study schematic (Figure 3).

Randomization of participants will be stratified by CCI and the accrual of CCI will be capped CCI among study participants. The intensive PK sampling subset (ie, CCI participants per treatment regimen) will not be stratified by CCI

3.3. Scientific Rationale

MET097 is a GLP-1RA. GLP-1RAs leverage the known physiology of native GLP-1. GLP-1 lowers glucose [Vilsbøll et al, 2003, Ramracheya et al, 2018] and slows gastric emptying [Nakatani et al, 2017]. While important in the regulation of glycemic control, GLP-1RAs also decrease appetite and are thought to lower weight primarily by this mechanism [Drucker, 2022].

MET097 is an analog of human GLP-1 being evaluated as an adjunct treatment for body weight loss to a reduced calorie diet and increased physical activity for chronic weight management in adults. MET097 may offer enhanced efficacy and tolerability aiming to provide better value and health outcomes with less burden for people with obesity. GLP-1RAs typically have a short half-life and have to be dose escalated to increase tolerability.

The study population will consist of a target population and includes males and females with obesity or overweight (BMI 27.0 to 50 kg/m^2).

It is well known that a gradual increase in plasma exposure to the target dose is required to mitigate gastrointestinal side effects with GLP-1RA treatment. For GLP-1RAs with a shorter half-life, this is accomplished through fixed-dose escalation regimens. MET097's half-life, which is at least twice as long as that of other GLP-1RAs, allows for a gradual increase in exposure without dose escalation, as confirmed in the MAD phase of Study MET097-23-101.

Part A

A 28-week treatment period is anticipated to be sufficient to capture the maximal or near-maximal weight loss effects, key cardiometabolic parameters (eg, HbA1c, blood pressure, and lipids), safety/tolerability profile, and PK characteristics of MET097. Additionally, this study will be used to inform dose selection for Phase 3 trials.

Participants that elect not to continue in the study extension (Part B) will complete the Part A Post-Treatment Follow-up Period as specified in Table 2.

Part B

To maintain blinding of participants and site personnel to Part A, the first 12 weeks of Part B will require uniform weekly visits across all treatment arms.

The study extension will evaluate the effect on body weight reduction and provide longer-term safety data with MET097 for an additional 12 weeks of double-blind treatment (baseline to Week 40). The 20-week open-label extension period will evaluate the effect on body weight with different MET097 dosing regimens, once-monthly doses of switching from QW to QM or Q2W

dosing of MET097. Additionally, Part B will assess the safety and tolerability of switching from QW to QM dosing of MET097.

Lastly, Part B will assess the effect on body weight following a switch from placebo to MET097 QW (1.6 mg or 2.4 mg; using a titration regimen) as well as to assess the safety and tolerability of the dose switch.

3.4. Dose Justification

3.4.1. Once Weekly, Twice Weekly (Q2W), and Once Monthly (QM) Dosing of MET097

Part A

MET097 doses selected for evaluation in Part A of this study were 0.4 mg, 0.6 mg, 0.9 mg, and 1.2 mg once weekly for 28 doses SC. These doses were selected based upon PK, safety, and activity data in participants with obesity or overweight, but otherwise healthy participants in study MET097-23-101.

In study MET097-23-101, data from the participants who were administered MET097 0.16 mg to 1.6 mg as a single SC dose or MET097 doses from 0.2 mg to 1.2 mg once weekly for five doses SC indicate that MET097 has been well tolerated. Accordingly, the dose levels for this study are within the range of the doses studied within the SAD/MAD segments of the MET097-23-101 study and deemed safe and tolerable for further evaluation in a longer Phase 2 trial.

The dose levels in this Phase 2b study were further selected to inform the benefit-risk of subsequent dose levels selected for future development of MET097. Preliminary exploratory population pharmacokinetic (POPPK), exposure-safety (ES), and exposure-response (ER) analyses were performed using available preliminary PK data and safety and body weight data from 06 August 2024. The preliminary ES analysis identified a statistically significant relationship (p-value < 0.05) between Week 1 MET097 maximum observed concentration (C_{max}) and incidence of moderate or severe nausea or any vomiting following the first weekly dose of MET097. Doses were selected to further inform distinct regions of the ES relationship between MET097 C_{max} and incidence of moderate or severe nausea or any vomiting. The preliminary ES model suggests the probability (90% confidence interval [CI]) of moderate or severe nausea or any vomiting following a single MET097 dose of 0.4 mg, 0.6 mg, 0.9 mg, and 1.2 mg would be 0.111 (0.05, 0.227), 0.165 (0.092, 0.276), 0.268 (0.173, 0.389), and 0.404 (0.251, 0.579), respectively. The preliminary ER analysis examined the relationship between available longitudinal change from baseline body weight data (ΔWT) and MET097 weekly average concentration via an indirect response PK/PD model. Doses were selected to further inform distinct regions of the ER relationship for ΔWT. The preliminary ER model suggests the Week 4 median ΔWT (90% CI) following MET097 0.4 mg, 0.6 mg, 0.9 mg, and 1.2 mg would be CCI [redacted] kg, respectively.

The GLP toxicity data support doses of 0.4 mg, 0.6 mg, 0.9 mg, and 1.2 mg in this Phase 2b study. In MET097 rat and minipig toxicology studies completed to date the expected pharmacology of GLP-1R agonists were observed. Reduced body weight gain and food consumption were considered on-target pharmacology. Secondary to reduced weight gain and

food consumption, clinical signs such as a decrease in activity, thin body condition and decreased appetite in the minipig were observed. Nonadverse minor changes in clinical chemistry parameters were also observed.

In the 4- and 13-week repeat-dose study in rats, which included an extended dose Ramping Phase, the three times weekly SC administration of MET097 doses up to CCI µg/kg/dose for 4 and 13-weeks during the Main Phase were well tolerated and did not result in overt signs of toxicity. No MET097-related microscopic changes were observed, and the no-observed-adverse effect level (NOAEL) was assigned at the high dose (CCI µg/kg/dose) in both studies.

In the 4- and 13-week repeat-dose study in minipigs, following an extended Dose Ramping Phase, the twice weekly SC administration of MET097 doses up to CCI µg/kg/dose for 4- and 13-weeks during the Main Phase was well tolerated and did not result in any overt signs of toxicity. In the 4-week study, MET097-related increases in lymphocyte cellularity of the white and red pulp were observed in the animals treated at dose level of CCI µg/kg. Microscopic changes at the dosing changes were also observed in individual animals dosed at CCI µg/kg. These changes partially/fully recovered at the end of recovery period. In both the 4- and 13-week studies the NOAEL was assigned at the high dose (CCI µg/kg/dose), and in the 13-week study, this dose level corresponds to a Main Phase Day 88/89 MET097 CCI

Twenty-six-week GLP toxicity studies in rats and Göttingen minipigs have recently completed. A summary of study results is provided in Section 1.3.2.

Part B

For Part B, QW, Q2W and QM dosing is to be explored. The QM and Q2W dosing regimens were selected based upon PK, safety, and PD/efficacy data in participants with obesity or overweight, but otherwise healthy participants in study MET097-23-101, as well as based on the design and selection of doses in the ongoing MET097-24-202 and MET097-24-203 studies. Data from single MET097 doses up to 4.8 mg have been well-tolerated when included as a titration regimen with multiple weeks of QW MET097 at 2X or 4X lower doses (MET097-23-101 Part C). Considering the totality of available preliminary results from Study MET097-23-101 Part C, the QW dose regimens of 0.4 mg/0.8 mg/1.6 mg and 0.4 mg/0.8 mg/1.6 mg/2.4 mg, the Q2W dose of 1.6 mg and the QM doses of 2.4, 3.2 mg or 4.8 mg of this study are expected to be well tolerated, and provide participants with clinically meaningful weight loss.

4. PARTICIPANT ENROLLMENT

Approximately 225 participants will be randomized in a 1:1:1:1:1 ratio into one of 5 treatment regimens (n=45/arm).

4.1. Inclusion Criteria

- Provision of signed and dated informed consent form (ICF)
- Adult (≥18 to ≤70 years) male and female participants
- Have a BMI at Screening of
  - BMI ≥30 kg/m^2 and ≤50.0 kg/m^2 (may have the weight-related co-morbidities listed below)
  - BMI ≥27.0 kg/m^2 to <30.0 kg/m^2 must have at least one of the following weight-related co-morbidities:
    - Hypertension: on blood pressure (BP)-lowering medication or having systolic BP ≥130 mmHg or diastolic BP ≥80 mmHg at Screening
    - Dyslipidemia: on lipid-lowering medication or having low-density lipoprotein-cholesterol (LDL-C) ≥160 mg/dL (4.1 mmol/L) or triglycerides ≥150 mg/dL (1.7 mmol/L), or high-density lipoprotein-cholesterol (HDL-C) <40 mg/dL (1.0 mmol/L) for men or HDL-C <50 mg/dL (1.3 mmol/L) for women at Screening
- Participant has stable body weight (defined as a self-reported change [increase or decrease] in body weight ≤5 kg) within 3 months prior to Screening.

4.1.1. Inclusion Criteria – Part B (Study Extension)

1. Completion of the Week 28 (Day 197) assessments and procedures for evaluation of the primary reporting milestone in Part A and demonstrated compliance with all protocol requirements throughout the duration of the primary study as designated by PI.
2. Provision of signed and dated ICF for Part B (Study Extension).
3. Willingness and ability to comply with scheduled visits, treatment plan, laboratory tests, and other protocol-specified assessments and procedures for Part B.

4.2. Exclusion Criteria

Pregnancy/contraception

1. Female who is lactating or who is pregnant according to the pregnancy test at Screening or prior to dosing on Day 1 or Day -1 for subset of intensive PK participants
2. Unwilling or unable to follow contraceptive requirements as detailed in Appendix 1

Labs, Vitals, ECG

3. Resting heart rate >100 beats per minute at Screening

4. Estimated glomerular filtration rate (eGFR) <75 mL/min/1.73 m^2, as determined by the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) at the Screening visit
5. Aspartate aminotransferase (AST) or ALT level ≥ 1.5 × upper limit of normal (ULN) or total bilirubin level ≥ 1.5 × ULN (except cases of Gilbert's Syndrome) at the Screening visit
6. Thyroid-stimulating hormone (TSH) level lower than 0.4 mIU/L or higher than 6.0 mIU/L at the Screening visit. Note: participants receiving treatment for hypothyroidism may be included, provided their thyroid hormone replacement dose has been stable for at least 6 months.
7. Calcitonin value > 1.5 × ULN at the Screening visit
8. Uncontrolled hyperlipidemia: LDL-C ≥ 5.2 mmol/L (≥200 mg/dL), or fasting triglycerides ≥ 5.6 mmol/L (≥500 mg/dL) whether on lipid lowering therapies or not at screening visit.
9. Poorly controlled hypertension, defined as any of the following:
    - Mean seated systolic BP ≥160 mm Hg or mean seated diastolic BP ≥95 mm Hg at Screening visit
    - A change in antihypertensive medications within 30 days of Screening visit
    - Renal artery stenosis, or evidence of labile blood pressure including symptomatic postural hypotension at Screening visit
10. Any other clinically significant abnormalities in laboratory test results at the Screening visit that would, in the opinion of the investigator, increase the participant's risk of participation, jeopardize complete participation in the study, or compromise interpretation of study data
11. Presence of clinically significant ECG abnormalities at the Screening visit or prior to dosing on Day 1

Medication Restrictions

12. Use of dietary weight loss supplements within 7 days or 5 half-lives (whichever is longer) of the first study drug administration
13. Exposure, defined as a single dose, of GLP-1, incretin, other nutrient-stimulated hormone (NuSH), or any investigational product in the prior 60 days, or five half-lives (whichever is longer), prior to first study drug administration
14. Treatment, defined as multiple doses for more than 28 days, of GLP-1, incretin, other NuSH, or any investigational product in the prior 6 months, prior to first study drug administration

Medical History Restrictions

15. Participant has significant cardiovascular disease including but not limited to unstable angina or valvular heart disease or has a history of myocardial infarction, coronary artery bypass graft, percutaneous coronary artery re-vascularization, or congestive heart failure.
16. History of stroke

17. Ongoing or history of frequent intermittent or chronic tachyarrhythmia syndromes (such as atrial fibrillation, supraventricular tachycardia, and positional orthostatic tachycardia syndrome).

    Note: Participants with history of premature atrial contractions or premature ventricular contractions may be included.

18. History of treatment with MET097
19. History of severe hypersensitivity reactions (like angioedema) to any drugs
20. Clinically significant gastric emptying abnormality (for example, severe diabetic gastroparesis or gastric outlet obstruction) or chronically take drugs that directly affect GI motility
21. History of significant active or unstable Major Depressive Disorder or other severe psychiatric disorder (for example, schizophrenia, bipolar disorder, or other serious mood or anxiety disorder) within the last 2 years
22. Any lifetime history of suicide attempt, as declared by the participants or reported in medical records
23. Showing suicidal tendency as per the Columbia-Suicide Severity Rating Scale (C-SSRS) at Screening (Applicable Version) by answering "yes" to Question 4 or 5 in the "Suicidal Ideation" sections or "yes" to any of the suicide-related behaviors within their lifetime in the “Suicidal Behavior” sections of questionnaires.
24. The participant has a Patient Health Questionnaire 9 (PHQ-9) score of ≥ 10 at Screening.
25. Diagnosis of diabetes (Type 1 or T2DM) or glycated hemoglobin A1c (HbA1c) ≥ 6.5% or fasting plasma glucose >125 mg/dL at the Screening visit or history of taking any medications to lower glucose
26. Personal or family history of medullary thyroid carcinoma or multiple endocrine neoplasia type 2
27. History of acute or chronic pancreatitis or pancreatic cancer
28. History of neoplastic disease with the exception of adequately treated basal cell skin cancer or carcinoma in situ of the cervix
29. Obesity induced by endocrinologic disorders (for example, Cushing’s syndrome) or diagnosed monogenetic or syndromic forms of obesity (for example, Melanocortin 4 Receptor deficiency or Prader–Willi Syndrome)
30. Have a history of symptomatic gallbladder disease within the past 2 years, defined by the presence of gallstones on an imaging study and abdominal pain attributed to the gallstones by the participant’s physician; participants who had a procedure to remove the gallstones and/or the gallbladder (cholecystectomy), with no long-term complications, are eligible for participation as long as the procedure was completed at least 3 months prior to Screening
31. Positive Screening visit results to human immunodeficiency virus (HIV) antigen/antibody combo, hepatitis B surface antigen, or hepatitis C virus tests

32. Relevant surgical history including all bariatric or weight loss surgeries (invasive, minimally invasive, and noninvasive approaches)
33. Acute gastrointestinal symptoms (eg, nausea, vomiting, diarrhea, heartburn) at the time of the Screening visit or prior to dosing on Day 1
34. Any clinically significant illness or hospitalization in the 28 days prior to the first study drug administration including acute infection (eg, influenza or Coronavirus Disease 2019)
35. Participant has participated (or has plans to do so) in a weight loss program with or without pharmacotherapy during the 3 months prior to study drug administration

Drug/Alcohol Use Restrictions

36. History of alcohol abuse or alcohol dependence according to medical history within the last 2 years
37. History of drug or substance abuse according to medical history within the last 2 years
38. Positive test result for drugs of abuse at screening. Periodic testing will be done throughout study; if a participant has a positive result the investigator will discharge the participant from the study
39. Positive test result for alcohol at screening. Otherwise, alcohol intake will be limited to a maximum of 2 units per day until end of study. One unit of alcohol is defined as 14 grams of pure alcohol, (ie, 360 mL [12 ounces] beer or lager [5% alcohol], 240 ml [8 ounces] malt liquor [7% alcohol), 160 mL [5 ounces] of wine [12% alcohol], or 45 mL [1.5 ounces] distilled spirits [40% alcohol]). Throughout the study (including in between the return visits), in case of any doubt about alcohol consumption, a test for alcohol may be performed if requested by an investigator

General Restrictions

40. Cannot communicate reliably with the investigator

Blood Donation Restrictions

41. Donation of plasma in the 7 days prior to the first study drug administration
42. Donation of one unit of blood or donation of over 500 mL of blood in the 56 days prior to the first study drug administration

Other Exclusions

43. Any investigator or site personnel directly affiliated with this study and/or their immediate families. Immediate family is defined as a spouse, parent, child, or sibling, whether biological or legally adopted.
44. Participant, in the opinion of the investigator or Sponsor, is unsuitable for inclusion in the study
45. Participating, or plan to participate, in any other ongoing clinical trials during the course of this study

4.3. Screen Failures/Re-screening

Individuals who do not meet the criteria for participation in this study (screen failures) due to out-of-range vital signs or laboratory values that do not meet study parameters that are, in the opinion of the investigator, due to a short-term acute condition or are not clinically significant, may be repeated **or** the participant may be rescreened only once at the discretion of the investigator.

Before rescreening is performed, the participant must sign a new ICF and receive a new identification number. If, in the opinion of the investigator, an ineligible lab test result is the result of an error or extenuating circumstance, then that parameter can be retested once (if feasible within the time constraints of the screening period) without the participant having to be rescreened. The exception to this rule is re-testing or re-screening if the lab in question is HbA1c.

4.4. Lifestyle and/or Dietary Requirements

- *Dietary and Lifestyle Recommendations:* Study participants will receive diet and exercise guidelines by a qualified professional prior to the first study drug administration. Participants should follow a healthy lifestyle plan throughout the course of the study as recommended by Dietary Guidelines for Americans, 2020.
- *Strategies to Mitigate GI Symptoms:* Participants will be provided food and dietary guidance that assists in minimizing GI symptoms such as avoiding high fat foods, eating high fiber foods, eating smaller portions more slowly and remaining upright but avoiding being too active immediately after eating. The participant's diet and lifestyle will be discussed at frequent timepoints outlined in Table 1, Table 2, Table 4, Table 5, Table 6, Table 7, and Table 8 between site personnel and the participant to maximize adherence. Additionally, participants will be educated regarding early use of anti-emetics.
- Participants will be instructed to refrain from consuming alcohol for 48 hours prior to each in-house stay (PK subset of participants only), during the in-house visit (PK subset of participants only), and for 24 hours prior to each return visit. Otherwise, alcohol intake will be limited to a maximum of 2 units per day until end of study (see Section 4.2, Exclusion Criteria 39).
- Participants will be asked to maintain their lifestyle with respect to eating and exercise habits, and sleeping patterns, based on guidance provided, from the Screening visit through to the end of study.
- Participants will be instructed not to donate blood or blood products during the study or for 8 weeks following the study.
- Participants will be required to fast for at least 8 hours prior to return visits.
- Female participants of childbearing potential will have to take appropriate measures to prevent pregnancy as described in Appendix 1. It is the participant's responsibility to notify the site if a pregnancy occurs from the end of their study participation until 90 days, after the last dose of the study drug.
- Males who are sexually active will be made aware of the possible male-mediated fetal toxicity associated with the study drug. Male participants will be expected to use an acceptable contraceptive regimen and not to donate sperm as described in Appendix 1. It

is the participant's responsibility to notify the site if their female partner gets pregnant from the start of their study participation until 90 days after the last dose of the study drug.

4.5. Concomitant Medications

4.5.1. Concomitant Medications for Concurrent Medical Conditions

Doses of other prescription medications (eg, thyroxine, estrogen or progesterone replacement, or selective estrogen receptor modulators) for treatment of concurrent medical conditions should remain constant during the study whenever possible. Additionally, doses for antihypertensives and lipid-lowering therapies must be stable for 30 days prior to randomization. Dose of these medications should not be changed during the trial, if possible.

4.5.2. Medications Known to Slow Gastric Emptying

GLP-1RAs are known to slow gastric emptying [Maideen, 2019]. The administration of concomitant medications affected by slowed gastric emptying should be determined by the site investigator based on relevant medical need.

4.5.3. Excluded Concomitant Medications

In addition to concomitant therapy outlined in the Exclusion Criteria (Section 4.2), the following concomitant medications are excluded:

- Chronic use of drugs that directly reduce GI motility including but not limited to anticholinergics, antiemetics, and opiates (eg, metoclopramide, phenergan, dicyclomine, and morphine)
- Chronic use of medications that directly promote motility (eg, bethanechol and cisapride)
- Prescription or over-the-counter medications to promote weight loss
- Systemic glucocorticoid therapy of greater than 14 consecutive days' duration (with the exception of topical, intranasal, intraocular, intra-articular, and inhaled preparations)
- Central nervous system stimulants (eg, Ritalin-SR)
- Any drug, other than those provided in this study, that has not received regulatory approval

4.5.4. Allowed Concomitant Medications in Certain Circumstances

If the need for additional concomitant medication arises, the participant may continue in the study on medication if, in the investigator's opinion, the addition of the new medication does not pose a safety risk. Any additional medication used during the course of the study (including those not requiring Sponsor notifications) must be documented on the appropriate electronic case report form (eCRF) from time ICF is signed until the end of study.

5. STUDY TREATMENTS

5.1. Study Treatments

5.1.1. Study Treatments – Part A

The following study drugs will be administered in Part A according to the Study Schema (Figure 3).

- Investigational Product: A single SC injection of MET097 will be administered once weekly (7 days apart).
- Placebo: A single SC injection of placebo-to-match MET097 will be administered once weekly (7 days apart).

After randomization, participants meeting all study eligibility criteria will receive 28 doses of study treatment once weekly from Week 0 (Day 1) through Week 27 (Day 190). The final Week 28 (Day 197) assessments will occur 1 week after the last dose of study treatment.

There are no restrictions on the time of day each dose of study treatment is given, but it is advisable to administer the SC injection at approximately the same time of day for each dose. The date, time and location of each dose will be recorded.

5.1.2. Study Treatments – Part B

The following study drugs will be administered in Part B according to the Study Schema (Figure 3).

Investigational Product:

- Treatment Arm 1: A single SC injection of MET097 will be administered once weekly (7 days apart) for Weeks 28 to Week 35. Followed by Q2W doses starting at Week 36 through Week 58.
- Treatment Arms 2, 3, and 4: A single SC injection of MET097 will be administered once weekly (7 days apart) for Weeks 28 to Week 35. Followed by QM doses starting at Week 36 through Week 56.
- Treatment Arm 5: A single SC injection of MET097 once weekly (7 days apart) from Week 28 through Week 59.

After completion of Part A, with participants meeting all Part B study eligibility criteria, and having signed a Part B ICF will receive treatments according to the Study Schema (Figure 3).

There are no restrictions on the time of day each dose of study treatment is given, but it is advisable to administer the SC injection at approximately the same time of day for each dose. The date, time and location of each dose will be recorded.

5.2. Treatment and Dosing

Approximately 225 participants will be randomized into one of five treatment arms (n=45/arm) (Figure 3).

5.2.1. Treatment Phase Dosing

Weekly dosing in Part A will consist of participants being randomized to MET097 (one of 4 dose levels) or placebo. Participants will be dosed 28 times once weekly. Part B will be open label dosing of 5 treatment regimens (weekly, biweekly, or monthly) as shown in Figure 3.

5.2.2. Activity Immediately After Dosing

Participants will remain seated or semi-reclined until the investigator determines it is safe for the participant to stand up. However, should AEs occur, participants may be placed in an appropriate position. During this interval, participants will be permitted to get up under supervision. Participants will not engage in strenuous activity at any time during outpatient visits.

5.3. Investigational Product

5.3.1. MET097 Drug Product Administered in Part A (Primary Study)

MET097 is being developed by the Sponsor for SC injection. MET097 will be supplied by the Sponsor and is for investigational use only. The MET097 is a sterile, CCI [redacted] supplied as CCI [redacted]. There are CCI [redacted]

5.3.2. MET097 Drug Product Administered in Part B (Study Extension)

For Part B (Study Extension), MET097 will be supplied by the Sponsor and is for investigational use only. The MET097 is supplied as CCI [redacted] mg/mL each containing CCI [redacted] mL. The drug product is comprised of MET097 active ingredient in CCI [redacted] prior to administration according to pharmacy instructions.

5.4. Control Products

5.4.1. Placebo - Part A and Part B

For Part A and Part B, sterile 0.9% (w/v) saline will be used as placebo treatment during the study. The placebo visually matches MET097 as constituted for injection.

5.5. Investigational Product Management

5.5.1. Packaging, Labeling and Dispensing

The Sponsor will be responsible for ensuring that MET097 is manufactured in accordance with applicable current Good Manufacturing Practice regulations and requirements.

The MET097 will be labeled according to the requirements of local law and legislation. The MET097 will be dispensed by the site's pharmacy.

The details of the diluent and MET097 preparation steps will be provided in the Pharmacy Manual.

5.5.2. Storage and Handling

The site's pharmacy will maintain an inventory record of MET097 received, stored (in a secure restricted area), and dispensed.

MET097 should be stored at CCI and kept in a tightly closed container. The product should not be used if expired and should not be frozen when administered.

Placebo (0.9% normal saline) will be stored according to the manufacturer's specifications.

5.5.3. Method of Assigning Participants to Treatment Arms

The randomization code will be generated according to the study design, the number of participants, the number of study sites, and the number of treatment arms. The random allocation of each treatment to each participant will be done in such a way that the study is balanced. Once generated, the randomization code will be final and will not be modified. The study will cap the number of CCI in order to have at least CCI in the study.

5.5.4. Blinding

Part A

Part A is double-blinded (sponsor-, investigator- and participant-blinded) from randomization until the primary reporting milestone at Week 28 (Day 197). Investigators, participants, and Sponsor personnel directly involved in the conduct of the study will remain blinded to participant-level treatment allocation for the entire duration of the Part A of the study. The preparation and/or administration of the products will be done by designated personnel that are not directly involved in the clinical aspects of the trial.

Part B

Part B is double-blinded (sponsor-, investigator- and participant-blinded) from the dosing at Week 28 (Day 197) until the first participant reaches Week 40 (Day 281). Investigators, participants, and Sponsor personnel directly involved in the conduct of the study will remain blinded to participant-level treatment allocation in Part B from the dosing at Week 28 (Day 197) until the first participant reaches Week 40 (Day 281). The preparation and/or administration of the products will be done by designated personnel that are not directly involved in the clinical aspects of the trial.

Randomization

The randomization code will not be available to the physician and clinical staff involved in the collection, monitoring, revision, or evaluation of AEs, as well as clinical staff who could have an impact on the outcome of the study until all the case report forms (CRFs) have been approved, signed and the End of Study visit has been completed.

The randomization code must not be broken except in emergency situations where the identification of a participant's study treatment is required by an investigator for further treatment to the participant or to complete an SAE report. Randomization information will be held by designated individual(s). The date and reason for breaking the blind must be recorded and communicated to the Sponsor.

5.5.5. Study Drug Accountability

Complete and accurate inventory records of all study drugs will be maintained. This includes acknowledgment of receipt of each shipment of study product (quantity and condition).

At the conclusion of the study, all unused MET097 and medication containers will be destroyed per the site standard operating procedure (SOP) unless the sponsor approves other arrangements. Drug accountability will be performed at the completion of the trial.

5.6. Treatment of Participants – Administration of Study Drug

A SC dose of the assigned formulation will be administered in the abdomen. Administration sites will be rotated between quadrants (right lower quadrant, right upper quadrant, left upper quadrant, and left lower quadrant). The date, time and location of each dose will be recorded. For each participant, all scheduled activities and assessments will be performed relative to the time of study drug administration.

There are no restrictions on the time of day each dose of study treatment is given, but it is advisable to administer the SC injection at approximately the same time of day for each dose.

5.6.1. Treatment Compliance

The study drugs will be dispensed only to eligible participants and administered under the supervision of study personnel. Treatment compliance will be verified according to the site's SOPs.

5.7. Discontinuation and Withdrawal

5.7.1. Before First Treatment Administration

Before the first treatment administration, inclusion/exclusion criteria will govern the participants to be dosed. Participants randomized and subsequently withdrawn before first treatment administration will not be followed up and will not undergo End of Study/Early Termination assessments. Other safety assessments may be performed if required.

Participants are free to withdraw their consent to participate in the study at any time, without prejudice. The reason for their withdrawal or for deciding to end their participation will be documented.

5.7.2. After First Treatment Administration

5.7.2.1. Discontinuation and Withdrawal of Participants from Study Treatment and the Study

All participants have the right to withdraw from the study or study treatment at any point without prejudice. In addition, the investigator can discontinue any participant at any time if medically necessary. It will be documented whether or not each participant completed the clinical study. If study treatment or observations are discontinued, the reason will be recorded, and the Sponsor should be notified promptly.

The reasons that a participant may permanently discontinue, or the investigator may permanently discontinue a participant from a clinical study could be from one or more of the following:

- AE(s)
- Death
- Participant withdrew consent
- Lost to follow-up
- Pregnancy
- Participant unable or unwilling to comply with study visit schedule
- Other, specify

All data collected up until the time of participant withdrawal is to be entered into the eCRF. The applicable reason(s) above will be recorded in the eCRF and the investigator will ask the participant as soon as possible, if he/she is willing, to do any of the following:

Part A

1. Preferred: attend all future visits per Schedule of Activities (SoA) (Table 1 and Table 2)
2. Secondary: Participants will be encouraged to attend at least two follow-up visits, A visit 30 [±3] days after the last study drug administration with assessments performed according to SoA Week 28 (Day 197) and a visit 75 [±3] days after the last study drug administration with assessments performed according to SoA Week 39 (Day 274) which is phone visit (Table 1 and Table 2). Note: if participants choose to only attend one follow-up visit it should be 30 [±3] days after the last study drug administration with assessments performed according to SoA Week 28 (Day 197).
3. Tertiary: if subject declines to attend an in-person follow-up visit, they will be contacted for an end of study phone call (75 [±3] days after the last study drug administration; assessments performed according to SoA Week 39 (Day 274)

Participants who are unable or unwilling to continue in the study or with study treatment for any reason and don't agree to any of the options above must have an ET visit performed at their earliest convenience.

Part B

If a participant discontinues from taking study drug or discontinues in the study, the expectation will be to attend an EOS visit 12 weeks post last dose.

5.7.3. Missed Study Treatment

Every effort should be made to avoid missed study treatments. At the first dosing visit, a participant will be reminded of the possibility of GI tolerability issues as well as provided guidance on avoiding/managing GI tolerability issues. The guidance will include the early use of anti-emetics as well as information on appropriate food and diet such as avoiding high fat foods, eating high fiber foods, eating smaller portions more slowly and remaining upright but avoiding

being too active immediately after eating. A dose should only be withheld if such action(s) does not sufficiently address GI tolerability issues. During each subsequent visit, the participant's diet and lifestyle will be discussed between site personnel and the participant to maximize adherence.

An Investigator may withdraw a participant at any time if it is determined that continuing the study would result in a significant safety risk to the participant or if their behavior is deleterious to the study environment.

The investigator should contact the Sponsor within 24 hours of a missed dose. Every effort should be made by the investigator to keep the participant in the study. If a participant misses a dose, every effort should be made to have the participant return to the site and receive the next scheduled dose, according to the SoA (Table 1, Table 2, Table 4, Table 5, Table 6, Table 7, and Table 8). The predefined protocol deviations regarding missed doses are described in Table 12 for Part A and Table 13 for Part B.

Table 12: Predefined Protocol Deviations Regarding Missed Doses for Part A (Study Week 0 through pre-dose Study Week 28)

Missed Dose(s)*	Deviation (Y/N)?
2 or more consecutive doses	Y
>3 of first 8 doses (Study Week 0 through Study Week 7)	Y
Single missed dose between dose 8 and dose 16 (Study Week 8 through Study Week 15)	Y
2 nonconsecutive missed doses between dose 17 and dose 28 (Study Week 16 through Study Week 27)	Y

*Investigator, in consultation with the Sponsor, may remove the participant from study drug/study if it is determined that the participant is chronically non-compliant. Otherwise, the participant will remain on study drug.

Table 13: Predefined Protocol Deviations Regarding Missed Doses for Part B (From Dosing at Study Week 28 through End of Study)

Missed Dose(s)*	Deviation (Y/N)?
2 or more missed doses from dose 29 through dose 36 (Study Week 28 through Study Week 35)	Y
1 or more missed Q2W or QM dose after dose 36 (Study Week 36 through End of Study)	Y

*Investigator, in consultation with the Sponsor, may remove the participant from study drug/study if it is determined that the participant is chronically non-compliant. Otherwise, the participant will remain on study drug.

5.8. Dose Modification

Dose modifications are only allowed during Part B of the study. Participants are encouraged to stay on study drug throughout the clinical trial, preferably at their assigned dose level. However, dose de-escalation or interruption may be necessary in Part B if there is excessive weight loss. The following steps should be followed to mitigate excessive weight loss in participants in Part B.

1. If at any time during the Part B Extension Phase the BMI is <22.5 kg/m^2, the participant should decrease one dose level. For example:

a) If at 4.8 mg QM, decrease to 3.2 mg QM; if at 3.2 mg QM, decrease to 2.4 mg QM;

BMI then should be reassessed at each clinic visit prior to the next scheduled dosing.

2. If BMI continues to decrease to <22 kg/m^2, participant should reduce a second dose level and BMI should be reassessed at each clinic visit as above.
3. If BMI is < 20 kg/m^2, interrupt dose and re-assess each visit.
   a) If BMI returns to >22 kg/m^2 after dose interruption, participant may restart dosing at the dose level they were on prior to dose interruption.

In addition, if a participant cannot tolerate the study drug at any dose level during Part B, the PI should consult the Sponsor's medical monitor for potential dose modification.

If during any steps listed above, the participant is already at the lowest dose, stop dose and reassess at each clinic visit.

5.9. Lost to Follow-up

A participant will be considered lost to follow-up if he/she repeatedly fails to return for scheduled visits or is unable to be contacted by the study site. Site personnel are expected to make diligent attempts to contact participants who fail to return for a scheduled visit or were otherwise unable to be followed up by the site.

Site personnel, or an independent third party, will attempt to collect the vital status of the participant within legal and ethical boundaries for all participants randomized.

5.10. Stopping Rules

5.10.1. Individual Participant Study Drug Stopping Rules

Participants will stop study drug for any of the following reasons:

1. If a participant experiences an unacceptable AE, dosing will be discontinued. An unacceptable AE is defined as any severe AE and/or SAE judged as related to study treatment by the investigator.

2. Suspicion or diagnosis of pancreatitis or pancreatic cancer

3. If the participant develops any of the following liver related abnormalities:
   a. ALT or AST >8x ULN
   b. ALT or AST >5x ULN for more than 2 weeks
   c. ALT or AST >3x ULN and either total bilirubin >2x ULN or international normalized ratio (INR) >1.5
   d. ALT or AST >3x ULN associated with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)

e. Alkaline phosphatase (ALP) >3x ULN when the source of ALP is the liver
f. ALP >2.5x ULN and total bilirubin >2x ULN
g. ALP >2.5x ULN associated with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)
h. Diagnosis of cirrhosis after randomization

4. Diagnosis of medullary thyroid cancer after randomization
5. If the participant becomes pregnant or is nursing
6. Diagnosis of type 1 diabetes mellitus
7. Clinically significant QTc findings after consultation with the Sponsor medical monitor
8. Investigator Decision
   - The investigator decides that the participant should be discontinued from the study medication
9. Any excluded medication (Section 4.5.3)
10. Simultaneous participation in another clinical study of an approved or non-approved investigational medicinal product
11. Any other reason for discontinuation, eg, if an illness occurs that may invalidate the trial result
12. When any one of the following events occur, Sponsor designee is to be contacted immediately:
    - Pancreatitis or pancreatic cancer (refer to Section 7.2.5 for details)
    - eGFR <30 mL/min
    - Any severe or serious injection site reaction or 2 or more moderate injection site reactions occurring a week or more apart
    - Any significant study drug-related hypersensitivity reaction
    - Any nonfatal major adverse cardiovascular events (MACE) (refer to Section 7.2.6 for details)
    - Any other treatment emergent adverse event (TEAE), SAE, or clinically significant laboratory value for which the investigator believes that permanent study drug discontinuation is the appropriate measure to be taken

If study drug administration is permanently discontinued, the participant should remain in the study, if possible (see Section 5.7.2.1).

5.10.2. Study Stopping Rules

There will be ongoing review of AEs, clinical laboratory measures, vital sign parameters, ECGs, physical examinations and questionnaires to monitor participant safety.

The Sponsor may terminate this study, after informing investigators, at any time. Investigators will be notified by the Sponsor or designee if the study is placed on hold, completed, or closed. Study enrollment and study treatment administration will be temporarily suspended, and all data will be reviewed if any participant dies from a treatment-related AE within 7 days of study treatment administration.

5.11. Meals

Meals for participants as part of the intensive PK subsets that will have inpatient stays will have food intake monitored for each confinement period. Meals will be served where the content and the caloric quantities are known but not required to be the exact same between groups and sites. Meals should be eaten within 60 minutes of being provided to participants and the participants should eat until comfortably full.

5.12. Fluids

Fluids for participants as part of the intensive PK subsets that will have inpatient stays will have fluid intake other than water be controlled for each inpatient visit.

6. STUDY PROCEDURES AND ASSESSMENTS

An overview of the study activities for each participant is detailed in the SoA (Table 1, Table 2, Table 4, Table 5, Table 6, Table 7, and Table 8).

Unless otherwise stated in the protocol, the SOPs of the study facilities, which are available for all activities relevant to the quality of the study, will be followed during this study. When the nominal time for multiple events occurs simultaneously, the events will be staggered using their acceptable windows (acceptable windows for each assessment are specified in the following sections of this protocol), with priority given to those events related to primary study endpoints.

Unless otherwise stated in the subsections below, all samples collected for specified laboratory tests will be destroyed within 60 days of receipt of confirmed test results. Certain samples may be retained for a longer period, if necessary, to comply with applicable laws, regulations, or laboratory certification standards.

6.1. Informed Consent

This study will be conducted in compliance with Title 21 Part 50 of the US Code of Federal Regulations (CFR), Federal Regulations, Good Clinical Practice (GCP) guidelines, and ICH Guidance Documents pertaining to informed consent. At the Screening Visit or after a protocol amendment, , prior to initiation of any study-related assessments/procedures, participants will be informed about the nature and purpose of the study, participation/termination conditions, and risks and benefits. Participants will be given adequate time to ask questions and become familiar with the study prior to providing consent to participate. Participants will give their written consent to participate in the study and will be provided with a copy of the fully executed consent form for their records.

6.2. Treatment Phase

6.2.1. Outpatient Visits

The Screening visit will occur within approximately 28 days prior to the first scheduled study drug administration. Screening visit data will be reviewed to determine participant eligibility. Participants who meet all inclusion criteria and none of the exclusion criteria and who consent to participation will receive their first weekly dose of study drug on Day 1 after a baseline evaluation prior to dosing. All Screening visit results (collected from Day -28 to Day -1) will be available prior to study drug administration. Day 1 assessments will (as applicable) be used to confirm trial eligibility.

Part A

Dosing of the study drug across all five treatment arms may run concurrently, starting from Week 0 (Day 1) and continuing through Week 27, for a total of 28 weekly doses of MET097 or matching placebo administered on Days 1, 8, 15, 22, 29, 36, 43, 50, 57, 64, 71, 78, 85, 92, 99, 106, 113, 120, 127, 134, 141, 148, 155, 162, 169, 176, 183, and 190. Study drug will be administered during outpatient visits and will be required to remain in-clinic and undergo

applicable efficacy and safety evaluations (Table 1 and Table 2). The investigator will release the participant when all assessments have been completed and there are no safety issues.

Part B

Dosing of the study drug across all five treatment arms may run concurrently, starting from Week 28 (Day 197) and continuing up to Week 59 (for weekly treatment regimen). Study drug will be administered during outpatient visits and will be required to remain in-clinic and undergo applicable efficacy and safety evaluations (Table 4, Table 5, Table 6, Table 7, and Table 8).

6.2.2. Inpatient Visits – PK Subset Only

For participants that are part of the intensive PK sampling groups, the treatment phase will occur in line with Section 6.2.1 except that there will be three 5-day inpatient visits:

- First study dose (Day -1 to Day 4)
- Sixteenth study dose (Day 105 to Day 109)
- Last study dose (Day 189 to Day 193)

This intensive PK subset will have additional assessments (Table 3) during the inpatient stays compared to those participants that only have outpatient visits (Table 1 and Table 2).

There will be no intensive PK subset for Part B.

6.3. Safety/Study Assessments

Safety assessments will include AE monitoring (Section 7), physical examination, vital signs, 12-lead ECG, safety laboratory tests, C-SSRS, PHQ-9, occurrence of anti-drug antibodies (ADAs), and injection site inspections. At the discretion of an investigator, additional safety assessments may be performed as needed to ensure participant safety.

6.3.1. Inclusion/Exclusion Review

At the Screening Visit, the eligibility of the participant to participate in this study will be reviewed confirming all inclusion criteria and exclusion criteria. Participant eligibility will be reconfirmed for study inclusion on Day 1, unless the inclusion/exclusion criteria state that assessment is only being reviewed for eligibility at Screening Visit.

6.3.2. Demographics/Medical History

The medical history at the Screening visit will include all queries by the medical and clinical staff related to the participant's well-being and history of relevant past medical events/experiences. Medical history will include a complete review of systems and all demographic data (age, sex, race, body weight, height, and BMI), baseline characteristics and significant recent (5 year) medical history, including chronic and acute medical conditions during this period. Alcohol and smoking habits will also be recorded.

6.3.3. Physical Examination

A physical examination will be performed by a medically qualified and licensed individual as indicated in the SoA (Table 1, Table 2, Table 4, Table 5, Table 6, Table 7, and Table 8).

The physical examination will include a general review of the following body systems (at minimum): head and neck (including complete thyroid exam), cardiovascular, respiratory, gastrointestinal, brief neurological and general appearance, unless a brief physical exam is indicated.

6.3.4. Brief and Targeted Physical Examination

Part A (Brief)

A brief physical examination will be performed by a medically qualified and licensed individual as indicated in the SoA (Table 1 and Table 2).

The brief physical examination will be a a targeted systems review based on any clinical signs, symptoms, and/or AEs reported by participants, including cardiovascular, respiratory, gastrointestinal systems, as well as general appearance and/or other systems as needed.

Part B (Targeted)

The targeted physical exam will be a limited systems review based on any clinical signs, symptoms, and/or AEs reported by participants, including cardiovascular, respiratory, gastrointestinal systems, as well as general appearance and/or other systems as needed. See SOA (Table 4, Table 5, Table 6, Table 7, and Table 8).

6.3.5. Vital Signs

Vital signs (heart rate, blood pressure, and body temperature) will be measured as indicated in the SoA (Table 1, Table 2, Table 4, Table 5, Table 6, Table 7, and Table 8). Blood pressure and heart rate will be measured after being in a seated position with feet on the floor for at least 5 minutes and collected in triplicate and a mean value calculated. For all post-Screening heart rate measurements, the range for measurement limits will be ≤100 beats per minute (high) and ≥50 beats per minute (low). For all post-Screening blood pressure measurements, the range for systolic blood pressure measurement limits will be ≤160 mmHg (high) and ≥90 mmHg (low). For diastolic blood pressure measurements, the range limits will be ≤100 mmHg (high) and ≥50 mmHg (low).

6.3.6. Electrocardiogram (ECG)

Twelve-lead ECGs will be performed as indicated in the SoA (Table 1, Table 2, Table 4, Table 5, Table 6, Table 7, and Table 8). Twelve-lead ECGs will be measured after being in a supine position for at least 5 minutes. The participants not undergoing intensive PK will have a single ECG recorded at all applicable timepoints. When collection times for the ECG align with the collection time of the PK draws, the PK is to be collected within ≤1 hour of the ECG. On-study ECG measurements are further detailed in Table 14.

All participants in the intensive PK subsets of each treatment arm will have triplicate ECGs performed at all timepoints except at Screening. All screening ECG assessments will be a single

reading. There is no need to wait in between ECG assessments. Participants not in the intensive PK subsets will have only have one ECG assessment at scheduled timepoints.

Table 14: ECG Recording Schedule – Part A

Day	Time Period	Collection Window
Day 1	Predose	≤1 hour of corresponding PK
Day 2 (intensive PK subset only)	24 hours postdose	≤1 hour of corresponding PK
Day 3 (intensive PK subset only)	48 hours postdose	≤1 hour of corresponding PK
Day 4 (intensive PK subset only)	72 hours postdose	≤1 hour of corresponding PK
Days 8, 15, 22, 29, 36, 43, 50, 57, 64, 71, 78, 85, 92, 99, 106, 113, 141,169,	Predose	≤1 hour of corresponding PK
Day 107 (intensive PK subset only)	24 hours postdose	≤1 hour of corresponding PK
Day 108 (intensive PK subset only)	48 hours postdose	≤1 hour of corresponding PK
Day 109 (intensive PK subset only)	72 hours postdose	≤1 hour of corresponding PK
Day 190 (intensive PK subset only)	Predose	≤1 hour of corresponding PK
Day 191 (intensive PK subset only)	24 hours postdose	≤1 hour of corresponding PK
Day 192 (intensive PK subset only)	48 hours postdose	≤1 hour of corresponding PK
Day 193 (intensive PK subset only)	72 hours postdose	≤1 hour of corresponding PK
Day 197	Collected once at visit	≤1 hour of corresponding PK
Day 220 (only done if not enrolling in Part B)	Collected once at visit	≤1 hour of corresponding PK

ECG = electrocardiogram; PK=pharmacokinetic

Part B

For Part B, ECGs will be performed according to the SOAs (Table 4, Table 5, Table 6, Table 7, and Table 8) and will be a single recording.

6.3.7. Safety Laboratory Evaluations

The laboratory evaluations will be performed as indicated in the SoA (Table 1, Table 2, Table 4, Table 5, Table 6, Table 7, and Table 8).

The investigator or delegate in charge will assess each abnormal value to determine if it is clinically significant. Post dose clinically significant laboratory values will be reported as AEs, if applicable, as judged by the investigator or delegate in charge.

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

The C-SSRS is a questionnaire designed for the assessment of suicidal ideation and behavior in adolescents and adults.

To monitor for a history of or for the emergence of suicidal ideation and behavior, participants will undergo C-SSRS evaluations at the time points indicated in the SoA (Table 1, Table 2, Table 4, Table 5, Table 6, Table 7, and Table 8).

The questionnaire must be administered by an investigator or other individual that is suitably qualified by education or training. C-SSRS “Baseline/Screening” and “Since Last Visit” questionnaires will be available to utilize for the appropriate visit.

A participant who has a positive result after the Screening visit for suicidality on the C-SSRS, based on the validated scoring instructions, will be evaluated by an investigator or medically qualified sub-investigator and the study drug will be discontinued.

If a participant becomes suicidal during the study, an investigator or medically qualified sub-investigator should provide the appropriate treatment to the participant.

6.3.9. Patient Health Questionnaire (PHQ-9)

The PHQ-9 is a questionnaire designed to monitor and measure the severity of depression in participants.

To monitor improvement or worsening of depression in response to treatment, participants will complete a PHQ-9 questionnaire at the timepoints indicated in the SoA (Table 1, Table 2, Table 4, Table 5, Table 6, Table 7, and Table 8).

If a participant scores ≥10, corresponding to moderate depression, moderately severe, or severe depression after the Screening visit, the participant will be evaluated by an investigator or medically qualified sub-investigator for continuation of the study drug.

6.3.10. Anti-Drug Antibodies

All participants will have samples drawn at timepoints per the SoA (Table 1, Table 2, Table 4, Table 5, Table 6, Table 7, and Table 8) to assess for the development of ADAs. The ADA assessment will be run once the validated assay is available.

Serum blood sample collection, processing and shipping details will be outlined in a separate laboratory manual. Blood samples will be processed and serum analyzed for ADAs using a validated assay.

All samples confirmed positive for cross reactivity to MET097 may be analyzed for in vitro neutralizing antibodies to MET097, pending the development of an appropriate bioanalytic methodology.

6.3.11. Injection Site Inspection

The injection sites will be monitored at each dose administration for residual pain, tenderness, erythema, swelling/induration, and itching by clinical staff following each weekly injection of study drug as outlined in the SoA (Table 1, Table 2, Table 4, Table 5, Table 6, Table 7, and Table 8).

The abdominal area will also be inspected prior to each drug administration to ensure the quadrant where the weekly injection is going to administered is acceptable for the injection.

During follow up visits after the last dose, the abdominal area will be inspected for any residual pain, tenderness, erythema, swelling/induration, and itching by clinical staff.

Evaluation of pain, tenderness, erythema, swelling/induration, or itching at the injection site will be rated according to Table 15.

Table 15: Injection Site Reaction Evaluation

Local Reaction	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Pain	Does not interfere with activity	Repeated use of non-narcotic pain reliever >24 hours or interferes with activity	Any use of narcotic pain reliever or prevents daily activity	Emergency room visit or hospitalization
Tenderness	Mild discomfort to touch	Discomfort with movement	Significant discomfort at rest	Emergency room visit or hospitalization
Erythema/Redness[a]	2.5–5 cm	5.1–10 cm	>10 cm	Necrosis or exfoliative dermatitis
Induration/Swelling[b]	2.5–5 cm and does not interfere with activity	5.1–10 cm or interferes with activity	>10 cm or prevents daily activity	Necrosis
Itching	Pruritus with minimal skin discomfort, occasional scratching	Pruritus with continuous scratching with or without excoriation	Pruritus requiring local or general therapy (steroids, antihistamines)	NA

[a] In addition to grading the measured local reaction at the greatest single diameter, the measurement should be recorded as a continuous variable.
[b] Induration/swelling should be evaluated and graded using the functional scale as well as the actual measurement.

6.4. Pharmacodynamic Assessments

6.4.1. Body Weight, BMI, and Waist Circumference

Body weight, and waist circumference measurements will be performed under fasting conditions, as outlined in the SoA (Table 1, Table 2, Table 4, Table 5, Table 6, Table 7, and Table 8). BMI will be derived from height and body weight measurements for data analysis. Participants will be weighed on a mechanical or digital scale at approximately the same time, if possible, after an overnight fast and evacuation of any bowel and bladder contents. Date and time of each assessment will be recorded. See Appendix 2 for the WHO stepwise guidance and more detailed information.

Waist circumference should be measured at the midpoint between the lower margin of the least palpable rib and the top of the iliac crest. The participant should stand with feet close together, arms at the side and body weight evenly distributed, and should wear little clothing. The participant should be relaxed, and the measurements should be taken at the end of a normal expiration.

6.5. Pharmacokinetic Assessments

Blood samples will be collected by direct venipuncture into a labeled tube containing the appropriate anticoagulant as specified by the bioanalytical facility. As an option to the participants or if judged necessary by the clinical staff, blood samples may be collected from a catheter placed in the participant's vein.

The time of PK blood sample collection will be calculated relative to the time of study drug injection. The actual time of all PK blood draws will be recorded and reported for all participants. If the PK collection aligns with the ECG collection time, PK will be drawn and the ECG will be performed ±1 hour from the corresponding PK draw.

For Part A, the complete blood sampling schedule for participants in the non-intensive PK subsets is presented in Table 16. The complete blood sampling schedule for participants in the intensive PK subsets is presented in Table 17.

Table 16: MET097 Pharmacokinetic Blood Sampling Schedule (non-intensive PK) – Part A

Day	Time Period	Collection Window
Weekly Dosing		
Days 1, 8, 15, 22, 29, 36, 43, 50, 57, 64, 71, 78, 85, 92, 99, 106, 113, 141, 169, and 190	Predose	Up to 60 minutes predose
Day 197	Once during visit	±1 day
Day 220 (only done if not enrolling in Part B)	Once during visit	±1 day

PK=pharmacokinetic

Table 17: MET097 Pharmacokinetic Blood Sampling Schedule (Intensive PK) – Part A Only

Day	Time Period	Collection Window
Weekly Dosing		
Day 1	Predose	Up to 60 minutes predose
	2 and 4 hours postdose	±15 minutes
	8 and 16 hours postdose	±1 hour
Day 2	24 and 36 hours postdose	±2 hours
Day 3	48 hours postdose	±2 hours
Day 4	72 hours postdose	±2 hours
Days 8, 15, 22, 29, 36, 43, 50, 57, 64, 71, 78, 85, 92, 99, 113, 141, and 169	Predose	Up to 60 minutes predose
Day 106	Predose	Up to 60 minutes predose
	2 and 4 hours postdose	±15 minutes
	8 and 16 hours postdose	±1 hour
Day 107	24 and 36 hours postdose	±2 hours
Day 108	48 hours postdose	±2 hours
Day 109	72 hours postdose	±2 hours
Day 190	Predose	Up to 60 minutes predose

Day	Time Period	Collection Window
Weekly Dosing		
	2 and 4 hours postdose	±15 minutes
	8 and 16 hours postdose	±1 hour
Day 191	24 and 36 hours postdose	±2 hours
Day 192	48 hours postdose	±2 hours
Day 193	72 hours postdose	±2 hours
Day 197	Once during visit	±1 day
Day 220 (only done if not enrolling in Part B)	Once during visit	±1 day

PK=pharmacokinetic

Part B

For the Part B PK blood sampling schedule, see the SoA (Table 4, Table 5, Table 6, Table 7, and Table 8).

6.5.1. Pharmacokinetic Sample Processing, Storage and Shipping

MET097 concentrations for PK assessments will be obtained through bioanalysis of the plasma derived from the blood samples drawn during this study, using a validated bioanalytical method. Blood samples for PK determination will be processed, stored, and shipped according to the sample processing instructions supplied by the bioanalytical facility.

7. SAFETY DEFINITIONS, MONITORING, AND REPORTING

Throughout the course of the study, every effort must be made to remain alert to possible AEs. Investigators are responsible for monitoring the safety of participants who have entered this study and for alerting the Sponsor regarding AEs. There will not be any independent data monitoring committee for this study.

7.1. Definitions

7.1.1. Adverse Event (AE)

According to the ICH E2A guideline Definitions and Standards for Expedited Reporting, and 21 CFR 312.32, IND Safety Reporting, an AE is defined as any untoward medical occurrence in a participant administered an investigational product and which does not necessarily have a causal relationship with the treatment. An AE can therefore be any unfavorable and unintended sign (including a clinically significant abnormal clinical laboratory finding, for example), symptom, or disease temporally associated with the use of an investigational product, whether or not related to the investigational product.

All AEs that occur after any participant has been enrolled, from signing of the ICF until the end of the study, whether or not they are related to the study treatment, must be recorded on forms provided by the Sponsor. An AE may be:

- A new illness,
- Worsening of a concomitant illness,
- An effect of the study drug including comparator; it could be a post dose clinically significant laboratory value, as well as a significant shift from baseline within normal range which an investigator considers to be clinically important.

Surgical procedures themselves are not considered AEs. They are therapeutic measures for conditions that required surgery. The condition for which the surgery is required is an AE, if it occurs or is detected during the study period. Planned surgical measures permitted by the clinical study protocol and the conditions(s) leading to these measures are not AEs, if the condition(s) was (were) known before the start of study treatment.

7.1.2. Serious Adverse Event (SAE)

An SAE is any untoward medical occurrence that at any dose:

- Results in death,
- Is life-threatening (an event which places the participant at immediate risk of death from the event as it occurred. It does not include an event that had it occurred in a more severe form might have caused death),
- Requires inpatient hospitalization or prolongation of existing hospitalization,
- Results in persistent or significant disability or incapacity (defined as a substantial disruption of a person’s ability to conduct normal life functions),
- Is a congenital anomaly or birth defect,
- Is an important medical event that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require intervention to

prevent one of the other outcomes listed above (eg, events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias, convulsions, or the development of drug dependency or abuse) according to medical judgment of the investigator.

Within 24 hours of receipt of follow-up information, the investigator must update the SAE form. SAEs must be reported using the contact information provided.

7.2. Adverse Events of Clinical Interest

The following AEs are considered to be AEs of clinical interest (AECI) for this study and will be recorded as such in the electronic data capture (EDC) system and on an AECI form (Section 7.6.2 and Section 7.7).

An AECI that meets the definition of an SAE (see Section 7.1.2) must be reported as an SAE. When any one of the following events occur, the Sponsor or its designee must be alerted as soon as possible, within 24 hours, whether it is assessed as an SAE or not:

- Any severe or serious injection site reaction or 2 or more moderate injection site reactions occurring a week or more apart in the same participant (Section 7.2.1)
- Any hypersensitivity reaction (Section 7.2.2)
- Hypoglycemia (Section 7.2.3)
- **Part A**: Severe or serious AEs of nausea, vomiting, or diarrhea. Mild and moderate AEs of nausea, vomiting, or diarrhea are also considered AECIs but should be reported within 72 hours (Section 7.2.4)
  Part B: Severe or serious gastrointestinal disorders, including AEs of nausea, vomiting, or diarrhea (Section 7.2.4)
- Suspicion of pancreatitis or pancreatic cancer (Section 7.2.5)
- Major Adverse Cardiovascular Events (MACE) (Section 7.2.6)
- Thyroid C-Cell Hyperplasia and C-Cell Neoplasms (Section 7.2.7)
- Any other AE, SAE, or clinically significant laboratory value for which the investigator believes that permanent study drug discontinuation for a participant is the appropriate measure to be taken

For information on recording and reporting of AECIs, see Section 7.6 and Section 7.7, respectively.

7.2.1. Injection Site Reactions

All severe or serious injection site reactions or two or more moderate injection site reactions occurring a week or more apart in the same participant must be reported as an AECI. Each AECI of injection site reaction will include documenting information including onset date, size of erythema/redness and induration/swelling, and amount of pruritus, as well as severity, investigator's assessment of relatedness to study drug, and resolution date will be recorded on

CRFs. In addition, if the reaction is clinically significant, the site should contact the Sponsor for potential follow-up procedures.

7.2.2. Hypersensitivity Reactions

All hypersensitivity reactions will be reported by the investigator as either AECIs or, if any serious criterion is met, as SAEs.

7.2.3. Hypoglycemia

Information that will be recorded includes onset date as well as severity, and investigator's assessment of relatedness to study drug, and resolution date will be recorded. Any event of hypoglycemia that occurs outside the study site (eg, local emergency room) will need to be documented by the clinical site staff. Hypoglycemia will be classified as follows [American Diabetes Association, 2005]:

- Documented Symptomatic Hypoglycemia: Any time a participant feels that he/she is experiencing symptoms and/or signs associated with hypoglycemia and has a plasma glucose level of ≤3.9 mmol/L (≤70 mg/dL)
- Asymptomatic Hypoglycemia: An event not accompanied by typical symptoms of hypoglycemia, but with ≤3.9 mmol/L (≤70 mg/dL) plasma glucose
- Severe Hypoglycemia: An episode requiring the assistance of another person to actively administer carbohydrate, glucagon, or other resuscitative actions. These episodes may be associated with sufficient neuroglycopenia to induce seizure or coma. Plasma glucose measurements may not be available during such an event, but neurological recovery attributable to the restoration of plasma glucose to normal is considered sufficient evidence that the event was induced by a low plasma glucose concentration
- Nocturnal Hypoglycemia: Any hypoglycemic event that occurs between bedtime and waking
- Probable Symptomatic Hypoglycemia: An event during which symptoms of hypoglycemia are not accompanied by a plasma glucose determination (but that was presumably caused by a plasma glucose concentration ≤3.9 mmol/L [≤70 mg/dL])

7.2.4. Nausea, Vomiting, or Diarrhea

7.2.4.1. Part A

All events of nausea, vomiting, or diarrhea will be considered as AECIs irrespective of severity. Severe and serious nausea, vomiting, or diarrhea events must be reported to the Sponsor, as soon as possible, within 24 hours. Mild and moderate nausea, vomiting, or diarrhea events should be reported to the Sponsor, as soon as possible, within 72 hours.

Severe and moderate nausea events and all events of vomiting and diarrhea will be reported to the Sponsor or designee on both the eCRF and AECI form. Mild nausea events only need to be reported on the eCRF (no AECI form is needed to be completed when reporting mild nausea events). Serious events of nausea, vomiting, and diarrhea will only need to be reported as SAEs. Guidance on AECI reporting is in Section 7.7. For each AECI (Section 7.7) the onset date and

time as well as severity, duration, investigator's assessment of relatedness to study drug, and resolution date and time will be captured.

7.2.4.2. Part B (Study Extension)

Severe and serious GI events will be considered as AECIs and should be reported to the Sponsor, as soon as possible, within 24 hours.

These events will be reported to the Sponsor or designee on both the eCRF and AECI form. Serious GI events will only need to be reported as SAEs. Guidance on AECI reporting is in Section 7.7. For each AECI (Section 7.7) the onset date and time as well as severity, duration, investigator's assessment of relatedness to study drug, and resolution date and time will be captured.

7.2.5. Acute Pancreatitis

Acute pancreatitis is an acute inflammatory process of the pancreas that may also involve peripancreatic tissues and/or remote organ systems [Banks and Freeman, 2006]. The diagnosis of acute pancreatitis requires two of the following three features:

- abdominal pain, characteristic of acute pancreatitis (generally located in the epigastrium and radiates to the back in approximately half the cases [Banks and Freeman, 2006; Koizumi et al, 2006]; the pain is often associated with nausea and vomiting);
- serum amylase (total and/or pancreatic) and/or lipase ≥3× ULN;
- characteristic findings of acute pancreatitis on computed tomography (CT) scan or magnetic resonance imaging (MRI).

If acute pancreatitis is suspected, appropriate laboratory tests (including levels of pancreatic amylase and lipase) should be obtained. Imaging studies, such as abdominal CT scan with or without contrast, MRI, or gallbladder ultrasound, should be performed. If laboratory values and/or abdominal imaging support the diagnosis of acute pancreatitis, the participant must discontinue therapy with investigational product, A review of the participant's concomitant medications should be conducted to assess any potential causal relationship with pancreatitis.

Each AE of pancreatitis must be reported and is considered an AECI. If typical signs and/or symptoms of pancreatitis are present and confirmed by laboratory values (lipase or amylase [total and/or pancreatic]) and imaging studies, the event must be reported as an SAE. For a potential case that does not meet all of these criteria, it is up to the investigator to determine the seriousness of the case (non-serious AE or SAE) and the relatedness of the event to study drug.

In addition to the diagnostic assessment in participants who develop symptoms of acute pancreatitis, each participant will have measurements of pancreatic amylase and lipase at screening, baseline, and at each non-PK-specific visit to assess any potential effects of MET097 on the exocrine pancreas (Table 1, Table 2, Table 4, Table 5, Table 6, Table 7, and Table 8). Further diagnostic assessment of asymptomatic pancreatic hyperenzymemia will be required whenever lipase and/or pancreatic amylase are ≥3× ULN at any time during the study.

7.2.6. Major Adverse Cardiovascular Events (MACE)

Deaths (cardiovascular and non-cardiovascular), nonfatal myocardial infarctions (MIs), supraventricular arrhythmias, transient ischemia attacks (TIAs), hospitalization for heart failure, coronary interventions (such as coronary artery bypass graft or percutaneous coronary intervention), hospitalization for unstable angina, and nonfatal strokes that occur during the treatment period or follow-up period are considered AECIs for this study and will be reported to the Sponsor within 24 hours. Cardiovascular event definitions will be based on the Standardized Definitions for Cardiovascular and Stroke Endpoint Events in Clinical Trials [Hicks et al, 2015] and the ESC/ACCF/AHA/WHF Expert Consensus Document Third Universal Definition of Myocardial Infarction [Thygesen et al, 2012].

7.2.7. Thyroid C-Cell Hyperplasia and C-Cell Neoplasms

Thyroid C-cell hyperplasia and C-cell neoplasms are considered AECIs for this study. The assessment of thyroid safety during the study will include reporting of thyroid AEs and measurements of calcitonin according to the SoA (Table 1, Table 2, Table 4, Table 5, Table 6, Table 7, and Table 8). The purpose of calcitonin measurements is to assess the potential of MET097 to affect thyroid C-cell function, which includes development of C-cell hyperplasia and neoplasms.

Participants who develop serum calcitonin increases ≥50% of the mean of the Screening visit values AND an absolute value ≥20 pg/mL and <35 pg/mL at any time post first dose, will be asked to repeat the measurement within 1 month. If this repeat value is increasing (≥10% increase), the participant will be encouraged to undergo additional endocrine assessment and longer-term follow-up by an endocrinologist to exclude a serious adverse effect on the gland.

Participants with an increase in serum calcitonin ≥50% of the mean of the Screening visit values AND an absolute value of ≥35 pg/mL at any time post first dose will be recommended to immediately undergo additional endocrine assessment and longer-term follow-up by an endocrinologist.

For participants who require additional endocrine assessment because of increased calcitonin concentration per criteria provided in this section, data from the follow-up assessment will be collected.

7.2.8. Hepatobiliary Disorders

Recent review of meta-analyses and real-world studies by the US FDA suggest a potential association between GLP-1RAs and hepatobiliary disorders (e.g., cholecystitis, cholelithiasis, other biliary tract disorders). The exact mechanism is unknown but potential contributing factors include rapid weight loss, suppression of cholecystokinin secretion and reduced gallbladder emptying [Woronow et al, 2022; Keller et al, 2012]. The US Prescribing Information for GLP-1RA products have recently been revised to include warnings and precautions about this risk and include product-specific data on acute gallbladder disease event rates compared with placebo from clinical studies [WEGOVY US Package Insert (USPI), 2022; ZEPBOUND USPI, 2023].

7.2.9. Excessive Weight Loss, Sarcopenia, Malnutrition and Inflammation

Ongoing nutritional assessment and counseling of patients treated on the study can facilitate the identification and management of pre-existing risk factors for malnutrition and can provide patients with goals for the intake of key nutrients including protein, dietary fiber, micronutrients, and fluid.

Ongoing monitoring of participants' nutritional status with biomarkers during treatment include serum albumin, transthyretin (pre-albumin), and high-sensitivity C-reactive Protein (hsCRP) in addition to electrolytes and BMI thresholds to enable early recognition and management of any concerns that may emerge with excessive weight loss and inadequate nutrient intake during the trial.

7.3. Relationship of the Adverse Event to Study Drug

The relationship between the AE and study drug will be assessed by using a binary assessment. The investigator should determine whether there is a 'reasonable possibility' or 'no reasonable possibility' that the study drug caused the event based on the following definitions:

Reasonable possibility (related) – There is a reasonable possibility that the administration of study drug caused the AE. There is evidence to suggest a causal relationship between the study drug and the AE.

No reasonable possibility (not related) – There is no reasonable possibility that the administration of study drug caused the AE. There is no temporal relationship between the study drug and event onset, or an alternative etiology has been established.

7.4. Expectedness

The Sponsor will be responsible for determining whether an AE is expected or unexpected for the purpose of reporting suspected unexpected serious adverse reactions (SUSARs) to regulatory authorities. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the safety information previously described for MET097 in the current/approved version of the IB.

7.5. Adverse Event Severity

AEs are graded according to the categories detailed below:

- Mild: Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
- Moderate: Minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living (eg, preparing meals, shopping for groceries or clothes, using the telephone, managing money)
- Severe: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living (eg, bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden); OR life-threatening consequences; urgent intervention indicated; OR death related to an AE

Changes in severity should be documented to allow assessment of the duration of the event at each level of severity. AEs characterized as intermittent require documentation of the start and stop of each incidence. When changes in the severity of an AE occur more frequently than once a day, the maximum severity for the experience that day should be noted. If the severity category changes over a number of days, then those changes should be recorded separately (with distinct onset dates).

Every effort will be made to obtain an adequate evaluation of the severity.

AE severity and seriousness are assessed independently. Severity is a measure of intensity. Seriousness is a regulatory definition and serves as a guide to the Sponsor for defining regulatory reporting obligations (see definition for SAE under Section 7.1.2). An AE of severe intensity is not necessarily considered a serious AE.

Classification of AEs will be performed by System Organ Class and Preferred Term using the Medical Dictionary for Regulatory Activities (MedDRA).

Concomitant medications will be coded using the WHO drug dictionary.

7.6. Eliciting and Reporting of Adverse Events

7.6.1. Eliciting Adverse Events

The participant should be asked about medically relevant changes in the participant's health since the last visit. The participant should also be asked if the participant has been hospitalized, had any accidents, used any new medications, or changed concomitant medication routines (both prescription and over-the-counter). In addition to participant observations, AEs will be documented for post-dose clinically significant laboratory values, physical examination findings, ECG changes, or other findings that are relevant to participant safety.

7.6.2. Recording/Reporting Adverse Events

The investigator is responsible for recording non-serious AEs that are observed or reported by the participant after the informed consent is signed, regardless of their relationship to study drug, through the end of study. Non-serious AEs will be followed until the end of study.

Non-clinically significant changes in laboratory values, blood pressure, and pulse need not be reported as AEs. However, abnormal values that constitute an SAE or lead to discontinuation of administration of study drug must be reported and recorded as an AE. The AE term should be reported in standard medical terminology, when possible. All non-serious AEs that occur from consent through the end of study must be assessed and recorded on the source documents. AEs for randomized participants will be entered into the CRF from time of consent onwards, regardless of causal relationship to study drug.

In addition to records of observations made at specific times, unexpected signs and symptoms and concomitant medications will be recorded in the clinical trial records throughout the study. Planned surgeries and nonsurgical interventions should not be reported as AEs unless the underlying medical condition has worsened during the course of the study.

If a participant's investigational product is discontinued as a result of an AE, study site personnel must report this to the Sponsor or its designee via the eCRF, clarifying if possible, the circumstances leading to discontinuations of study treatment.

The investigator is responsible for recording SAEs that are observed or reported by the participant after the informed consent is signed, regardless of their relationship to study drug, through the end of study. SAEs will be followed until satisfactory resolution, until the baseline level is reached, or until the SAE is considered by the investigator to be chronic or the participant is stable, as appropriate.

For SAEs, record the event(s) on both the eCRF and the SAE form.

For AEs that are considered AECIs see Section 7.2 and Section 7.7.

Additional clinical and laboratory information may be collected.

7.7. Reporting Adverse Events of Clinical Interest (AECI) to Sponsor/Designee

For AEs that are considered AECIs (Section 7.2), the Sponsor or its designee should be notified within 24 hours (Part A: except for mild or moderate nausea, vomiting and diarrhea events, which should be reported within 72 hours) and documented appropriately on both the eCRF and the AECI form (Part A: mild nausea events only need to be documented on the eCRF). Any AECI that also meets the definition of an SAE (Section 7.1.2) must be reported following appropriate SAE guidelines and only as an SAE (reported within 24 hours and on the SAE form). For each AECI the onset date and time as well as severity, duration, investigator's assessment of relatedness to study drug, and resolution date and time will be captured.

7.8. Reporting Serious Adverse Events

An assessment of the seriousness of each AE will be made by the investigator. Any AE and laboratory abnormality that meets the SAE criteria in Section 7.1.2 must be reported to the Sponsor or designee within 24 hours from the time that clinical study center staff first learns of the event. All SAEs must be reported regardless of the relationship to study drug.

The initial report should include at least the following information:

- Participant's study number
- Description and date of onset of the event
- Criterion for seriousness
- Preliminary assignment of relationship to study drug, and
- Investigator/site information

The investigator will be responsible to complete, sign and date the SAE documentation, verify the accuracy of the information recorded with the corresponding source documents, and send a copy via email to the Sponsor or its designee.

The investigator is responsible for the appropriate medical care of participants during the study. Appropriate remedial measures should be taken by the investigator using his/her best medical judgment to treat the SAE. These measures and the participant's response to these measures should be recorded. All SAEs, regardless of relationship to study drug, will be followed by the investigator until satisfactory resolution or until the investigator deems the SAE to be chronic or stable or fully explained. The frequency of follow up evaluations of the AE is left to the discretion of the investigator. Clinical, laboratory, and diagnostic measures should be employed by the investigator as needed to adequately determine the etiology of the event.

7.9. Pregnancy Reporting

Pregnancy in a female participant that occurs up to and including 90 days from the last study drug administration shall be reported to the Sponsor within 24 hours of the knowledge of its occurrence by the Qualified Investigator or delegate. Because of the possibility the fetus/embryo could have been exposed to the study drug through the parent and for the participant's safety, the pregnancy will be followed up to determine its outcome, including spontaneous or voluntary termination, details of birth, presence or absence of any birth defects, congenital anomalies, or maternal and/or newborn complications.

Pregnancy that occurs within 90 days after the last drug administration in a female partner of a male study participant shall be reported to the Sponsor within 24 hours of the knowledge of its occurrence by the clinical site. Because of the possibility that the fetus/embryo could have been exposed to the study drug through the parent and for the safety of the participant's female partner, the pregnancy will be followed up to determine its outcome, including spontaneous or voluntary termination, details of birth, presence or absence of any birth defects, congenital anomalies, or maternal and/or newborn complications.

Should a pregnancy occur, it must be reported and recorded on the study pregnancy form. Pregnancy in itself, is not regarded as an AE unless there is a suspicion that MET097 may have interfered with the effectiveness of a contraceptive medication.

The outcome of all pregnancies (spontaneous miscarriage, elective termination, normal birth, or congenital abnormality) must be followed up and documented even if the participant was discontinued from the study.

All reports of congenital abnormalities/birth defects are SAEs. Spontaneous miscarriages should also be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs.

7.10. Sponsor Safety Reporting to Regulatory Authorities

The Sponsor or its representative will report certain study events in an expedited manner to the FDA and/or to all country Regulatory Authorities where the study is being conducted, according to local applicable regulations.

7.11. Serious Adverse Event Notification to the Institutional Review Boards/Independent Ethics Committee

SUSARs will be reported to the Institutional Review Board (IRB)/ Independent Ethics Committee (IEC) per their institutional policy by the investigator or Sponsor (or Sponsor designee) according to country requirements. Copies of each report and documentation of IRB/IEC notification and acknowledgement of receipt will be kept in the investigator's study file.

7.12. Medication Errors

A medication error is an unintended failure or mistake in the treatment process by study drug that either causes harm to the participant or has the potential to cause harm to the participant.

The situations designated as medication errors in this study include:

- Study drug not administered as indicated, eg, wrong route or wrong site of administration
- Wrong study drug administered to the participant
- Accidental overdose (see Section 7.13)
- Study drug not stored as instructed eg, kept at room temperature when it should be in the refrigerator

Medication errors are not regarded as AEs, but AEs may occur as a consequence of a medication error. Medication errors with or without an associated AE should be recorded as medication errors in the eCRF.

Medication errors and an associated SAE should be recorded in the eCRF and reported as described in Section 7.1.2. Medication errors and an associated non-serious AE should be recorded in the eCRF as described in Section 7.1.1.

7.13. Overdose Reporting

An overdose is defined as any dose administered to a participant (accidentally or intentionally) that exceeds the highest daily dose, or is at a higher frequency, than included in the protocol. The investigator will decide whether a dose is to be considered an overdose, in consultation with the Sponsor. In the event of an overdose, the actual dose administered must be recorded in the eCRF.

All reports of overdose (with or without an AE) must be reported within 24 hours to the Sponsor or designee. The process to report an overdose will be outlined in the Safety Management Plan.

8. DATA COLLECTION

8.1. Use of Electronic Case Report Form

Participant data will be collected using an EDC system that complies with 21 CFR Part 11 and data integrity requirements. External data collected outside of EDC system will be transferred and processed according to study-specific data agreements. To access EDC, the users are required to be trained by a qualified person on the technical features of the EDC including the content of the eCRFs created within the EDC system for study data collection. Upon completion of training, each user is assigned a password-protected user ID to access the EDC system. User ID is a unique account and must not be shared with anyone including the study staff.

Entry of data into the eCRFs must be completed by investigative site staff within 3 days after each visit per clinical trial agreement with the Site. Prior to the database being locked, the investigator or designee will review, approve and sign/date each completed eCRF. This signature serves as attestation of the investigator's responsibility for ensuring that all data entered in the eCRF are complete, accurate and authentic. At the end of the study, a copy of the data will be provided to the site containing the final data of all participants at the site, an audit trail of activity on the data, and any data queries and responses. The data will be electronically delivered using storage devices.

8.2. Study Site Monitoring

The Sponsor has ethical, legal and scientific obligations to carefully follow this study in accordance with established research principles and applicable regulations. The investigator, as part of his/her responsibilities, is expected to cooperate with the Sponsor in ensuring that the study adheres to the protocol and GCP requirements.

As part of a concerted effort to fulfill these obligations, the Sponsor's monitor will visit the center(s) during the study in accordance with the Monitoring Plan set forth for this study. The investigator will permit the Sponsor to monitor the study as frequently as is deemed necessary and provide access to medical records/source documents to ensure that data are being recorded adequately, that data are verifiable, and that protocol adherence is satisfactory.

9. DATA ANALYSIS AND STATISTICAL CONSIDERATIONS

9.1. General Statistical Considerations

Details on the statistical analysis methods, including plans for any administrative looks will be described in the study SAP which will be completed and approved prior to the planned reporting milestone for the primary analyses (Part A, Day 197). Part A and Part B will be reported separately unless otherwise specified. Study endpoints will be summarized by treatment group and visit. Summary statistics for all continuous endpoints will include the following: total number of participants, arithmetic mean, standard deviation, median, interquartile range, and range. Binary and other categorical variables will be summarized using total number of participants, frequencies and percentages. Baseline will be defined as the last non-missing measurement prior to the first dose. Any changes to the statistical methods described below will be documented in the SAP, unless they represent a significant change to the protocol-specified statistical analysis plans-in which case it will be documented as a protocol amendment. All CIs reported will be 2-sided and with a 95% confidence coefficient and all p-values reported will be associated with 2-sided hypotheses tests unless specified otherwise.

9.1.1. Data Blinding

Part A

Part A is double-blinded (sponsor-, investigator- and participant-blinded) from randomization until the primary reporting milestone at Week 28 (Day 197). Investigators, participants, and Sponsor personnel directly involved in the conduct of the study will remain blinded to participant-level treatment allocation for the entire duration of the Part A of the study. The preparation and/or administration of the products will be done by designated personnel that are not directly involved in the clinical aspects of the trial. Sponsor Clinical Pharmacology/ Pharmacometrics personnel may be unblinded prior to the release of the 28-week primary analysis results to allow for model-building. If these personnel are unblinded, they will no longer be directly involved in the conduct of the study.

Part B

Part B is double-blinded (sponsor-, investigator- and participant-blinded) from the dosing at Week 28 (Day 197) until the first participant reaches Week 40 (Day 281). Investigators, participants, and Sponsor personnel directly involved in the conduct of the study will remain blinded to participant-level treatment allocation in Part B from the dosing at Week 28 (Day 197) until the first participant reaches Week 40 (Day 281). The preparation and/or administration of the products will be done by designated personnel that are not directly involved in the clinical aspects of the trial.

9.1.2. Interim Analysis

Part A: No interim analyses (for potential modification of the ongoing trial) are planned. The first unblinded analyses for reporting the primary Week 28 (Day 197) analysis results will occur on completion of the dosing period but prior to completion of the safety follow-up period. Specifically, this reporting milestone for the primary Week 28 analysis will occur when all (ie,

N=~225) participants have completed their Day 197 visit (or permanently discontinued from the study prior to Day 197). Specifically, this reporting milestone will occur when all participants have completed their dosing period but before all participants have completed their safety follow-up period. Complete details will be documented in the study SAP which will be finalized prior to unblinding for this planned reporting milestone.

Final Study Analysis: The final study database lock and final study analysis (for inclusion in the clinical study report), will occur after all participants have completed both Part A and Part B dosing periods as well as the subsequent safety follow-up period.

9.2. Decision Criteria/Statistical Hypotheses

Part A: In the primary efficacy analysis, pairwise statistical hypothesis tests (2-sided) will be performed to compare each of the four MET097 doses (0.4 mg, 0.6 mg, 0.9 mg and 1.2 mg) to placebo with respect to mean percent change from baseline body weight at Week 28 (Day 197). The p-value from each of the four tests, will be used to assess statistical significance for the corresponding comparison of a MET097 dose to placebo, with the overall Type 1 error for the primary efficacy analysis controlled at 5%.

9.3. Multiplicity Adjustment

Part A: The overall Type 1 error rate for the primary efficacy analyses (ie, primary and supplementary estimands for the primary efficacy endpoint) will be controlled at 5% using the Hochberg procedure to adjust for multiplicity for the four pairwise statistical comparisons of MET097 dose arms to placebo. There will be no multiplicity adjustments for any of the secondary or exploratory analyses.

9.4. Handling of Missing Data

Part A Primary Efficacy Estimand:

Missing data will be assumed to be missing at random (MAR) for the primary efficacy estimand. The MMRM methodology planned for the primary efficacy estimand yields valid estimates of the efficacy estimand under MAR, so no imputation of missing data is planned. Any sensitivity analyses to test the robustness of the MAR assumption will be detailed in the study SAP.

Part A Supplementary Efficacy Estimand:

Missing values will be imputed using participants in the same treatment arm with similar intercurrent events but non-missing values (ie, retrieved dropout imputation). In cases where there are not enough retrieved dropouts to provide a reliable imputation model, missing data will be imputed using the placebo-washout approach as recommended by Wang et al. (2023). Complete details on the imputation methodology will be described in the SAP.

9.5. Analysis Sets

For the purposes of the analysis the following analysis sets are defined Table 18 and Table 19.

Table 18: Participant Analysis Sets

Participant Analysis Set	Description
Enrolled	All participants who signed informed consent
Full Analysis Set (FAS)	All randomized participants
Safety Analysis Set (SAS)	All participants who received at least one dose of treatment
Modified FAS (mFAS)	All randomized participants who received at least one dose of study treatment

Table 19: Analysis Datasets

Analysis Dataset	Description
Efficacy Adherence to Study Dataset [1]	Data obtained during the treatment period from the FAS analysis set, excluding the following data points: i. Weight measurements after permanent discontinuation of study drug (last dose date + 7 days); ii. Weight measurements after first non-adherence to additional protocol specified study treatment compliance requirements: a) 2 or more consecutive missed doses b) >3 of first 8 doses missed (Study Week 7) c) Single missed dose between dose 8 and dose 16 (between Study Week 7 and Study Week 15) d) 2 nonconsecutive missed doses after dose 16 (Study Week 15) or iii. Weight measurements after lifestyle change has occurred
Efficacy Non-Adherence to Study Dataset [2]	Data obtained during treatment period from the FAS analysis set, regardless of adherence to study treatment or change in lifestyle changes

FAS = Full Analysis Set
[1] This dataset will be used for the primary efficacy analysis and the secondary and exploratory efficacy analysis
[2] This dataset will be used for any alternative efficacy estimands explored as part of sensitivity or supplementary analyses to be explored in the SAP

PK Analysis Set

The PK Analysis Set will be described in more detail in a PK analysis plan. Generally, the PK population includes all the participants who received at least one treatment with sufficient PK data to derive at least one PK parameter for at least one analyte and without having any major protocol deviations or AEs thought to significantly affect the PK profile. Participants who do not complete the sampling schedule may be included in the PK analysis for only the PK parameters that are judged not to be affected by the missing sample(s).

9.6. Statistical Analysis Methods

9.6.1. Demographic Data and Other Baseline Characteristics

The demographic and baseline characteristics include age, height, body weight, ethnicity, waist circumference, and BMI.

9.6.2. Demographic Data and Other Baseline Characteristics Analysis

The demographic and baseline characteristics will be summarized using descriptive statistics as described in the general statistical considerations (Section 9.1).

9.6.3. Safety Endpoints

Safety endpoints are listed in Section 2.

9.6.3.1. Safety Statistical Analysis

In addition to reporting by Part A and Part B as described below, safety data will also be reported for the overall study. Further details will be provided in the SAP.

Part A

The safety endpoints will be summarized using descriptive statistics as described in the general statistical considerations (Section 9.1) and will use the Safety Analysis Set.

AEs, SAEs, and AEs leading to discontinuation will be summarized by System Organ Class, Preferred Term, and severity in tables with the number of participants with at least 1 AE and number of AEs from each formulation and overall.

Part B

The safety endpoints will be summarized for Part B as described for Part A.

9.6.4. Efficacy Endpoints

Efficacy endpoints are as listed in the objectives and endpoints section (Section 2).

Primary Efficacy Endpoint:

The primary efficacy endpoint is percent change from baseline in body weight at Week 28 (Day 197) and is calculated as follows:

$$100 \times \left(\frac{\text{body weight at Day 197} \quad - \text{body weight at baseline}}{\text{body weight at baseline}}\right)$$

Secondary efficacy and exploratory efficacy endpoints

Derivations for the secondary and exploratory efficacy endpoints will be provided in the SAP.

9.6.4.1. Efficacy Statistical Analysis

Part A

Primary Efficacy Analysis (for the primary endpoint and the Primary Efficacy Estimand): The primary efficacy estimand is as described in Section 2. The main analytic approach will be a mixed effects repeated measures model (MMRM) used to analyze the primary efficacy endpoint of percent change from baseline at Week 28 (Day 197). The appropriate contrasts will be constructed for comparing each of the four MET097 dose arms to placebo at Week 28 (Day 197). The MMRM model will include terms for treatment, visit, and treatment-by-visit interaction, stratification factors, and baseline measurement as a covariate. Least square means for the treatment differences from placebo will be reported along with p-values and two-sided 95% CIs. P-values associated with 2-sided tests (for each statistical comparison of a MET097 dose-arm to placebo) will be used for assessing statistical significance, using the Hochberg procedure for multiplicity adjustment (as described in Section 9.3). The Efficacy Adherence to Study Analysis Dataset (as described in Section 9.5) will be used for the primary efficacy analysis. The MAR assumption will be made for missing data. The MMRM model yields valid

estimates of the efficacy estimand under MAR, so no imputation of missing data is needed. Further details will be provided in the SAP.

Supplementary Efficacy Analysis (for the primary endpoint and the Supplementary Efficacy Estimand): The supplementary efficacy analysis will use the same MMRM methodology for treatment comparisons as used for the primary efficacy analysis and will use the Efficacy Non-Adherence to Study Dataset (see Table 9), with missing data imputation as described in Section 9.4. Further details will be provided in the SAP.

Secondary and Exploratory Efficacy Analysis: The secondary and exploratory endpoints that are continuous and longitudinal will be analyzed using the same MMRM methodology for treatment comparisons and Efficacy Adherence to Study Dataset, as used for the primary efficacy analysis, with the same descriptive statistics used for summarization. A logistic regression model will be used for making treatment comparisons in binary endpoints, with p-values and 2-sided 95% CIs for point-estimates. The logistic regression model will include terms for treatment, visit, and treatment-by-visit interaction, stratification factors, and baseline measurement as a covariate. Further details will be provided in the SAP.

Summary statistics will be reported for each visit and treatment arm, including the number of participants, arithmetic mean, standard deviation, median, interquartile range and range. Binary and other categorical endpoints will be summarized using counts, frequencies and percentages. There will be no multiplicity adjustment for any of the secondary or exploratory analyses.

Part B

Exploratory Analysis: The exploratory endpoints of body weight reduction and other weight-related parameters will be summarized descriptively as outlined in Section 9.1. Further details will be provided in the SAP.

9.6.5. Pharmacokinetics

The PK analysis will be described in more detail in a PK analysis plan. PK assessments for MET097 include minimum observed concentration (C_{min}) for all participants, and for the subset of CCI participants of each treatment arm, PK assessments will include area under the concentration versus time curve during the dosing interval (AUC(0-τ)), maximum observed concentration (C_{max}), time to maximum concentration (T_{max}). Additional parameters such as apparent $t_{1/2}$ may be calculated as appropriate and as data allow.

Individual and mean MET097 concentration versus time data will be tabulated plotted by treatment arm. The PK parameters of MET097 will be tabulated and summary statistics will be provided by treatment arm.

The relationship between PK parameters and selected safety and PD variables may be explored via modeling.

9.6.5.1. Sample Size Determination

Part A: For the primary efficacy analysis comparing each of the MET097 doses to placebo with respect to the primary efficacy endpoint at week 28, the following assumptions were made in the power calculation: total study sample size is approximately 225 participants with ~45

participants per arm, true common standard deviation is CCI the overall study dropout rate is CCI%, the overall Type 1 error rate for the primary efficacy analysis will be controlled at 5% using the Hochberg procedure to adjust for multiplicity for the four pairwise statistical comparisons of MET097 dose arms to placebo. With these assumptions, the power is CCI% for each MET097 dose-comparison to placebo, if the assumed true placebo-corrected mean percent change from baseline at Week 28 for 0.4 mg, 0.6 mg, 0.9 mg and 1.2 mg is CCI % respectively.

With a dropout rate of CCI%, if the assumed true placebo-corrected mean percent change from baseline at Week 28 for 0.4 mg, 0.6 mg, 0.9 mg and 1.2 mg is CCI , the power will be CCI % respectively, for the 0.4 mg, 0.6 mg, 0.9 mg and 1.2 mg statistical comparisons to placebo.

These power calculations are based on simulating 5000 studies for each treatment difference scenario and dropout rate and analyzing percent change from baseline at Day 197 using the ANOVA model along with Hochberg's adjustment for multiple comparisons to placebo.

10. REGULATORY AND REPORTING REQUIREMENTS

10.1. Compliance with Laws and Regulations

The study will be conducted according to the principles of the Declaration of Helsinki (World Medical Association 2013), ICH-GCP E6(R2), applicable laws and regulations of the country in which the research is being conducted, and the requirements of all local regulatory authorities regarding the conduct of the study and protection of human participants. The study will be conducted by scientifically and medically qualified persons and the rights and welfare of the participants will be respected.

10.2. Informed Consent / Assent (if applicable)

The investigator or the appropriate designee is responsible for obtaining written informed consent(s) from each study participant prior to conducting any study-specific procedures. The investigator must use the most current IRB/EC approved consent form when obtaining consent. At all times, all signed and dated consent forms must be available for review by Sponsor or designee.

10.3. Institutional Review Board / Ethic Committee

The investigator must receive IRB/EC approval prior to enrolling participants. The study must be approved on an annual basis by the IRB/EC representing the participating institution. Such IRB/EC must meet all requirements as described in Title 21, Part 56 of the US Code of Federal Regulations.

10.4. Public Clinical Trial Registry

The study will be listed on a public clinical trial registry per applicable regulations.

10.5. Confidentiality

The investigator and designees, employees and agents involved in this study must comply with relevant local, state, federal and regional laws, as applicable, relating to the confidentiality, privacy, and security of participant's health information. Data generated during this study or disclosed by the Sponsor to the investigator must be used as appropriate for the execution, analysis, review, and reporting of this study. Such information shall not be used for any other purposes and will remain confidential. To ensure participant safety and in adherence with regulatory guidelines, participant personal and medical information may be reviewed by representative of the Sponsor, the IRB/EC or regulatory authorities in the case of inspection. Every reasonable effort will be made to maintain strict confidentiality. Participant names will never be used when presenting in reports, published scientific journal or medical meetings.

10.6. Financial Disclosure

The investigator must maintain compliance with the current country-specific guidelines and regulations concerning disclosure of financial interest.

10.7. Data Quality Assurance

It is expected that the investigator will adhere to GCP guidelines to ensure accurate, consistent, and reliable data.

10.8. Records Retention

The US FDA regulations require all investigators participating in clinical study drug/device studies to maintain detailed clinical data for one of the following periods:

- At least two years following the date on which a New Drug Application is approved
- Two years after the Sponsor notifies the investigator that no further application is to be filed with the FDA

Similarly, current EU Directives / Regulations and ICH guidelines collectively require that essential clinical study documents (including case report forms) other than patient's medical files must be retained for the following time period:

- For at least 15 years after completion or discontinuation of the study
- Or for at least two years after the granting of the last marketing authorization in the European Community and when there are no pending or contemplated marketing applications in the European Community
- Or for at least two years after formal discontinuation of clinical development of the study drug/device

Participant's medical files should be retained in accordance with applicable legislation and in accordance with the maximum period of time permitted by the hospital, institution or private practice. The documents can be retained for a longer period, however, if required by the applicable regulatory requirements or by agreement with the Sponsor.

To comply with these requirements, the investigator will not dispose of any records relevant to this study without either (1) written permission from the Sponsor or (2) providing an opportunity for the Sponsor to collect such records. The investigator shall take responsibility for maintaining adequate and accurate hard copy source documents of all observations and data generated during this study, including the hard copy or discs of the final data received from the Sponsor. Such documentation is participant to inspection by the Sponsor or its agents, the FDA and/or other regulatory agencies.

11. QUALITY CONTROL AND QUALITY ASSURANCE

11.1. Protocol Deviations

This study will be conducted as described in this protocol, except for an emergency situation in which the protection, safety, and well-being of the participant requires immediate intervention, based on the judgment of the investigator (or a responsible, appropriately trained professional designated by the investigator). In the event of a deviation from the protocol due to an emergency, accident, or mistake, the investigator or designee must contact the Sponsor, or their agent, at the earliest possible time via the Medical Hotline. This will allow an early joint decision regarding the participant's continuation in the study. The investigator and the Sponsor will document this decision. The IRB/IEC will be informed of all protocol changes by the investigator in accordance with the IRB/IEC established procedure. No deviations from the protocol of any type will be made without complying with all the IRB/IEC established procedures.

At all times, the investigator and staff must adhere to study procedures and requirements described in the IRB/IEC approved protocol and study-specific guidance. There must not be any preemptive changes without first notifying the Sponsor or the IRB/IEC. This applies to granting any exceptions to study entry eligibility or procedures.

Important protocol deviations may significantly impact the completeness, accuracy, and/or reliability of key study data or significantly affect a participant's rights, safety, or well-being. Data will be reviewed at sufficiently frequent periodic intervals to identify, remediate, and report those important protocol deviations as appropriate.

11.2. Protocol Amendments

The investigator should communicate requests for protocol amendments directly to the Sponsor or designee. The Sponsor may be required to discuss potential protocol amendments with the appropriate regulatory agencies. The Sponsor will notify the investigator of protocol amendment, and potential changes to the informed consent. Protocol amendments must receive regulatory and ethical review and approval, including those of the institution IRB/EC.

11.3. Audits and Inspections

The Sponsor, authorized representatives of the Sponsor, an IEC, or and IRB may conduct audits or inspections at the study center(s). Audits will include, but not be limited to, study drug supply, presence of required documents, the informed consent process, and comparison of eCRFs with source documents. The investigator agrees to permit audits or inspections conducted at a reasonable time in a reasonable manner.

Regulatory authorities worldwide may also conduct GCP inspections of investigative sites during or after the study. If notified by a regulatory authority that a Sponsor study is being inspected, the investigator must contact the Sponsor immediately and must permit regulatory authority inspections to be conducted according to regulations.

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13. APPENDICES

APPENDIX 1: CONTRACEPTIVE CRITERIA AND DEFINITIONS

Male participants must meet one of the following criteria:

a. Agrees to use one of the accepted contraceptive regimens and not to donate sperm from the first study drug administration to at least 90 days after the last drug administration. An acceptable method of contraception includes one of the following:
   - Abstinence from heterosexual intercourse
   - Male condom with spermicide or male condom with a vaginal spermicide (gel, foam, or suppository)

Female participant must meet one of the following criteria:

a. Is of childbearing potential and agrees to use an acceptable contraceptive method and not donate ovum from the first study drug administration to at least 90 days after the last drug administration. Acceptable contraceptive methods include:
   - Abstinence from heterosexual intercourse
   - At least 1 *of the following highly-effective* methods in combination with one *effective* method of contraception:
     i) The following are examples of *highly-effective* contraceptive methods:
        - Systemic contraceptives (combined birth control pills, injectable/implant/insertable hormonal birth control products, or transdermal patch)
        - Intrauterine device (IUD; with or without hormones)
        - Male partner vasectomized at least 6 months prior to the Screening visit

     ii) The following are examples of *effective* contraceptive methods:
        - Male condom with spermicide
        - Female condom, or cervical cap, or diaphragm, each used with spermicide
        - Contraceptive sponge
   - If the highly effective methods of contraception for women of childbearing potential cannot be achieved, the following physical double-barrier contraceptive method should be used by the women of childbearing potential and their male partner:
     iii) Male condom used simultaneously with diaphragm plus spermicide
     iv) Male condom used simultaneously with cervical cap plus spermicide

OR

b. Is of non-childbearing potential, defined as:
   - surgically sterile (ie, has undergone complete hysterectomy, bilateral oophorectomy, bilateral salpingectomy, bilateral tubal occlusion, or tubal ligation)

OR is in a postmenopausal state:
   i) At least 1 year without menses and without an alternative medical condition prior to the Screening visit.

APPENDIX 2: WORLD HEALTH ORGANIZATION STANDARDIZED PROTOCOLS FOR THE MEASUREMENT OF HEIGHT AND WEIGHT

The following information has been adapted from the standardized physical measurement proposals for the World Health Organization's STEP wise approach to Surveillance (STEPS) program (WHO 2017) accessed here 30 June 2024: chrome-extension://efaidnbmnnnibpcajpcglclefindmkaj/https://cdn.who.int/media/docs/default-source/ncds/ncd-surveillance/steps/part3.pdf?sfvrsn=9bb0f167_2

Measuring Height:

Step 1- Ask the participant to remove their footwear (shoes, slippers, sandals, etc.), head gear (hat, cap, hair bows, comb, ribbons, etc.), and any fancy or high hairdos may have to be pressed.

Note: If it would be insensitive to seek removal of a scarf or veil, the measurement may be taken over light fabric.

Step 2- Ask the participant to stand on the board facing you.

Step 3- Ask the participant to stand with feet together, heels against the back board, knees straight.

Step 4- Ask the participant to look straight ahead and not tilt their head up.

Step 5- Make sure eyes are the same level as the ears.

Step 6- Move the measurement arm gently down onto the head of the participant and ask the participant to breathe in and stand tall.

Step 7- Read and record the height in centimeters at the exact point to the nearest mm.

Step 8- Ask the participant to step away from the measuring board.

Measuring Weight:

Body weight measurements should be done in a consistent manner using a calibrated scale (mechanical or digital scales are acceptable). All weights for a given participant should be measured using the same scale, whenever possible, after the participant has emptied their bladder.

Step 1- Ask the participant to remove their footwear (shoes, slippers, sandals, etc.), head gear (hat, cap, hair bows, comb, ribbons, etc.), and socks. They should also take off any heavy belts and empty out their pockets of mobiles, wallets and coins.

Step 2- Ask the participant to stand still, face forward, place arms on their side, and wait until asked to step off.

Step 3- Read and record the weight in kilograms (kg) and ask the participant to step off the scale.

APPENDIX 3: EXCIPIENTS

Excipients for MET097 for injection (CCI [redacted])

No excipients are used in the manufacture of MET097 for injection (CCI [redacted]).

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