Statistical Analysis Plan

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)

Protocol Number: MET097-24-201

Compound Number: MET097

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

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Version History

This Statistical Analysis Plan (SAP) for study **MET097-24-201** is based on protocol version Protocol Version 6.0 – Amendment 5 (29 August 2025).

SAP Version	Date	Change
1.0	03JUN2025	Original version
2.0	26JUN2025	Added additional methodologies for primary and supplementary analyses if the protocol-specified model has model fit or convergence issues. Added clarifications for the visualizations, derivations, and imputations. Language aligned for consistency.
3.0	14JUL2025	Align with Protocol Version 4.0 Amendment 3 (21APR2025)
4.0	16MAR2026	Updated the Part B design updates in Section 1.2.1.2 to align with the Protocol Version 6.0. Updated Table 4 with the dosing information in Protocol Version 6.0. Updated the Study Schematic in Figure 1 for the Part B Open-label phase, as updated in the Protocol Version 6.0. Updated Table 5 Analysis Sets to Enrolled Set – Part A, Full Analysis Set (FAS) – Part A, Safety Analysis Set – Part A, Enrolled Set - Part B, Safety Analysis Set - Part B, and Safety Analysis Set - Week 36 onwards. In Section 4.2, 5.2, 5.3, 5.4, 5.5, 6.1, 7.6, 8.3 clarified Analysis set is FAS – Part A. Section 6.2 clarified Analysis set is Enrolled Set – Part B. Amended the definition of Treatment Emergent Adverse event in Section 7.2 to align with Pfizer standards. Section 8.2, 8.4, 8.5, 8.7 included Analysis Sets for FAS – Part A and Enrolled Set – Part B. Section 12.1.3 Added 'Outputs at baseline or screening use the study baseline or screening information'. Section 12.2.1 Added: If no nominal visit exists, then all data will be windowed. Windowing for all measurements following the week 60 visit will be performed to establish the safety follow up visit. Section 7.9 clarified that details of the analyses to be performed for Anti-Drug Antibodies will be detailed in a separate ADA Analysis Plan. The immunogenicity results will be provided as an Addendum to the CSR.

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List of Abbreviations

Abbreviation	Definition
ADA	anti-drug antibodies
AE	adverse event
AECI	adverse event of clinical interest
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the curve
BMI	body mass index
BP	blood pressure
CI	confidence interval
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
C_{max}	maximum plasma 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
eGFR	estimated glomerular filtration rate
ET	early termination
GI	gastrointestinal
GLP	Good Laboratory Practice
GLP-1	Glucagon-like peptide-1
GLP-1RA	Glucagon-like peptide-1 receptor agonist
HbA1c	glycated hemoglobin A1c
hGLP-1	human glucagon-like peptide-1
HDL-C	high-density lipoprotein-cholesterol
ICE	intercurrent event
IQR	interquartile range
IUD	intrauterine device
LDL-C	low-density lipoprotein-cholesterol

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Abbreviation	Definition
MACE	major adverse cardiovascular events
MAR	missing at random
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed-effects Model for Repeated Measures
MRI	magnetic resonance imaging
NOAEL	no-observed-adverse effect level
PHQ-9	Patient Health Questionnaire 9
PK	pharmacokinetic
QTc	QT interval corrected
SAE	serious adverse event
SAP	Statistical Analysis Plan
SC	subcutaneous
SD	standard deviation
SoA	Schedule of Activities
SUSAR	suspected unexpected serious adverse reaction
$t_{1/2}$	elimination half-life
TEAE	treatment emergent adverse event
T_{max}	time to maximum concentration
TSH	Thyroid-stimulating hormone
ULN	upper limit of normal

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1. Introduction

This SAP provides a detailed description of the statistical methods and procedures to be implemented for the analysis of data from the clinical study protocol MET097-24-201.

Italics are used in this SAP to identify text extracted directly from the clinical study protocol.

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/m2).

MET097-24-201 is a 28-week Phase 2b study designed to examine the safety and efficacy of four weekly MET097 dosing arms (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 (e.g., titration or titration-free QW dosing, intermittent (e.g., 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. *Evaluation of PK will be found in a separate analysis plan.*

Specifications of tables, figures, and listings (TFLs) are contained in a separate document.

Any reference to "weeks" in this document refers to Study Weeks. Conversion from Study Weeks to Analysis Weeks can be found in Section 12.2.1.

Any changes to the protocol planned analyses are described in Section 10.

1.1. Objectives, Endpoints, and Estimands

1.1.1. Objectives and Endpoints

Objectives and endpoints for:

- Part A (from Study Week 0 [Day 1] through pre-dose Study Week 28 [Day 197]) (from Study Week 0 [Day 1] through pre-dose Study Week 28 [Day 197]) are described in Table 1.
- Part B (from dosing at Study Week 28 [Day 197] through Week 68 [Day 477]) are described in

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Table 2.

Table 1 Objective and Endpoints – Part A

Objectives	*Endpoints*
Primary	
• *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	
• *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:* o *Body weight (kg)* o *BMI (kg/m²)* o *Waist circumference (cm)*
• *To assess the safety and tolerability of MET097 compared to placebo*	*The following safety and tolerability endpoints measured for the duration of the weekly dosing:* • *Occurrence, severity and relatedness of TEAEs AEs of clinical interest: gastrointestinal AEs of Nausea, Vomiting and Diarrhea.* • *Occurrence, severity, and relatedness of other TEAEs* • *Occurrence of abnormal clinically significant physical examination* • *12-lead ECG measurements* • *Laboratory measurements* • *Columbia-Suicide Severity Rating Scale (C-SSRS)* • *Patient Health Questionnaire (PHQ-9)* • *Occurrence of ADAs*

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Objectives	*Endpoints*
• *To characterize the 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 for all participants:* • C_{min} *The following endpoints measured for the duration of the weekly dosing for subset of* CCI *participants of each arm:* • $AUC_{(0-\tau)}$ • C_{max} • T_{max} • *Other PK parameters may be evaluated*
Exploratory	
• *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 the following glucose metabolism parameters: fasting insulin, glycated HbA1c, fasting glucose, fasting glucagon, and HOMA-IR* • *Change from baseline (at all protocol-specified post-baseline measurements) in lipid levels (triglycerides, HDL-C, LDL-C, Non-HDL, and ratio of triglycerides to HDL)*

Abbreviations: ADA = anti-drug antibody; AE = adverse event; $AUC_{(0-\tau)}$ = area under the concentration versus time curve during the dosing interval; BMI = body mass index; C_{min} = minimum observed concentration; C_{max} = maximum observed concentration; C-SSRS = Columbia-Suicide Severity Rating Scale; ECG = electrocardiogram; HbA1c = hemoglobin A1c; HDL-C = high-density lipoprotein-cholesterol; LDL-C = low-density lipoprotein-cholesterol; PHQ-9 = Patient Health Questionnaire 9; PK = pharmacokinetic; TEAE = treatment-emergent adverse event; T_{max} = time to maximum concentration.

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Table 2 Objective and Endpoints – Part B

Objectives	*Endpoints*
Exploratory	
• *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:* o *Body weight (kg)* o *BMI (kg/m²)* o *Waist circumference (cm)*
• *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 TEAEs* • *Occurrence of abnormal clinically significant physical examination* • *Occurrence of abnormal clinically significant 12-lead ECG measurements* • *Occurrence of abnormal clinically significant clinical laboratory measurements* • *C-SSRS* • *PHQ-9* • *Occurrence of ADAs*
• *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*

Abbreviations: ADA = anti-drug antibody; AE = adverse event; BMI = body mass index; C_{min} = minimum observed concentration, C-SSRS = Columbia-Suicide Severity Rating Scale; ECG = electrocardiogram; PHQ-9 = Patient Health Questionnaire 9; PK = pharmacokinetic; TEAE = treatment-emergent adverse event.

1.1.2. Estimands for the Primary Endpoint

The primary clinical question of interest is: What is the effect 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?

The estimands of the primary endpoint are described in Table 3.

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Table 3 Estimands for the Primary Endpoint

Attribute	Primary Estimand (Hypothetical Strategy or Trial Product Estimand)	Supplementary Estimand (Treatment Policy Estimand)
Population	All overweight and obese adults aged 18 to 70 years with a BMI of 27 to 50 kg/m²	Same as primary estimand
Variable	Percent change from baseline in body weight at Week 28 (Day 197) as defined in Section 4.1	Same as primary estimand
Treatment of Interest	Once-weekly MET097 doses of 0.4 mg, 0.6 mg, 0.9 mg and 1.2 mg or Placebo	Same as primary estimand

Handling of Intercurrent Events (ICEs)	**ICEs:**
	• Permanent treatment discontinuation before Week 28 (Day 197)
	• Non-adherence to the following additional protocol-specified study treatment compliance requirements:
	  ○ 4 or more missed doses of dose 1 through dose 8
	  ○ 1 or more missed doses of dose 9 through dose 16
	  ○ 2 or more missed doses of dose 17 through dose 28
	  ○ 2 or more consecutive missed doses at any time
	• The following lifestyle changes that could impact weight loss:
	  ○ use of other weight-loss medications
	  ○ use of bariatric surgery
	  ○ use of commercial weight loss programs
	
	Handling of ICEs:
	ICEs will be handled under the Hypothetical Strategy (or Trial Product Estimand) that participants adhered to protocol-specified study treatment compliance requirements, without any changes to lifestyle that could impact weight loss (i.e., use of other weight loss interventions such as weight-loss medications or bariatric surgery or commercial weight-loss programs).
	Data obtained following the ICEs will be set to missing
	Missing data strategy is described in Section 2.4.
		ICEs:
		Same as primary estimand.
		
		Handling of ICEs:
		ICEs will be handled under the Treatment Policy Strategy in which the data will be evaluated for participants regardless of adherence to study treatment or lifestyle changes.
		Data obtained following the ICEs will be used as collected.
		Missing data strategy is described in Section 2.4.

Summary Measure	Mean difference in the percent change from baseline at Week 28 (Day 197) between MET097 doses of 0.4 mg, 0.6 mg, 0.9 mg or 1.2 mg and Placebo	Same as primary estimand

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1.2. Study Design

1.2.1. General Description

1.2.1.1. 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 1). 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 (i.e.,* 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 (i.e., the first unblinded analysis) for the primary analysis (Part A, Day 197) will occur when all (i.e., N=~225) participants have completed their Day 197 visit (or permanently discontinued from 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.

1.2.1.2. 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 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 the switch to a QW, Q2W, or QM dose for an additional 24 weeks as described in Table 4. 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.

Table 4: 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

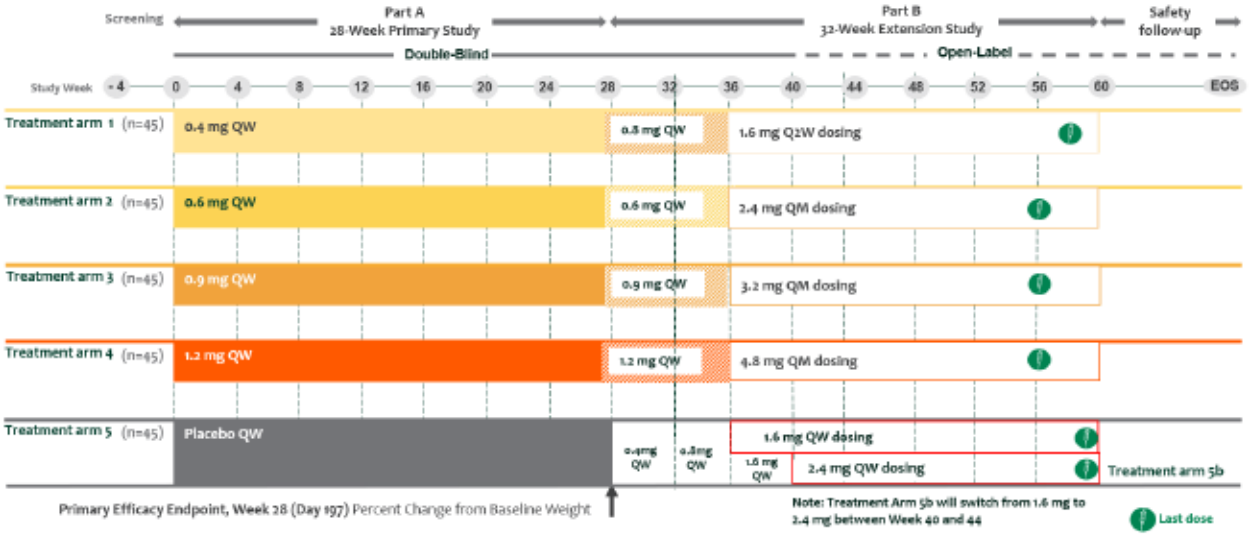
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	*From Study Week 0 through pre-dose Study Week 28**	*From the dosing of Study Week 28 through pre-dose Study Week 36*	*From the dosing Study Week 36 through pre-dose Study Week 40*	*From the dosing Study Weeks 40 through End of Study*
Treatment Arm 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.

Figure 1: 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).

1.2.2. Treatments

The following study treatments will be administered:

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- Investigational Product: MET097

  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 *supplied as* CCI *. There are* CCI

- Control Product: Placebo

  Sterile 0.9% (w/v) saline will be used as placebo treatment during the study. The placebo visually matches MET097 as constituted for injection.

1.2.3. Study Procedures

Details on the study assessments to be performed will be found in the protocol.

1.2.4. 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 schematics.

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 (i.e.,* CCI *participants per treatment regimen) will not be stratified by* CCI

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.*

1.2.5. Blinding Procedures

1.2.5.1. 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 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.

1.2.5.2. 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 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.

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1.2.6. Reporting Milestones

1.2.6.1. Primary Reporting Milestone

The primary reporting milestone, i.e., the Week 28 analysis will occur when all (i.e., N=~225) participants have completed their Week 28 (Day 197) visit (or permanently discontinued from the study prior to Day 197).

1.2.6.2. Final Reporting Milestone

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.

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2. General Considerations

Specifications and considerations in this SAP apply only to the analyses described in this SAP.

Reference to study treatment, or treatment, refers to each of the MET097 dosing arms and placebo. Endpoints will be summarized by treatment and visit, unless otherwise specified.

All p-values reported will be associated with 2-sided hypotheses tests unless specified otherwise

Source listings will be provided for all measurements and endpoints for which statistical analysis (including descriptive summaries) is performed.

General definitions and conventions can be found in Section 12.

2.1. Statistical Methods

This section describes the general statistical methods based on the type of endpoint. Unless otherwise specified, these methods will be used for the corresponding endpoint type.

2.1.1. Continuous Endpoints

2.1.1.1. Descriptive Statistics for Continuous Endpoints

Summary statistics for all continuous endpoints will include the following:

- total number of participants
- arithmetic mean [shown to 1 decimal place more than reported in the eCRF]
- standard deviation (SD) [shown to 2 decimal places more than reported in the eCRF]
- standard error (SE) [shown to 2 decimal places more than reported in the eCRF]
- median [shown to 1 decimal place more than reported in the eCRF]
- interquartile range (IQR), including the 1st quartile (Q1) and 3rd quartile (Q3) [shown to 1 decimal place more than reported in the eCRF]
- range, including the minimum and maximum [shown to the same number of decimal places as reported in the eCRF]

2.1.1.2. Single Timepoint Analyses

Comparisons of continuous endpoints to be analyzed at a single timepoint between MET097 dosing arms and placebo will be performed using an Analysis of Covariance (ANCOVA) model adjusting for treatment, CCI and the baseline measurement (if applicable). The baseline measurement will be used for all evaluations where the dependent variable is a measurement of change from baseline or change from baseline; otherwise, the baseline measurement will be removed from the model. If a cross tabulation for the corresponding dataset used in the model of treatment and CCI results in less than 5 participants in any bin, CCI will be removed from the model. The evaluation of treatment effect will report the following statistics for each of the MET097 dosing arms: the LS mean, SE of the LS mean, the LS mean difference from placebo, SE of the LS mean difference from placebo, 2-sided 95% CIs for the LS mean, the LS mean difference from placebo, and p-value.

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2.1.1.3. Longitudinal Analyses

Comparisons of longitudinal continuous endpoints between MET097 dosing arms and placebo will be performed using an MMRM model and include terms for treatment, visit, treatment-by-visit interaction, CCI and the baseline measurement (if applicable) as fixed effects. An unstructured covariance (UN) structure will model the relationship between within-patient errors. If this model fails to converge, the following variance-covariance structures will be tested in order until convergence is achieved: (i) heterogeneous Toeplitz, (ii) heterogeneous compound symmetry. The baseline measurement will be used for all evaluations where the dependent variable is a measurement of change from baseline or change from baseline; otherwise, the baseline measurement will be removed from the model. If a cross tabulation for the corresponding dataset used in the model of treatment, visit, and CCI results in less than 5 participants in any bin, CCI will be removed from the model. Contrasts will be constructed for comparing each of the four MET097 dosing arms to placebo. The evaluation of treatment effect will report the following statistics for each of the MET097 dosing arms: the LS mean, SE of the LS mean, the LS mean difference from placebo, SE of the LS mean difference from placebo, and 2-sided 95% CIs for the LS mean, the LS mean difference from placebo, and p-value.

2.1.2. Categorical Endpoints

2.1.2.1. Descriptive Statistics for Categorical Endpoints

Summary statistics for all binary and other categorical variables will include the following:

- total number of participants
- frequencies
- Percentages [shown to 1 decimal place except 0 and 100 which will be reported with no decimal places]

2.1.2.2. Single Timepoint Analyses

Comparisons of binary endpoints between MET097 and placebo will be performed using a logistic regression model adjusting for treatment, CCI and baseline measurement (if applicable). The baseline measurement will be used for all evaluations where the dependent variable is categorized version of a continuous measurement; otherwise, the baseline measurement will be removed from the model. If a cross tabulation for the corresponding dataset used in the model of treatment and CCI results in less than 5 participants in any bin, CCI will be removed from the model. The evaluation of treatment effect will report the following statistics for each of the MET097 dosing arms: the odds ratio (OR) relative to placebo, SE of the OR, risk difference from the placebo, SE of the risk difference, 2-sided 95% CIs, and p-value.

The risk difference from the placebo and SE of the risk difference will be estimated using the generalized linear model framework (Wacholder, 1986).

2.2. Statistical Hypotheses

For the primary analysis, the following four pairwise 2-sided statistical hypothesis tests will be performed, to compare each of the four MET097 dosing arms (0.4 mg, 0.6 mg, 0.9 mg and 1.2 mg) to placebo:

$$H_{1,0}: \mu_{0.4\,mg} - \mu_{PBO} = 0 \text{ vs } H_{1,A}: \mu_{0.4\,mg} - \mu_{PBO} \neq 0$$

$$H_{2,0}: \mu_{0.6\,mg} - \mu_{PBO} = 0 \text{ vs } H_{2,A}: \mu_{0.6\,mg} - \mu_{PBO} \neq 0$$

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$$H_{3,0}: \mu_{0.9\,mg} - \mu_{PBO} = 0 \text{ vs } H_{3,A}: \mu_{0.9\,mg} - \mu_{PBO} \neq 0$$

$$H_{4,0}: \mu_{1.2\,mg} - \mu_{PBO} = 0 \text{ vs } H_{4,A}: \mu_{1.2\,mg} - \mu_{PBO} \neq 0$$

where $\mu_{i\,mg}$ and μ_{PBO} are the mean percent change from baseline in body weight at Week 28 (Day 197) for MET097 i mg and Placebo, respectively, where i is 0.4, 0.6, 0.9, and 1.2.

The p-values from each of the four tests will be used to assess statistical significance for each pairwise comparison of MET097 dosing arm to placebo hypothesis, while controlling the overall Type 1 error at 5%, as described in Section 2.3.

2.3. Multiplicity Adjustment

The overall Type 1 error rate for the analysis of the primary efficacy estimand will be controlled at 5% using the Hochberg procedure to adjust for multiplicity for the four pairwise statistical comparisons of MET097 dosing arms to placebo. The analysis of the supplementary efficacy estimand will use the same approach for multiplicity adjustment as the primary efficacy estimand.

There will be no multiplicity adjustments for any of the secondary or exploratory analyses.

2.4. Missing Data Handling

For missing data under the primary estimand that assumes missing at random (MAR) and is analyzed using MMRM, no imputation of missing data will be performed. Missing data will be handled implicitly by the MMRM.

Imputation of missing data not assumed to be MAR was recommended to be performed using retrieved dropout imputation as in Wang et al. (2023). However, given the small sample size per treatment group in this Phase 2b trial, the implementation of a reliable retrieved dropout imputation is not feasible. As a result, placebo-washout imputation as in Wang et al. (2023) will be performed for the imputation of missing data not assumed to be MAR. The details for placebo-washout imputation for a given endpoint are as follows:

(1) Set a seed of 202509724201.

(2) Missing Week 28 assessment in the placebo arm:

   a. For each of M = 200 imputation datasets:

      i. Use baseline, the post-baseline monthly visits, and Week 27 (i.e., a total of 6 visits) to impute missing data in the placebo arm at Week 28 using the MCMC method.

(3) Missing Week 28 assessment in the MET097 dosing arms:

   a. Perform linear regression amongst placebo participants of Week 28 adjusting for baseline and CCI as covariates. Include only the actual values for the placebo at Week 28 without imputed values (i.e., subset the placebo to include only Week 28 completers).

   b. Extract estimates for the coefficients ($\widehat{\boldsymbol{\beta}}$), the variance-covariance matrix ($\widehat{\boldsymbol{\Sigma}}$) of ($\widehat{\boldsymbol{\beta}}$), the estimate of the residual variance ($\hat{\sigma}$), and the degrees of freedom (df = regression sample size – 3) from the linear regression model.

   c. For each of M = 200 imputation datasets:

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i. Sample from the posterior distribution of the residual variance using a chi-square distribution such that $\sigma^2 \sim \frac{\hat{\sigma}^2 df}{\chi^2(df)}$.

ii. Sample from the posterior distribution of the regression coefficients using a multivariate normal distribution with mean and variance-covariance matrix from b) above, $B \sim MVN(\hat{\boldsymbol{\beta}}, (\mathrm{X'X})^{-1}\sigma^2)$.

iii. For each participant in an MET097 dosing arm with missing Week 28 data:

1. Predict their missing Week 28 measurements with the regression model using the coefficients generated in i).
2. Add a random normal residual error generated from a normal distribution with mean 0 and variance generated in ii), i.e., $\epsilon \sim N(0, \sigma^2)$.

(4) For each of the M = 200 imputation datasets, combine the Week 28 data for the placebo completers, imputed placebo participants, the MET097 dosing arm completers, and the imputed MET097 dosing arm participants.

(5) Perform analysis of each of the M = 200 complete datasets.

(6) Use Rubin's formula (Rubin, 1987) to integrate the estimates from each of the M = 200 analyses into the final results.

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3. Analysis Sets

The analysis sets are described in Table 5 and Table 6.

Table 5 Participant Analysis Sets

Analysis Set	Description
Enrolled Set – Part A	All participants who signed informed consent at study start
Full Analysis Set (FAS) – Part A	All randomized participants Analyses conducted using the FAS – Part A will be evaluated by randomized treatment arm.
Safety Analysis Set – Part A	All participants who received at least one dose of treatment Analyses conducted using the Safety Analysis Set – Part A will be evaluated by actual treatment arm.
Enrolled Set - Part B	All participants who signed Informed Consent for Part B
Safety Analysis Set - Part B	All participants who signed Informed Consent for Part B and received at least one dose in Part B Analyses conducted using the Safety Analysis Set – Part B will be evaluated by the Part B treatment regimens*
Safety Analysis Set - Week 36 onwards	All participants who signed Informed Consent for Part B and received at least one dose from week 36 onwards Analyses conducted using the Safety Analysis Set – Week 36 onwards will be evaluated by the Part B treatment regimens*
Pharmacokinetic (PK) Analysis Set	Described in a separate analysis plan

* See Table 4

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Table 6 Analysis Datasets

Analysis Dataset	Description
Efficacy Adherence to Study Dataset	Data obtained during the treatment period from the FAS – Part A, excluding the following data points: • Measurements after the last dose date + 7 days for participants who permanently discontinue treatment before Week 28 (Day 197) • Measurements after the first non-adherence to the following additional protocol-specified study treatment compliance requirements: o 4 or more missed doses of dose 1 through dose 8 o 1 or more missed doses of dose 9 through dose 16 o 2 or more missed doses of dose 17 through dose 28 o 2 or more consecutive missed doses at any time • Measurements after the first lifestyle changes that could impact weight loss of the following: o use of other weight-loss medications o use of bariatric surgery o use of commercial weight loss programs
All Efficacy Study Dataset	Data obtained during treatment period from the FAS – Part A, regardless of adherence to study treatment or change in lifestyle changes

Abbreviations: FAS = full analysis set; PK = pharmacokinetic

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4. Analyses Supporting the Primary Objective

This section includes the analysis details for the primary objective and associated endpoint (Table 1).

4.1. Definition of the Primary Endpoint

Percent change from baseline in body weight is calculated as follows:

$$\left(\frac{\text{body weight}_i - \text{body weight}_{\text{baseline}}}{\text{body weight}_{\text{baseline}}}\right) \times 100$$

where i is weekly post-baseline through Week 28 (Day 197) (i.e., Week 1, Week 2, etc.).

The primary efficacy endpoint is percent change from baseline in body weight at Week 28 (Day 197).

The primary and supplementary estimands are defined in Section 1.1.2.

4.2. Main Analytical Approach

The percent change from baseline in body weight between MET097 dosing arms and placebo will be analyzed using the MMRM method described in Section 2.1.1.3, including the baseline body weight measurement, for the *Efficacy Adherence to Study Set*. Data from the weekly post-baseline measurements through Week 28 (Day 197) will be used in the analysis (i.e., Week 1, Week 2, etc.). Missing data will be assumed to be missing at random (MAR). Missing data will not be imputed (see Section 2.4).

Hypothesis testing of the treatment effect will be performed as described in Section 2.2. Statistical significance will be determined with adjustment for multiplicity as described in Section 2.3.

Summary statistic (see Section 2.1.1.1) for percent change from baseline in body weight using the FAS – Part A by visit and treatment will be provided through Week 28 (Day 197) In addition, the mean difference from placebo and SE of the mean difference from placebo will be provided.

The following graphical presentations will be provided:

- spaghetti plot by individual participant showing percent change from baseline weight over time through Week 28 (Day 197) using the FAS – Part A
- spaghetti plot by individual participant showing change from baseline weight over time through Week 28 (Day 197) using the FAS – Part A
- spaghetti plot by individual participant showing observed weight over time through Week 28 (Day 197) using the FAS – Part A
- line plot with error bars showing the arithmetic mean (+/- SE) percent change from baseline in body weight at all protocol-specified weekly post-baseline measurements through Week 28 (Day 197) by treatment group using the FAS – Part A
- line plot with error bars showing the LS mean (with 95% CI) percent change from baseline in body weight at all protocol-specified weekly post-baseline measurements through Week 28 (Day 197) by treatment group using the *Efficacy Adherence to Study Set*
- forest plot of the LS mean difference from placebo for MET097 dosing arms in percent change from baseline in body weight showing the 95% CI at Week 28 (Day 197) using the *Efficacy Adherence to Study Set*

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4.3. Sensitivity Analysis

No sensitivity analyses are planned for the primary analysis.

4.4. Supplementary Analysis

The percent change from baseline in body weight between MET097 dosing arms and placebo at Week 28 (Day 197) will be analyzed using the ANCOVA method described in Section 2.1.1.2, including the baseline body weight measurement, for the *All Efficacy Study Set*. Missing data is not assumed to be MAR. Missing data will be imputed with placebo-washout imputation (see Section 2.4).

The following graphical presentations will be provided:

- forest plot of the LS mean difference from placebo for MET097 dosing arms in percent change from baseline in body weight showing the 95% CI at Week 28 (Day 197) using the *All Efficacy Study Set*

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5. Analyses Supporting Secondary Objectives

This section includes the analyses details for the secondary objectives and associated endpoints (Table 1).

5.1. Percent Change from Baseline in Body Weight prior to Week 28

Analyses of percent change from baseline in body weight prior to Week 28 (Day 197) are captured in Section 4.

5.2. Occurrence of Body Weight Reduction (Weight Loss) from Baseline of ≥ 5%, ≥ 10%, and ≥ 15% at Week 28

Body weight reduction (weight loss) from baseline at Week 28 (Day 197) is calculated as follows:

$$-\left(\frac{\text{body weight}_{\text{Week 28 (Day 197)}} - \text{body weight}_{\text{baseline}}}{\text{body weight}_{\text{baseline}}}\right) \times 100$$

The occurrence of body weight reduction of ≥ 5%, ≥ 10%, and ≥ 15% is determined for each subject at Week 28 (Day 197).

Body weight reduction of ≥ 5%, ≥ 10%, and ≥ 15% between MET097 dosing arms and placebo at Week 28 (Day 197) will be analyzed using the logistic regression method described in Section 2.1.2.2 for the *Efficacy Adherence to Study Set*. Missing data will be assumed to be MAR. Missing data will not be imputed (see Section 2.4).

Body weight reduction of ≥ 5%, ≥ 10%, and ≥ 15% between MET097 dosing arms and placebo at Week 28 (Day 197) will be analyzed using the logistic regression method described in Section 2.1.2.2 for the *All Efficacy Study Set*. Missing data is not assumed to be MAR. Missing data will be imputed with placebo-washout imputation described in Section 2.4.

Summary statistics (see Section 2.1.2.1) for body weight reduction of ≥ 5%, ≥ 10%, and ≥ 15% using the FAS – Part A will be provided through Week 28 (Day 197).

The following graphical presentations will be provided:

- bar plot of the occurrence of body weight reduction of ≥ 5%, ≥ 10%, and ≥ 15% at Week 28 (Day 197) by treatment group using the FAS – Part A

5.3. Change from Baseline in Body Weight (kg) at all Protocol-Specified Weekly Post-Baseline Measurements through Week 28

The change from baseline in body weight (kg) is calculated as follows:

$$\text{body weight}_i - \text{body weight}_{\text{baseline}}$$

where i is all protocol-specified weekly post-baseline visits (i.e., Week 1, Week 2, etc.).

The change from baseline in body weight (kg) between MET097 dosing arms and placebo will be analyzed using the MMRM method described in Section 2.1.1.3, including the baseline body weight measurement, for the *Efficacy Adherence to Study Set*. Data from all protocol-specified weekly post-baseline measurements through Week 28 (Day 197) will be used in the analysis (i.e., Week 1, Week 2, etc.). Missing data will be assumed to be MAR. Missing data will not be imputed (see Section 2.4).

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The change from baseline in body weight (kg) between MET097 and placebo at Week 28 (Day 197) will be analyzed using the ANCOVA method (see Section 2.1.1.2), including the baseline body weight measurement, for the *All Efficacy Study Set*. Missing data is not assumed to be MAR. Missing data will be imputed with placebo-washout imputation (see Section 2.4.

Summary statistics (see Section 2.1.1.1) for change from baseline in body weight (kg) using the FAS – Part A by visit and treatment will be provided through Week 28 (Day 197). In addition, the mean difference from placebo, and SE of the mean difference from placebo will be provided.

The following graphical presentations will be provided:

- line plot with error bars showing the arithmetic mean (+/- SE) change from baseline in body weight (kg) at all protocol-specified weekly post-baseline measurements through Week 28 (Day 197) by treatment group using the FAS – Part A
- line plot with error bars showing the LS mean (with 95% CI) change from baseline in body weight (kg) at all protocol-specified weekly post-baseline measurements through Week 28 (Day 197) by treatment group using the *Efficacy Adherence to Study Set*
- forest plot of the LS mean difference from placebo for MET097 dosing arms in change from baseline in body weight (kg) showing the 95% CI at Week 28 (Day 197) using the *Efficacy Adherence to Study Set*
- forest plot of the LS mean difference from placebo for MET097 dosing arms in change from baseline in body weight (kg) showing the 95% CI at Week 28 (Day 197) using the *All Efficacy Study Set*

5.4. Change from Baseline in Body Mass Index at all Protocol-Specified Weekly Post-Baseline Measurements through Week 28

The change from baseline in BMI (kg/m^2) is calculated as follows:

$$BMI_i - BMI_{baseline}$$

where i is all protocol-specified weekly post-baseline visits (i.e., Week 1, Week 2, etc.).

Summary statistics (see Section 2.1.1.1) for change from baseline in BMI (kg/m^2) using the FAS - Part A by visit and treatment will be provided through Week 28 (Day 197).

5.5. Change from Baseline in Waist Circumference at all Protocol-Specified Weekly Post-Baseline Measurements through Week 28

The change from baseline in waist circumference (cm) is calculated as follows:

$$\text{waist circumference}_i - \text{waist circumference}_{baseline}$$

where i is all protocol-specified weekly post-baseline visits (i.e., Week 1, Week 2, etc.).

The change from baseline in waist circumference (cm) between MET097 dosing arms and placebo will be analyzed using the MMRM method described in Section 2.1.1.3, including the baseline body weight measurement, for the *Efficacy Adherence to Study Set*. Data from all protocol-specified weekly post-baseline measurements through Week 28 (Day 197) will be used in the analysis (i.e., Week 1, Week 2, etc.). Missing data will be assumed to be MAR. Missing data will not be imputed (see Section 2.4).

The change from baseline in waist circumference (cm) between MET097 dosing arms and placebo at Week 28 (Day 197) will be analyzed using the ANCOVA method described in Section 2.1.1.2, including

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the baseline body weight measurement, for the *All Efficacy Study Set*. Missing data is not assumed to be MAR. Missing data will be imputed with placebo-washout imputation (see Section 2.4).

Summary statistics (see Section 2.1.1.1) for change from baseline in waist circumference (cm) using the FAS – Part A by visit and treatment will be provided through Week 28 (Day 197). In addition, the mean difference from placebo, and SE of the mean difference from placebo will be provided.

The following graphical presentations will be provided:

- line plot with error bars showing the arithmetic mean (+/- SE) change from baseline in waist circumference (cm) at all protocol-specified weekly post-baseline measurements through Week 28 (Day 197) using the FAS – Part A
- line plot with error bars showing the LS mean (with 95% CI) change from baseline in waist circumference (cm) at all protocol-specified weekly post-baseline measurements through Week 28 (Day 197) using the *Efficacy Adherence to Study Set*
- forest plot of the LS mean difference from for MET097 dosing arms in placebo change from baseline in waist circumference (cm) showing the 95% CI at Week 28 (Day 197) using the *Efficacy Adherence to Study Set*
- forest plot of the LS mean difference from for MET097 dosing arms in placebo change from baseline in waist circumference (cm) showing the 95% CI at Week 28 (Day 197) using the *All Efficacy Study Set*

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6. Analyses Supporting Exploratory Objectives

This section includes the analyses details for the exploratory objectives and associated endpoints (Table 1).

6.1. Part A

6.1.1. Glucose Metabolism Parameters

The following glucose metabolism parameters will be evaluated:

- Fasting insulin (uIU/mL)
- Glycated HbA1c (%)
- Fasting glucose (mg/dL)
- Fasting glucagon (pg/mL)
- HOMA-IR, calculated as

  fasting glucose (mg/dL) X fasting insulin (uIU/mL) / 405

For each of the parameters identified above, change from baseline is calculated as follows:

$$\text{parameter}_i - \text{parameter}_{\text{baseline}}$$

where parameter is the glucose metabolism parameter (i.e., fasting insulin, glycated HbA1c, fasting glucose and fasting glucagon) and i is all protocol-specified weekly post-baseline visits (i.e., Week 1, Week 2, etc.).

The change from baseline for each glucose metabolism parameter between MET097 dosing arms and placebo will be analyzed using the MMRM method described in Section 2.1.1.3, including the baseline body weight measurement, for the *Efficacy Adherence to Study Set*. Data from all protocol-specified weekly post-baseline measurements through Week 28 (Day 197) will be used in the analysis (i.e., Week 1, Week 2, etc.). Missing data will be assumed to be MAR. Missing data will not be imputed (see Section 2.4).

The change from baseline for each glucose metabolism parameter between MET097 dosing arms and placebo at Week 28 (Day 197) will be analyzed using the ANCOVA method described in Section 2.1.1.2, including the baseline body weight measurement, for the *All Efficacy Study Set*. Missing data is not assumed to be MAR. Missing data will be imputed with placebo-washout imputation (see Section 2.4).

Summary statistics (see Section 2.1.1.1) for change from baseline for each glucose metabolism parameter using the FAS – Part A by visit and treatment will be provided through Week 28 (Day 197). In addition, the mean difference from placebo, and SE of the mean difference from placebo will be provided.

The following graphical presentations will be provided:

- line plot with error bars showing the arithmetic mean (+/- SE) change from baseline for each glucose metabolism parameter at all protocol-specified weekly post-baseline measurements through Week 28 (Day 197) by treatment group using the FAS – Part A
- line plot with error bars showing the LS mean (with 95% CI) change from baseline for each glucose metabolism parameter at all protocol-specified weekly post-baseline measurements through Week 28 (Day 197) by treatment group using the *Efficacy Adherence to Study Set*

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- forest plot of the LS mean difference from placebo for MET097 dosing arms in change from baseline for each glucose metabolism parameter showing the 95% CI at Week 28 (Day 197) using the *Efficacy Adherence to Study Set*
- forest plot of the LS mean difference from placebo for MET097 dosing arms in change from baseline for each glucose metabolism parameter showing the 95% CI at Week 28 (Day 197) using the *All Efficacy Study Set*

6.1.2. Lipid Levels

The following lipid level parameters will be evaluated:

- Triglycerides (mg/dL)
- HDL-C (mg/dL)
- LDL-C (mg/dL)
- Non-HDL (mg/dL), calculated as

  Total cholesterol (mg/dL) – LDL-C (mg/dL)
- Ratio of Triglycerides to HDL-C, calculated as

  Triglycerides (mg/dL) / HDL-C (mg/dL)

For each of the parameters identified above, change from baseline is calculated as follows:

$$\text{parameter}_i - \text{parameter}_{\text{baseline}}$$

where parameter is the lipid level parameter (i.e., triglycerides, HDL-C, and LDL-C) and i is all protocol-specified weekly post-baseline visits (i.e., Week 1, Week 2, etc.).

The change from baseline for each lipid level parameter between MET097 dosing arms and placebo will be analyzed using the MMRM method described in Section 2.1.1.3, including the baseline body weight measurement, for the *Efficacy Adherence to Study Set*. Data from all protocol-specified weekly post-baseline measurements through Week 28 (Day 197) will be used in the analysis (i.e., Week 1, Week 2, etc.). Missing data will be assumed to be MAR. Missing data will not be imputed (see Section 2.4).

The change from baseline for each lipid level parameter between MET097 dosing arms and placebo at Week 28 (Day 197) will be analyzed using the ANCOVA method described in Section 2.1.1.2, including the baseline body weight measurement, for the *All Efficacy Study Set*. Missing data is not assumed to be MAR. Missing data will be imputed with the placebo-washout imputation (see Section 2.4).

Summary statistics (see Section 2.1.1.1) for change from baseline for each lipid level parameter using the FAS – Part A by visit and treatment will be provided through Week 28 (Day 197). In addition, mean difference from placebo, and SE of mean difference from placebo will be provided.

The following graphical presentations will be provided:

- line plot with error bars showing the arithmetic mean (+/- SE) change from baseline for each lipid level parameter at all protocol-specified weekly post-baseline measurements through Week 28 (Day 197) by treatment group using the FAS – Part A
- line plot with error bars showing the LS mean (with 95% CI) change from baseline for each lipid level parameter at all protocol-specified weekly post-baseline measurements through Week 28 (Day 197) by treatment group using the *Efficacy Adherence to Study Set*

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- forest plot of the LS mean difference from placebo for MET097 dosing arms in change from baseline for each lipid level parameter showing the 95% CI at Week 28 (Day 197) using the *Efficacy Adherence to Study Set*
- forest plot of the LS mean difference from placebo for MET097 dosing arms in change from baseline for each lipid level parameter showing the 95% CI at Week 28 (Day 197) using the *All Efficacy Study Set*

6.2. Part B

6.2.1. Percent Change from Baseline in Weight-Related Parameters (continuous) at all Protocol-Specified Measurements Week 28 through EOS

The following continuous weight-related parameters will be evaluated from Week 28 (Day 197) through EOS:

- percent change from baseline body weight (defined in Section 4.1)
- change from baseline body weight (kg) (defined in Section 5.3)
- change from baseline in BMI (kg/m^2) (defined in Section 5.4)
- change from baseline in waist circumference (cm) (defined in Section 5.5)

Summary statistics (see Section 2.1.1.1) for each continuous weight-related parameter using the Enrolled Set – Part B, by visit and treatment will be provided from Week 28 (Day 197) through EOS.

The following graphical presentations will be provided:

- line plot with error bars showing the arithmetic mean (+/- SE) for each continuous weight-related parameter at all protocol-specified weekly post-baseline measurements from Week 28 (Day 197) through EOS by treatment group using the Enrolled Set for Part B.

6.2.2. Percent Change from Baseline in Weight-Related Parameters (binary) at all Protocol-Specified Measurements Week 28 through EOS

Summaries will be provided for Part B.

Body weight reduction (weight loss) from baseline is defined in Section 5.2.

Summary statistics (see Section 2.1.2.1)for body weight reduction of ≥ 5%, ≥ 10%, and ≥ 15% using the Enrolled Set – Part B, will be provided from Week 28 (Day 197) through EOS.

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7. Safety Analyses

Unless otherwise specified, the Safety Analysis Set – Part A will be used for Part A and the Safety Analysis Set – Part B will be used for Part B to perform the safety analyses.

Unless otherwise specified, safety analyses will be performed by Part A and Part B.

7.1. Extent of Exposure

Total number of doses and cumulative exposure (mg) will be summarized by treatment.

7.2. Adverse Events

AEs will be summarized for Part A and Part B.

Classification of AEs will be performed by SOC and PT using MedDRA v27.1.

- An adverse event is identified as a TEAE when the event begins on or after the participant's study medication start date and time.

If there is any uncertainty whether an AE is treatment-emergent or not, it will be assumed treatment-emergent.

If there is any uncertainty whether an AE is related or not, it will be assumed related.

Gastrointestinal TEAEs of clinical interest (AECI) are defined as Nausea, Vomiting and Diarrhea

The following summaries will be provided by treatment and overall:

- Overall summary of AEs
- Number (%) of participants with TEAEs by SOC and PT
- Number (%) of participants with TEAEs by PT
- Number (%) of participants with most common TEAEs (>= 5%) by PT
- Number (%) of participants with TEAEs by SOC, PT, and severity
- Number (%) of participants with TEAEs by SOC, PT, and maximum severity
- Number (%) of participants with treatment-related TEAEs by SOC and PT
- Number (%) of participants with treatment-related TEAEs by PT
- Number (%) of participants with most common treatment-related TEAEs (>= 5%) by PT
- Number (%) of participants with treatment-related TEAEs by SOC, PT, and severity
- Number (%) of participants with treatment-related TEAEs by SOC, PT, and maximum severity
- Number (%) of participants with TEAEs leading to treatment discontinuation by SOC and PT
- Number (%) of participants with TEAEs leading to treatment discontinuation by PT
- Number (%) of participants with TEAEs leading to treatment discontinuation by SOC, PT, and severity
- Number (%) of participants with TEAEs leading to treatment discontinuation by SOC, PT, and maximum severity

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- Number (%) of participants with GI AECIs by PT
- Number (%) of participants with GI AECIs by PT and severity
- Number (%) of participants with GI AECIs by PT and maximum severity
- Number (%) of participants by onset time relative to first dose administered for:
    - Nausea, vomiting, or diarrhea
    - Nausea
    - Vomiting
    - Diarrhea
- Number (%) of participants with AECIs where the AECIs are defined as:
    - 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
    - Any study drug-related hypersensitivity reaction
    - Hypoglycemia
    - 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
    - Suspicion of pancreatitis or pancreatic cancer
    - Major Adverse Cardiovascular Events (MACE)
    - Thyroid C-Cell Hyperplasia and C-Cell Neoplasms
    - 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
- Number (%) of post-dose injection site reactions by maximum severity

Deaths and serious adverse events (SAEs) will be listed.

All analyses above will also be repeated using the Safety Analysis Set – Week 36 onwards.

7.3. Vital Signs

The following vital sign parameters will be reported:

- pulse (beats/min)
- systolic blood pressure (SBP) (mmHg)
- diastolic blood pressure (DBP) (mmHg)
- body temperature (°C)

If pulse, SBP, and DBP are collected in triplicate, a mean value will be calculated.

Observed and change from baseline for vital signs parameters will be summarized by visit and treatment.

Potentially clinically significant (PCS) criteria are derived as follows:

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- Pulse
  - < 50 beats/min or decrease > 20 beats/min
  - > 100 beats/min or increase > 25 beats/min
- SPB
  - < 90 mmHg or decrease > 30 mmHg
  - > 160 mmHg or increase > 30 mmHg
- DBP
  - < 50 mmHg or decrease > 20 mmHg
  - > 100 mmHg or increase > 20 mmHg
- Temperature
  - > 37.5 °C
  - < 35 °C

PCS criteria for vital signs will be summarized by visit.

7.4. Physical Examination

Physical examinations will be listed.

7.5. Electrocardiogram

If numeric ECG parameters are collected in triplicate, a mean value will be calculated.

For numeric ECG parameters, observed and change from baseline for will be summarized by visit and treatment.

Potentially clinically significant (PCS) criteria are derived as follows:

- Heart Rate (HR) (beats/min)
  - ≥ 100 beats/min
  - > 20 change from baseline in beats/min
  - ≥ 100 beats/min or > 20 change from baseline in beats/min

PCS criteria for ECG will be summarized by visit. In addition, PCS criteria occurring at ≥ consecutive visits and ≥ 3 visits will be summarized.

7.6. Laboratory Measurements

A summary by visit and treatment and a shift table by baseline to the worst post-baseline range-defined category (< LLN, normal, > ULN) will be provided for the following laboratory parameters:

- Amylase, Lipase
  - Amylase (U/L)
  - Lipase (U/L)

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- Biochemistry
  - Alanine Aminotransferase (U/L)
  - Albumin (g/dL)
  - Alkaline Phosphatase (U/L)
  - Aspartate Aminotransferase (U/L)
  - Calcium (mg/dL)
  - Carbon Dioxide (mmol/L)
  - Chloride (mmol/L)
  - Creatine Kinase (U/L)
  - Creatinine (mg/dL)
  - Direct Bilirubin (mg/dL)
  - eGFR (Ckd-Epi) (mL/min/1.73m2)
  - Indirect Bilirubin (mg/dL)
  - Magnesium (mg/dL)
  - Potassium (mmol/L)
  - Sodium (mmol/L)
  - Total Bilirubin (mg/dL)
  - Urea Nitrogen (mg/dL)
- Coagulation
  - Activated Partial Thromboplastin Time (Seconds)
  - Prothrombin Intl. Normalized Ratio (Ratio)
  - Prothrombin Time (Seconds)
- Glucose Metabolism
  - Glucagon (pg/mL)
  - Glucose (mg/dL)
  - Hemoglobin A1C (%)
  - Insulin (mU/L)
- Hematology
  - Basophils (10^3/uL)
  - Basophils/Leukocytes (%)
  - Eosinophils (10^3/uL)
  - Eosinophils/Leukocytes (%)
  - Ery. Mean Corpuscular Hemoglobin (pg)

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  - Ery. Mean Corpuscular Volume (fL)
  - Erythrocytes (10^6/uL)
  - Hematocrit (%)
  - Hemoglobin (g/dL)
  - Leukocytes (10^3/uL)
  - Lymphocytes (10^3/uL)
  - Lymphocytes/Leukocytes (%)
  - Monocytes (10^3/uL)
  - Monocytes/Leukocytes (%)
  - Neutrophils (10^3/uL)
  - Neutrophils/Leukocytes (%)
  - Platelets (10^3/uL)
- Lipids Level
  - Total Cholesterol (mg/dL)
  - HDL Cholesterol (mg/dL)
  - LDL Cholesterol (mg/dL)
  - Total Cholesterol (mg/dL)
  - Triglycerides (mg/dL)
- Urinalysis
  - Urine Protein (mg/dL)

A line plot with error bars showing the arithmetic mean (+/- SE) change from baseline for the above defined laboratory parameters by treatment group may be provided.

If the FAS – Part A and the Safety Analysis Set – Part A are equivalent, summary statistics for the glucose and lipid parameters will only be provided on the FAS – Part A as described in Section 6.1.1 and Section 6.1.2, respectively.

PCS criteria for selected laboratory parameters are derived as follows:

- Alanine Aminotransferase (U/L)
  - >1xULN
    - >3xULN
    - >5xULN
- Alkaline Phosphatase (U/L)
  - >2xULN
- Amylase (U/L)
  - >1xULN

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        - >3xULN
- Aspartate Aminotransferase (U/L)
    - >1xULN
        - >3xULN
        - >5xULN
- eGFR (Ckd-Epi) (mL/min/1.73m2)
    - < 60 mL/min/1.73m2
    - 60-90 mL/min/1.73m2
    - >90 mL/min/1.73m2
- Lipase (U/L)
    - >1xULN
        - >3xULN
- Neutrophils (10^3/uL)
    - <1.5
        - <0.5
        - 0.5-<1
        - 1-<1.5
- Total Bilirubin (mg/dL)
    - >2xULN

PCS criteria for selected laboratory parameters will be summarized by visit.

A shift table by baseline to the worst post-baseline PCS category will be provided for eGFR. All other parameters will be listed.

7.7. Columbia-Suicide Severity Rating Scale

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

The following C-SSRS parameters will be evaluated:

- Category 1 through 10
- Self-injurious behavior without suicidal intent
- Suicidal ideation score, defined as the maximum suicidal ideation category (i.e., Category 1-5), with 0 assigned if no ideation is present
- Suicidal ideation, defined as 'Yes' if 'Yes' was present in any of Category 1-5
- Suicidal behavior, defined as 'Yes' if 'Yes' was present in any of Category 6-10
- Suicidal ideation or behavior, defined as 'Yes' if 'Yes' was present in any of Category 1-10

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The C-SSRS questionnaires will be summarized by visit and treatment.

7.8. Patient Health Questionnaire 9

The total score for the PHQ-9 will be calculated and the following categories will be assigned:

- Minimal depression: total score 1-4
- Mild depression: total score 5-9
- Moderate depression: total score 10-14
- Moderately severe depression: 15-19
- Severe depression: 20-27

The PHQ-9 total score, and its associated category, will be summarized by visit and treatment.

7.9. Anti-Drug Antibodies

Details of the analyses to be performed for Anti-Drug Antibodies will be detailed in a separate ADA Analysis Plan. The immunogenicity results will be provided as an Addendum to the CSR.

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8. Other Analyses

8.1. Analysis Sets

The analysis populations will be listed.

8.2. Participant Disposition

Participant disposition will be reported using the FAS – Part A for Part A and Enrolled Set – Part B for Part B, and include:

- Number (%) of participants included in each of the analysis populations
- Number (%) of participants by study status
- Number (%) of participants who discontinued study by primary reason for discontinuation
    - AE(s)
    - Death
    - Participant withdrew consent
    - Lost to follow-up
    - Pregnancy
    - Participants are unable or unwilling to comply with the study visit schedule
    - Other
- Duration on study (days), calculated as last known date – date of randomization + 1
- Number (%) of participants by treatment status
- Number (%) of participants who discontinued treatment by primary reason for discontinuation
    - AE(s)
    - Death
    - Participant withdrew consent
    - Lost to follow-up
    - Pregnancy
    - Participants are unable or unwilling to comply with the study visit schedule
    - Other
- Duration on treatment (days), calculated as last dose date – first dose date + 1

8.3. Protocol Deviations

Protocol deviations for the entire study will be listed using the FAS – Part A.

8.4. Demographic and Other Baseline Characteristics

Demographic and baseline characteristics include the following parameters:

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- Age
- Age Classification (18-<40, 40-<55, 55-<65, 65-70)
- Gender (Male, Female)
- Ethnicity (Hispanic or Latino, Not Hispanic or Latino)
- Race (Asian, Black or African American, Hawaiian or Other Pacific Islander, White, American Indian or Alaska Native, Other, Multiple)
- Height (m)
- Weight (kg) at baseline
- BMI (kg/m^2) at baseline
- Waist circumference (cm) at baseline

Demographic and baseline characteristics will be summarized by treatment using the FAS – Part A for Part A and Enrolled Set –Part B for Part B.

8.5. Prior Medications

Prior medications will be coded using the WHO drug dictionary.

Prior medications are defined as any medication with a start date prior to the first dose of study drug.

Prior medications will be summarized by Medication Class and Preferred Term using the FAS – Part A for Part A and Enrolled Set – Part B for Part B.

8.6. Concomitant Medications

Concomitant medications will be coded using the WHO drug dictionary.

Concomitant medications are defined as any medications with an end date after first dose of study drug.

Concomitant medications will be summarized by Medication Class and Preferred Term using the FAS – Part A for Part A and Enrolled Set – Part B for Part B.

8.7. Other

The following participant data will also be listed using the FAS – Part A for Part A and Enrolled set – Part B for Part B.

- Medical History
- Childbearing Potential and Contraceptive Method
- Alcohol and Smoking Habits

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9. Interim Analysis

9.1. Part A

No interim analyses are planned with the intent of modifying the ongoing trial for Part A. See Section 1.1.1 for the primary reporting milestone.

9.2. Part B

No interim analyses are planned for the objective of potentially modifying the ongoing trial during Part B. Unblinded summary statistics (as specified in Section 2.1.1.1 and Section 2.1.2.1) for demographics, disposition, other endpoints related to safety/tolerability, and protocol-specified Part B exploratory endpoints including percent change from baseline weight may be generated after all participants who are to receive a QM dose in Part B complete 4 weeks after each of the following QM doses: Weeks 44, 48, 52, 56 and 60. Access to these unblinded summaries and individual treatment allocation will be restricted to designated Sponsor personnel.

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10. Changes to Protocol-planned Analyses

Table 7 Changes to Protocol-Planned Analyses

Protocol Section	Protocol Described Analysis	SAP Section	Change from Protocol	Rationale
Section 9.6.5.1	Supplementary analysis uses the MMRM to perform comparisons between the MET097 arms and placebo.	Section 4.4	Supplementary analysis updated to use ANCOVA to perform comparisons between the MET097 arms and placebo.	FDA feedback
Section 2 (Table 4)	HOMA-IR is not included as a protocol-defined objective/endpoint.	Section 1.1.1; Section 6.1.1	HOMA-IR added as a parameter to be evaluated as part of the exploratory objective regarding glucose metabolism parameters.	Interest in comparing treatment differences HOMA-IR, derived using already collected measurements, as an exploratory endpoint
Section 2 (Table 4)	Non-HDL is not included as protocol-defined objectives/endpoints.	Section 1.1.1; Section 6.1.2	Non-HDL added as parameter to be evaluated as part of the exploratory objective regarding lipid level parameters.	Interest in comparing treatment differences non-HDL, available using already collected measurements, as an exploratory endpoint
Section 2 (Table 4)	Ratio of triglycerides to HDL is not included as protocol-defined objectives/endpoints.	Section 1.1.1; Section 6.1.2	Ratio of triglycerides to HDL added as parameter to be evaluated as part of the exploratory objective regarding lipid level parameters.	Interest in comparing treatment differences ratio of triglycerides to HDL, derived using already collected measurements, as an exploratory endpoint
Section 2	The primary estimand describes the approach to handle the ICEs as a hypothetical strategy that participants remained on treatment for the entire duration of the study.	Section 1.1.2	The primary estimand describes the approach to handle the ICEs as a hypothetical strategy that participants adhered to protocol-specified study	Clarification in the definition

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Protocol Section	Protocol Described Analysis	SAP Section	Change from Protocol	Rationale
			treatment compliance requirements.	
Section 9.5 (Table 11)	There is an analysis dataset called the "Efficacy Non-adherence to Study Dataset".	Section 3	The "Efficacy Non-adherence to Study Dataset" was renamed the "All Efficacy Study Dataset".	Clarification in the name
Section 9.1.2	There are no specified interim analyses for Part B.	Section 9.2	Interim analyses may be performed after all participants who are to receive a QM dose in Part B complete 4 weeks after each of the following QM doses: Weeks 44, 48, 52, 56 and 60	No interim analyses are planned for the objective of potentially modifying the ongoing trial during Part B. However, statistical summaries may be produced at identified timepoints to assist with ongoing review of the open-label period (Part B).

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11. Sample Size Determination

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 dosing 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 *% respectively, 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.

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12. Supporting Documentation

12.1. Definitions

12.1.1. A priori Analyses

Analyses described in this SAP are considered a priori in that they have been defined prior to database lock and/or prior to breaking the blind.

12.1.2. Post-hoc Analyses

Analyses performed after database lock and/or breaking the blind will be considered post-hoc.

12.1.3. Baseline

The last available measurement prior to first dose of study treatment received in Part A will be used as baseline for both Part A and Part B. Outputs at baseline or screening use the study baseline or screening information.

12.1.4. Day 1

Day 1 is the first dosing date of study treatment.

12.1.5. Study Day

Study day is defined relative to Day 1 as:

- If on or after Day 1: date – date of Day 1 + 1
- If before Day 1: date – date of Day 1

12.1.6. End of Treatment

End of treatment is defined as the last date of study drug.

The time on treatment (days) is calculated as:

the date of the last dose of study drug – the date of the first dose of study drug + 1

For participants in Part A who do not consent to continue to Part B, the schedule of assessments would be according to the protocol and the participant would be a treatment discontinuation for administrative reasons at the time of the last date of study drug for Part A.

12.1.7. End of Study

End of study is defined as the last available date for a participant.

The time on study (days) is calculated as:

the last available– date of informed consent + 1

For participants in Part A who do not consent to continue to Part B, the schedule of assessments would be according to the protocol and the participant would be a study discontinuation for administrative reasons at the time of the last date available for Part A.

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12.2. Derivations

12.2.1. Visit Windows

For the primary Week 28 (Day 197) analysis as defined in Section 1.1.1, the following visits will be included:

(i) scheduled visits up to and including the Week 28 visit as defined in the SOA of the protocol

(ii) Unscheduled and early termination (ET) visits occurring <= Day 199

Analysis visit windowing will apply to unscheduled and ET visits. Measurements from a scheduled visit, if available, will be used for analysis. If the measurements from a scheduled visit are not available, measurements from an unscheduled or ET visit may be used for analysis. If both measurements from a scheduled visit and an unscheduled or ET visit assigned to the same analysis visit are available, the measurements from the scheduled visit will be used for analysis. If multiple unscheduled and/or ET visit measurements are available and assigned to the same analysis visit window and no scheduled visit measurements are available, the measurements with the study day closest to the target study day will be used for analysis.

If no nominal visit exists, then all data will be windowed. Windowing for all measurements following the week 60 visit will be performed to establish the safety follow up visit.

12.3. Analysis Software

Analyses will be performed using SAS version 9.4 or higher (SAS Institute, Cary, NC, 27513) or R version 4.4.3 (R Core Team, 2025).

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12.4. Summary of Analyses and Outputs

Table 8 Summary of Efficacy Analyses

Endpoint	Interpretation	Analysis Dataset	Missing Data	Statistical Method	Model / Covariates / Strata
Percent Change from Baseline in Body Weight at Day 197	Descriptive Statistics of the Primary Endpoint (Section 4.2)	FAS – Part A	N/A	Descriptive Statistics (Section 2.1.1.1)	Summary of percent change from baseline in body weight at all protocol-specified weekly post-baseline measurements through Day 197
	Primary Analysis (Section 4.2)	*Efficacy Adherence to Study Set* (Section 3)	No imputation	MMRM (Section 2.1.1.3)	Treatment, visit, treatment-by-visit interaction, the stratification factor (i.e., CCI, baseline body weight as fixed effects and repeated measures within subject modeled with UN+ covariance structure using all protocol-specified weekly post-baseline measurements through Day 197
	Supplementary Analysis for the Primary Endpoint (Section 4.4)	*All Efficacy Study Set* (Section 3)	Placebo-washout Imputation (Section 2.4)	ANCOVA (Section 2.1.1.2)	Treatment, the stratification factor (i.e., CCI, baseline body weight
Percent Change from Baseline in Body Weight for weekly post-baseline visits prior to Day 197	Secondary Analysis (Section 5.1)	Analyses included as part of Primary Analysis and Supplementary Analysis for the Primary Endpoint			
Body weight reduction (weight loss) from baseline at Day 197 of ≥ 5%	Descriptive Statistics of the Secondary Endpoint (Section 5.2)	FAS – Part A	N/A	Descriptive Statistics (Section 2.1.2.1)	Summary of the proportion of weight loss from baseline at Day 197 ≥ 5%
	Secondary Analysis (Section 5.2)	*Efficacy Adherence to Study Set* (Section 3)	No imputation	Logistic regression (Section 2.1.2.2)	Treatment, the stratification factor (i.e., CCI, baseline body weight
	Supplementary Analysis of Secondary Endpoint (Section 5.2)	*All Efficacy Study Set* (Section 3)	Placebo-washout Imputation (Section 2.4)	Logistic regression (Section 2.1.2.2)	Treatment, the stratification factor (i.e., CCI, baseline body weight
Body weight reduction (weight loss) from baseline at Day 197 of ≥ 10%	Descriptive Statistics of the Secondary Endpoint (Section 5.2)	FAS – Part A	N/A	Descriptive Statistics (Section 2.1.2.1)	Summary of the proportion of weight loss from baseline at Day 197 ≥ 10%
	Secondary Analysis (Section 5.2)	*Efficacy Adherence to Study Set* (Section 3)	No imputation	Logistic regression (Section 2.1.2.2)	Treatment, the stratification factor (i.e., CCI, baseline body weight

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Endpoint	Interpretation	Analysis Dataset	Missing Data	Statistical Method	Model / Covariates / Strata
	Supplementary Analysis of Secondary Endpoint (Section 5.2)	*All Efficacy Study Set* (Section 3)	Placebo-washout Imputation (Section 2.4)	Logistic regression (Section 2.1.2.2)	Treatment, the stratification factor (i.e., CCI, baseline body weight
Body weight reduction (weight loss) from baseline at Day 197 of ≥ 15%	Descriptive Statistics of the Secondary Endpoint (Section 5.2)	FAS – Part A	N/A	Descriptive Statistics (Section 2.1.2.1)	Summary of the proportion of weight loss from baseline at Day 197 ≥ 15%
	Secondary Analysis (Section 5.2)	*Efficacy Adherence to Study Set* (Section 3)	No imputation	Logistic regression (Section 2.1.2.2)	Treatment, the stratification factor (i.e., CCI, baseline body weight
	Supplementary Analysis of Secondary Endpoint (Section 5.2)	*All Efficacy Study Set* (Section 3)	Placebo-washout Imputation (Section 2.4)	Logistic regression (Section 2.1.2.2)	Treatment, the stratification factor (i.e., CCI, baseline body weight
Change from Baseline in Body Weight for weekly post-baseline visits to Day 197	Descriptive Statistics of the Secondary Endpoint (Section 5.3)	FAS – Part A	N/A	Descriptive Statistics (Section 2.1.1.1)	Summary of observed and change from baseline in body weight at all protocol-specified weekly post-baseline measurements through Day 197
	Secondary Analysis (Section 5.3)	*Efficacy Adherence to Study Set* (Section 3)	No imputation	MMRM (Section 2.1.1.3)	Treatment, visit, treatment-by-visit interaction, the stratification factor (i.e., CCI, baseline body weight as fixed effects and repeated measures within subject modeled with UN[+] covariance structure using all protocol-specified weekly post-baseline measurements through Day 197
	Supplementary Analysis of Secondary Endpoint (Section 5.3)	*All Efficacy Study Set* (Section 3)	Placebo-washout Imputation (Section 2.4)	ANCOVA (Section 2.1.1.2)	Summary of observed and change from baseline in body weight at all protocol-specified weekly post-baseline measurements through Day 197
Change from Baseline in BMI (kg/m^2) for weekly post-baseline visits to Day 197	Descriptive Statistics of the Secondary Endpoint (Section)	FAS – Part A	N/A	Descriptive Statistics (Section 2.1.1.1)	Summary of observed and change from baseline in BMI at all protocol-specified weekly post-baseline measurements through Day 197
Change from Baseline in waist circumference (cm) for weekly post-baseline visits to Day 197	Descriptive Statistics of the Secondary Endpoint (Section 5.5)	FAS – Part A	N/A	Descriptive Statistics (Section 2.1.1.1)	Summary of observed and change from baseline in waist circumference at all protocol-specified weekly post-baseline measurements through Day 197
	Secondary Analysis (Section 5.5)	*Efficacy Adherence to Study Set* (Section 3)	No imputation	MMRM (Section 2.1.1.3)	Treatment, visit, treatment-by-visit interaction, the stratification factor (i.e., CCI, baseline waist circumference as fixed effects and repeated measures within subject modeled with UN[+] covariance structure using all protocol-specified weekly post-baseline measurements through Day 197
	Supplementary Analysis of Secondary Endpoint (Section 5.5)	*All Efficacy Study Set* (Section 3)	Placebo-washout Imputation (Section 2.4)	ANCOVA (Section 2.1.1.2)	Treatment, the stratification factor (i.e., CCI, baseline waist circumference

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Endpoint	Interpretation	Analysis Dataset	Missing Data	Statistical Method	Model / Covariates / Strata
Change from Baseline in fasting insulin for weekly post-baseline visits to Day 197	Descriptive Statistics of the Exploratory Endpoint (Section 6.1.1)	FAS – Part A	N/A	Descriptive Statistics (Section 2.1.1.1)	Summary of observed and change from baseline in fasting insulin at all protocol-specified weekly post-baseline measurements through Day 197
	Exploratory Analysis (Section 6.1.1)	*Efficacy Adherence to Study Set* (Section 3)	No imputation	MMRM (Section 2.1.1.3)	Treatment, visit, treatment-by-visit interaction, the stratification factor (i.e., CCI, baseline fasting insulin as fixed effects and repeated measures within subject modeled with UN+ covariance structure using all protocol-specified weekly post-baseline measurements through Day 197
	Supplementary Analysis of Exploratory Endpoint (Section 6.1.1)	*All Efficacy Study Set* (Section 3)	Placebo-washout Imputation (Section 2.4)	ANCOVA (Section 2.1.1.2)	Treatment, the stratification factor (i.e., CCI), baseline fasting insulin
Change from Baseline in glycated HbA1c for weekly post-baseline visits to Day 197	Descriptive Statistics of the Exploratory Endpoint (Section 6.1.1)	FAS – Part A	N/A	Descriptive Statistics (Section 2.1.1.1)	Summary of observed and change from baseline in glycated HbA1c at all protocol-specified weekly post-baseline measurements through Day 197
	Exploratory Analysis (Section 6.1.1)	*Efficacy Adherence to Study Set* (Section 3)	No imputation	MMRM (Section 2.1.1.3)	Treatment, visit, treatment-by-visit interaction, the stratification factor (i.e., CCI, baseline glycated HbA1c as fixed effects and repeated measures within subject modeled with UN+ covariance structure using all protocol-specified weekly post-baseline measurements through Day 197
	Supplementary Analysis of Exploratory Endpoint (Section 6.1.1)	*All Efficacy Study Set* (Section 3)	Placebo-washout Imputation (Section 2.4)	ANCOVA (Section 2.1.1.2)	Treatment, the stratification factor (i.e., CCI), baseline glycated HbA1c
Change from Baseline in fasting glucose for weekly post-baseline visits to Day 197	Descriptive Statistics of the Exploratory Endpoint (Section 6.1.1)	FAS – Part A	N/A	Descriptive Statistics (Section 2.1.1.1)	Summary of observed and change from baseline in fasting glucose at all protocol-specified weekly post-baseline measurements through Day 197
	Exploratory Analysis (Section 6.1.1)	*Efficacy Adherence to Study Set* (Section 3)	No imputation	MMRM (Section 2.1.1.3)	Treatment, visit, treatment-by-visit interaction, the stratification factor (i.e., CCI, baseline fasting glucose as fixed effects and repeated measures within subject modeled with UN+ covariance structure using all protocol-specified weekly post-baseline measurements through Day 197
	Supplementary Analysis of Exploratory Endpoint (Section 6.1.1)	*All Efficacy Study Set* (Section 3)	Placebo-washout Imputation (Section 2.4)	ANCOVA (Section 2.1.1.2)	Treatment, the stratification factor (i.e., CCI), baseline fasting glucose
Change from Baseline in fasting glucagon for weekly	Descriptive Statistics of the Exploratory Endpoint (Section 6.1.1)	FAS – Part A	N/A	Descriptive Statistics (Section 2.1.1.1)	Summary of observed and change from baseline in fasting glucagon at all protocol-specified weekly post-baseline measurements through Day 197

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Endpoint	Interpretation	Analysis Dataset	Missing Data	Statistical Method	Model / Covariates / Strata
post-baseline visits to Day 197	Exploratory Analysis (Section 6.1.1)	*Efficacy Adherence to Study Set* (Section 3)	No imputation	MMRM (Section 2.1.1.3)	Treatment, visit, treatment-by-visit interaction, the stratification factor (i.e., CCI, baseline fasting glucagon as fixed effects and repeated measures within subject modeled with UN+ covariance structure using all protocol-specified weekly post-baseline measurements through Day 197
	Supplementary Analysis of Exploratory Endpoint (Section 6.1.1)	*All Efficacy Study Set* (Section 3)	Placebo-washout Imputation (Section 2.4)	ANCOVA (Section 2.1.1.2)	Treatment, the stratification factor (i.e., CCI, baseline fasting glucagon
Change from Baseline in HOMA-IR for weekly post-baseline visits to Day 197	Descriptive Statistics of the Exploratory Endpoint (Section 6.1.1)	FAS – Part A	N/A	Descriptive Statistics (Section 2.1.1.1)	Summary of observed and change from baseline in HOMA-IR at all protocol-specified weekly post-baseline measurements through Day 197
	Exploratory Analysis (Section 6.1.1)	*Efficacy Adherence to Study Set* (Section 3)	No imputation	MMRM (Section 2.1.1.3)	Treatment, visit, treatment-by-visit interaction, the stratification factor (i.e., CCI, baseline HOMA-IR as fixed effects and repeated measures within subject modeled with UN+ covariance structure using all protocol-specified weekly post-baseline measurements through Day 197
	Supplementary Analysis of Exploratory Endpoint (Section 6.1.1)	*All Efficacy Study Set* (Section 3)	Placebo-washout Imputation (Section 2.4)	ANCOVA (Section 2.1.1.2)	Treatment, the stratification factor (i.e., CCI, baseline HOMA-IR
Change from Baseline in triglycerides for weekly post-baseline visits to Day 197	Descriptive Statistics of the Exploratory Endpoint (Section 6.1.2)	FAS – Part A	N/A	Descriptive Statistics (Section 2.1.1.1)	Summary of observed and change from baseline in triglycerides at all protocol-specified weekly post-baseline measurements through Day 197
	Exploratory Analysis (Section 6.1.2)	*Efficacy Adherence to Study Set* (Section 3)	No imputation	MMRM (Section 2.1.1.3)	Treatment, visit, treatment-by-visit interaction, the stratification factor (i.e., CCI, baseline triglycerides as fixed effects and repeated measures within subject modeled with UN+ covariance structure using all protocol-specified weekly post-baseline measurements through Day 197
	Supplementary Analysis of Exploratory Endpoint (Section 6.1.2)	*All Efficacy Study Set* (Section 3)	Placebo-washout Imputation (Section 2.4)	ANCOVA (Section 2.1.1.2)	Treatment, the stratification factor (i.e., CCI, baseline triglycerides
Change from Baseline in HDL-C for weekly post-baseline visits to Day 197	Descriptive Statistics of the Exploratory Endpoint (Section 6.1.2)	FAS – Part A	N/A	Descriptive Statistics (Section 2.1.1.1)	Summary of observed and change from baseline in HDL-C at all protocol-specified weekly post-baseline measurements through Day 197
	Exploratory Analysis (Section 6.1.2)	*Efficacy Adherence to Study Set* (Section 3)	No imputation	MMRM (Section 2.1.1.3)	Treatment, visit, treatment-by-visit interaction, the stratification factor (i.e., CCI, baseline HDL-C as fixed effects and repeated measures within subject modeled with UN+ covariance structure using all protocol-specified weekly post-baseline measurements through Day 197

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Endpoint	Interpretation	Analysis Dataset	Missing Data	Statistical Method	Model / Covariates / Strata
	Supplementary Analysis of Exploratory Endpoint (Section 6.1.2)	*All Efficacy Study Set* (Section 3)	Placebo-washout Imputation (Section 2.4)	ANCOVA (Section 2.1.1.2)	Treatment, the stratification factor (i.e., CCI, baseline HDL-C
Change from Baseline in LDL-C for weekly post-baseline visits to Day 197	Descriptive Statistics of the Exploratory Endpoint (Section 6.1.2)	FAS – Part A	N/A	Descriptive Statistics (Section 2.1.1.1)	Summary of observed and change from baseline in LDL-C at all protocol-specified weekly post-baseline measurements through Day 197
	Exploratory Analysis (Section 6.1.2)	*Efficacy Adherence to Study Set* (Section 3)	No imputation	MMRM (Section 2.1.1.3)	Treatment, visit, treatment-by-visit interaction, the stratification factor (i.e., CCI, baseline LDL-C as fixed effects and repeated measures within subject modeled with UN+ covariance structure using all protocol-specified weekly post-baseline measurements through Day 197
	Supplementary Analysis of Exploratory Endpoint (Section 6.1.2)	*All Efficacy Study Set* (Section 3)	Placebo-washout Imputation (Section 2.4)	ANCOVA (Section 2.1.1.2)	Treatment, the stratification factor (i.e., CCI, baseline LDL-C
Change from Baseline in Non-HDL for weekly post-baseline visits to Day 197	Descriptive Statistics of the Exploratory Endpoint (Section 6.1.2)	FAS – Part A	N/A	Descriptive Statistics (Section 2.1.1.1)	Summary of observed and change from baseline in non-HDL at all protocol-specified weekly post-baseline measurements through Day 197
	Exploratory Analysis (Section 6.1.2)	*Efficacy Adherence to Study Set* (Section 3)	No imputation	MMRM (Section 2.1.1.3)	Treatment, visit, treatment-by-visit interaction, the stratification factor (i.e., CCI, baseline non-HDL as fixed effects and repeated measures within subject modeled with UN+ covariance structure using all protocol-specified weekly post-baseline measurements through Day 197
	Supplementary Analysis of Exploratory Endpoint (Section 6.1.2)	*All Efficacy Study Set* (Section 3)	Placebo-washout Imputation (Section 2.4)	ANCOVA (Section 2.1.1.2)	Treatment, the stratification factor (i.e., CCI, baseline non-HDL
Change from Baseline in ratio of triglycerides to HDL-C for weekly post-baseline visits to Day 197	Descriptive Statistics of the Exploratory Endpoint (Section 6.1.2)	FAS – Part A	N/A	Descriptive Statistics (Section 2.1.1.1)	Summary of observed and change from baseline in ratio of triglycerides to HDL-C at all protocol-specified weekly post-baseline measurements through Day 197
	Exploratory Analysis (Section 6.1.2)	*Efficacy Adherence to Study Set* (Section 3)	No imputation	MMRM (Section 2.1.1.3)	Treatment, visit, treatment-by-visit interaction, the stratification factor (i.e., CCI, baseline ratio of triglycerides to HDL-C as fixed effects and repeated measures within subject modeled with UN+ covariance structure using all protocol-specified weekly post-baseline measurements through Day 197
	Supplementary Analysis of Exploratory Endpoint (Section 6.1.2)	*All Efficacy Study Set* (Section 3)	Placebo-washout Imputation (Section 2.4)	ANCOVA (Section 2.1.1.2)	Treatment, the stratification factor (i.e., CCI, baseline ratio of triglycerides to HDL-C

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Endpoint	Interpretation	Analysis Dataset	Missing Data	Statistical Method	Model / Covariates / Strata
Percent Change from Baseline in Body Weight Day 197 through EOS	Descriptive Statistics of the Exploratory Endpoint (Section 6.2.1)	Enrolled Set – Part B	N/A	Descriptive Statistics (Section 2.1.1.1)	Summary of percent change from baseline in body weight at all protocol-specified weekly post-baseline measurements Day 197 through EOS
Body weight reduction (weight loss) from baseline Day 197 through EOS of ≥ 5%	Descriptive Statistics of the Exploratory Endpoint (Section 6.2.2)	Enrolled Set – Part B	N/A	Descriptive Statistics (Section 2.1.2.1)	Summary of the proportion of weight loss from baseline Day 197 through EOS ≥ 5%
Body weight reduction (weight loss) from baseline Day 197 through EOS of ≥ 10%	Descriptive Statistics of the Exploratory Endpoint (Section 6.2.2))	Enrolled Set – Part B	N/A	Descriptive Statistics (Section 2.1.2.1)	Summary of the proportion of weight loss from baseline Day 197 through EOS ≥ 10%
Body weight reduction (weight loss) from baseline Day 197 through EOS of ≥ 15%	Descriptive Statistics of the Exploratory Endpoint (Section 6.2.2)	Enrolled Set – Part B	N/A	Descriptive Statistics (Section 2.1.2.1)	Summary of the proportion of weight loss from baseline Day 197 through EOS ≥ 15%
Change from Baseline in Body Weight for weekly post-baseline visits Day 197 through EOS	Descriptive Statistics of the Exploratory Endpoint (Section 6.2.1)	Enrolled Set – Part B	N/A	Descriptive Statistics (Section 2.1.1.1)	Summary of observed and change from baseline in body weight at all protocol-specified weekly post-baseline measurements Day 197 through EOS
Change from Baseline in BMI (kg/m^2) for weekly post-baseline visits Day 197 through EOS	Descriptive Statistics of the Exploratory Endpoint (Section)	Enrolled Set – Part B	N/A	Descriptive Statistics (Section 2.1.1.1)	Summary of observed and change from baseline in BMI at all protocol-specified weekly post-baseline measurements Day 197 through EOS
Change from Baseline in waist circumference (cm) for weekly post-baseline visits Day 197 through EOS	Descriptive Statistics of the Exploratory Endpoint (Section 5.5)	Enrolled Set – Part B	N/A	Descriptive Statistics (Section 2.1.1.1)	Summary of observed and change from baseline in waist circumference at all protocol-specified weekly post-baseline measurements Day 197 through EOS

+ An UN structure will model the relationship between within-patient errors. If this model fails to converge, the following variance-covariance structures will be tested in order until convergence is achieved: (i) heterogeneous Toeplitz, (ii) heterogeneous compound symmetry.

13. References

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