Statistical Analysis Plan

An Exploratory Phase 2a, Randomised, Double-blind, Placebo-controlled Study to Evaluate the Effect of MEDI0382 on Energy Balance in Overweight and Obese Subjects with Type 2 Diabetes Mellitus

Protocol Number: D5670C00021

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List of Abbreviations

Abbreviation or Specialized Term	Definition
ADA	Anti-drug antibody/antibodies
AE	Adverse event
AEE	activity energy expenditure
AIRg	Acute insulin response
ALT	alanine aminotransferase
ANCOVA	Analysis of covariance
AST	aspartate aminotransferase
ATC	anatomical therapeutic chemical class
BMI	Body mass index
DEBQ	Dutch Eating Behavior Questionnaire
DXA	Dual X-ray absorptiometry
ECG	Electrocardiogram
EE	energy expenditure
ExEE	exercise energy expenditure
GIP	Glucose-dependent insulinotropic polypeptide
GLP-1	Glucagon-like peptide-1
IPD	important protocol deviations
IVGTT	Intravenous glucose tolerance test
IWRS	Interactive web response system
MedDRA	Medical Dictionary for Regulatory Activities
MMTT	Mixed-meal tolerance test
PK	Pharmacokinetics
PRO	Patient reported outcome
PT	preferred term
REE	resting energy expenditure
SAE	Serious adverse event
SAP	Statistical analysis plan
SC	Subcutaneous
SOC	system organ class
SPP	Statistical programming plan
T2DM	type 2 diabetes mellitus
TEAE	Treatment-emergent adverse event

Abbreviation or Specialized Term	Definition
TEE	total energy expenditure
TESAE	Treatment-emergent serious adverse event
ULN	Upper limit of reference range
WHO-DD	World Health Organization Drug Dictionary enhanced

1 INTRODUCTION

This document describes the statistical analysis methodology for protocol D5670C00021, a Phase 2a randomised, double-blind, parallel group study to evaluate the evaluate the effect of MEDI0382 on energy balance during 42 days of treatment in overweight or obese subjects with type 2 diabetes mellitus. This document details the statistical summaries relating to each study objective and describes the general conventions and definitions that will be used. In addition, a set of table templates and specifications will be included in a statistical programming plan (SPP) to complement this document.

2 STUDY OVERVIEW

2.1 Study Objectives

2.1.1 Primary Study Objective(s)

- To assess the effect of MEDI0382 titrated up to a dose level of [redacted] on body weight versus placebo

2.1.2 Secondary Study Objectives

- To assess the effect of MEDI0382 titrated up to a dose level of [redacted] versus placebo on energy intake during ad libitum lunchtime meals
- To assess the effect of a 16-day period of single-blind placebo on energy intake during an ad libitum lunchtime meal
- To assess the effect of MEDI0382 titrated up to a dose level of [redacted] versus placebo on TEE, AEE, and REE as measured by whole room indirect calorimetry
- To assess the effect of a 16-day period of MEDI0382 titrated up to a dose level of [redacted] versus placebo on REE
- To assess the effect of MEDI0382 titrated up to a dose level of [redacted] versus placebo on TEE as measured by doubly-labelled water
- To assess the effect of MEDI0382 titrated up to a dose level of [redacted] on measures of body weight and composition versus placebo
- To assess the effect of MEDI0382 titrated up to a dose level of [redacted] on glucose homeostasis versus placebo
- To evaluate the safety and tolerability of MEDI0382 titrated up to a dose level of [redacted] versus placebo
- To characterize the immunogenicity profile of MEDI0382 exposure titrated up to a dose level of [redacted] versus placebo

2.1.3 Exploratory Study Objectives

- [redacted]

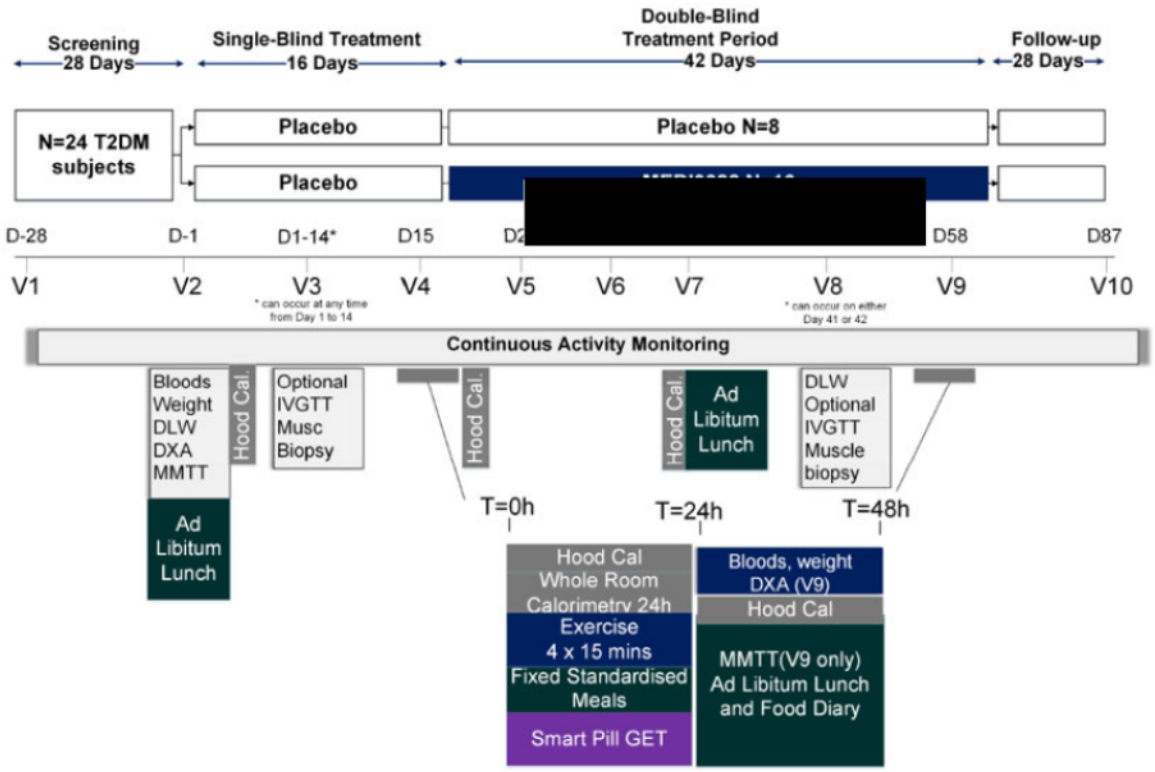
- [redacted]

2.2 Study Design

This is an exploratory Phase 2a randomised, double-blind, placebo-controlled study to evaluate the effect of MEDI0382 titrated up to [redacted] on energy balance in overweight or obese subjects with T2DM.

The study is planned to randomise 24 subjects at one site in the United Kingdom. Subjects will be randomised within 28 days of screening to receive single-blind placebo for 16 days, and then either double-blind MEDI0382 titrated up to [redacted], or placebo in a 2:1 ratio administered once daily via SC injection for 42 days (16-day single-blind and 42-day double-blind treatment periods). Subjects randomised to MEDI0382 will receive [redacted]

Figure 1 Study Flow Diagram



7/7 = 7 days, 28/7 = 28 days, Hood Cal = Hood-based calorimetry, DLW = doubly-labelled water, DXA = Dual X-ray absorptiometry, h = hours, IVGTT = intravenous glucose tolerance test, mins = minutes; MMTT = mixed-meal tolerance test, GET = gastric emptying time, T = time, V = visit.

2.3 Treatment Assignment and Blinding

An IWRS will be used for randomization to assign a treatment to subjects and to assign blinded investigational product kit numbers. Twenty-four (24) subjects will be randomised using a 2:1 ratio to receive either MEDI0382 (16 subjects) or placebo (8 subjects).

This is a double-blind study in which MEDI0382 and placebo prefilled syringes are identical except the fill volumes are not identical/indistinguishable in appearance. The different fill volumes of MEDI0382 and placebo prefilled syringes and the relative position of the plunger rods will be visually distinct during administration. Neither the subject/legal representative nor any of the investigator or sponsor staff who are involved in the treatment or clinical evaluation of the subjects will be aware of the treatment received. The blind will be maintained by having the study drug administered at the clinical site by an unblinded person not involved in the treatment or clinical evaluation of the subjects. This unblinded person will also dispense and receive drug from the subject and reconcile drug accountability.

2.4 Sample Size

Sixteen subjects in the MEDI0382 group and 8 subjects in the placebo group will provide > 90% power to detect a 2.5% weight change from baseline difference between [redacted] and placebo at Day 59, assuming a standard deviation of 2.0%, a 2-sided 0.1 alpha.

3 STATISTICAL METHODS

3.1 General Considerations

Data will be presented in data listings sorted by treatment, subject number and date collected, where appropriate. Tabular summaries will be presented for each treatment. Categorical data will be summarized by treatment with the number and percentage of subjects within each category. Continuous variables will be summarized by treatment with descriptive statistics including mean, standard deviation, median, minimum, and maximum. For some variables, the geometric mean and 95% CI will be presented. Baseline values will be defined as the last valid assessment prior to the first administration of investigational product unless otherwise specified.

All available data will be included in the analyses and missing data will not be imputed, except in a last observation carried forward (LOCF) analysis and as specified in the calculation of the AUC values. When last observation carried forward (LOCF) is used to impute for missing post-baseline data, only post-baseline data will be carried forward (e.g., baseline data will not be carried forward).

All statistical tests will be 2-sided at an alpha = 0.10 significance level unless stated otherwise. There will be no adjustment for multiplicity.

Data analyses will be performed using SAS® version 9.4 or higher (SAS Institute Inc., Cary, NC). The analytical results generated from SAS programs will follow MedImmune SAS programming standards and will be validated according to MedImmune SAS validation procedures.

3.2 Analysis Populations

The analysis populations are defined in Table 1.

Table 1 Analysis Populations

Population	Description
Intent-to-treat (ITT) population	Subjects who receive any study investigational product will be included in the ITT population and subjects will be analyzed according to their randomized treatment group.
Modified Intent-to-treat (mITT) population	Subjects in the ITT population who receive at least one dose of the investigational product in the double-blind treatment period, and subjects will be analyzed according to their randomized treatment group.
As-treated population	Subjects who receive any study investigational product will be included in the as-treated population and will be analyzed according to the treatment they actually receive.
Per-protocol population	Subjects in the mITT population (receive at least one dose of the investigational product in the double-blind treatment period) who complete treatment up to Day 58.
PK population	Subjects in the As-treated population who have at least one PK sample taken with a value that is above the lower limit of quantitation.
Immunogenicity population	Subjects in the As-treated population who have at least one serum sample for immunogenicity testing.

3.3 Study Subjects

3.3.1 Subject Disposition and Completion Status

A summary of subject eligibility and randomization (including a summary of subjects randomised but not treated with double-blind investigational product) as well as treatment administered will be provided. In addition, disposition of subjects throughout the study with respect to completion of treatment and end of study will be provided.

3.3.2 Demographics and Baseline Characteristics

Demographic information related to sex, age, race, weight, height, and body mass index (BMI) will be presented by treatment group and for all subjects combined. A summary of baseline disease characteristics may include duration of diabetes, specified diabetes complications, and smoking and alcohol history.

3.3.3 Study Drug Exposure

The number of doses and total dose received will be summarized for each investigational product (MEDI0382 or placebo) by descriptive statistics and frequencies.

3.3.4 Concomitant Medications

Concomitant medications will be coded using the current WHO Drug Dictionary enhanced (WHO-DD). The number and percentage of subjects who took concomitant medications for the highest anatomical therapeutic chemical (ATC) class and preferred term will be summarized by study part and treatment for the As-treated population. The summary of concomitant medications will include all concomitant medications taken on or after the date of first dose of investigational product or any concomitant medication started prior to first dose of investigational product that continued beyond the date of first dose of investigational

product. Concomitant medications will be summarized separately for the double-blinded treatment period and for the single-blinded treatment period.

3.4 Efficacy Analyses

3.4.1 Primary Efficacy Endpoint(s) and Analyses

3.4.1.1 Primary Efficacy Endpoint(s)

Percentage change in body weight in kg from Day 17 to 59

3.4.1.2 Handling of Dropouts and Missing Data

If a subject has a missing Day 17 (baseline) weight value, the last weight value prior to Day 17 will be used as the baseline in the analysis. If a subject has a missing weight value on Day 59, the subject will be included in the analysis using the last value after the start of the double-blind period, ie, last observation carried forward (LOCF).

3.4.1.3 Primary Efficacy Analysis

The analysis of the primary efficacy endpoint will be performed using the mITT population. The primary efficacy endpoint of percentage change in body weight from Day 17 to 59 will be compared between MEDI0382 and placebo groups using an analysis of covariance (ANCOVA) model adjusting for treatment group and baseline weight. LOCF will be used for missing data imputation if the Day 59 evaluation is missing.

3.4.2 Secondary Efficacy Endpoint(s) and Analyses

3.4.2.1 Secondary Efficacy Endpoint(s)

- Percentage and absolute change in total energy intake in kJ from the ad libitum lunch from Day 16 to 32 and Day 16 to 59
- Percentage and absolute change in total energy intake in kJ during the ad libitum lunch from Day -1 to 16
- Percentage and absolute change in TEE, AEE, and REE as measured by whole room indirect calorimetry in kJ per kg of fat body mass from Day 15 to 58
- Percentage and absolute change in REE as measured by hood indirect calorimetry in kJ per kg of fat body mass in kJ from Day 16 to 32
- Percentage and absolute change in total energy expenditure as measured by doubly labelled water in kJ per kg of fat body mass from baseline (Day 17) to the end of treatment (Day 58 or 59)
- Absolute change in body weight in kg from Day 17 to 59
- Change in absolute and percentage change in total body fat mass as measured by DXA in kg from Day -1 to 59
- Change in absolute and percentage change in total body fat mass: lean mass ratio as measured by DXA from Day -1 to 59
- Change in fasting glucose during a MMTT from Day -1 to 59

- Percentage change in glucose AUC_{4h} during a MMTT from Day -1 to 59

3.4.2.2 Handling of Dropouts and Missing Data

Generally, both a measurement at the baseline time point and at the final time point for each endpoint are needed for a subject to be included in the analysis for change or percent change. If the measurement at the final time point for an endpoint is missing, LOCF will be used for missing data imputation if applicable.

3.4.2.3 Secondary Efficacy Analyses

The analysis of the secondary efficacy endpoints will be performed using the mITT population for endpoints comparing MEDI0382 and placebo during the double-blind treatment period. For secondary efficacy endpoints that allow comparison of MEDI0382 and placebo, the endpoints will be analyzed by an ANCOVA model similar to that used for the primary efficacy analysis. Selected secondary endpoints will also be analysed using the Per-protocol population.

3.4.3 Exploratory Efficacy Endpoint(s) and Analyses

3.4.3.1 [redacted]

[redacted]

3.5 Patient Reported Outcomes

3.5.1 PRO Endpoints

- Change in hunger and satiety scores as measured with the DEBQ restrained, emotional, and external eating factors and the 4-item visual analog scale from Day 15 to 58
- Change in total reported energy intake in kJ as recorded in a food diary from:
  - Day 16 to 32
  - Day 16 to 59

3.5.2 PRO Analyses

The analysis of the PRO endpoints will be performed using the mITT population. The patient reported outcomes (PRO) endpoints include hunger (4 self-reported items) and satiety (33

self-reported items). Each item will be analyzed by an ANCOVA model similar to that used for the primary efficacy analysis.

3.6 Pharmacodynamic Endpoint(s) and Analyses

3.6.1.1 Pharmacodynamic Endpoint(s)

3.7 Safety Analyses

The analyses of the secondary safety endpoints will be performed using the As-treated population.

3.7.1 Adverse Events and Serious Adverse Events

Adverse events will be coded with MedDRA version 21.0 or later. Analysis of adverse events will include the type, incidence, severity and relationship to study investigational product summarized by MedDRA System Organ Class (SOC) and Preferred Term (PT), by treatment group as well as overall. The AEs summaries will include only treatment-emergent AEs, ie, those starting after the first administration of double-blind investigational product. Subjects will be counted once for specific PT or MedDRA SOC when calculating incidence rates. If the same AE Preferred Term occurs multiple times within a subject, the highest severity and level of relationship observed will be reported. Non-treatment-emergent AEs/serious adverse events (SAEs), ie, those AEs with onset after screening including during the single-blind placebo treatment but before the start of double-blind treatment will be presented in the listings. The percentage of subject with nausea, vomiting and either nausea or vomiting on each day during the dose titration period (Days 17 to 28) will be summarized with the 80% confidence interval. Note that this is not just onset of a new event but includes events where the day is included in the AE start and stop dates. A similar analysis including event rates will be performed for each of the 4-day dose titration period (Days 17-20, 21-24, and 25 to 28) and other dosing periods. Adverse events will be summarized separately for the double-blinded treatment period and for the single-blinded treatment period.

3.7.2 Other Events

3.7.2.1 Hepatic Function Abnormality

Cases where a subject shows elevations in liver biochemistry may require further evaluation and occurrences of aspartate transaminase (AST) or alanine transaminase (ALT) $\geq 3 \times$ ULN together with total bilirubin $\geq 2 \times$ ULN may need to be reported as SAEs. Tests for AST, ALT, and total bilirubin must be conducted concurrently, defined as deriving from a single blood draw or from separate blood draws taken within 8 days of each other, and assessed concurrently.

The cases of hepatic function abnormality will be summarized overall, as well as categorized by MedDRA system organ class and preferred term by treatment group.

3.7.2.2 Injection Site Reactions

Treatment-emergent injection site reactions will be summarized overall, as well as categorized by MedDRA system organ class and preferred term by treatment group.

3.7.2.3 Nausea or Vomiting

Treatment-emergent nausea or vomiting events will be summarized overall, as well as categorized by MedDRA system organ class and preferred term by treatment group.

3.7.3 Deaths and Treatment Discontinuations due to Adverse Events

Death and AEs resulting in permanent discontinuation from the study drug will be summarized by treatment. The summary includes overall, categorized by MedDRA system organ class, and preferred term.

3.7.4 Clinical Laboratory Evaluation

Hematology, serum chemistry, and urinalysis laboratory evaluations will be performed during the study. The hematology and serum chemistry (including calcitonin, lipase, and amylase) parameters as well as their changes from baseline and percent changes from baseline will be summarized with descriptive statistics (number of subjects, mean, and standard deviation, median, minimum and maximum) by treatment group. The hematology and serum chemistry results will also be classified as low (below lower limit of reference range), normal (within reference range), or high (above upper limit of reference range). The urinalysis results will be classified as normal or abnormal. The shift from baseline hematology, serum chemistry, and urinalysis results will be summarized by treatment at each evaluation time.

3.7.5 Other Safety Evaluations

3.7.5.1 Vital Signs

Vital signs including pulse rate (beats/min), systolic and diastolic blood pressure (mm Hg), temperature (ºC), and respiratory rate (breaths/min), as well as the change from baseline for each of those parameters, will be descriptively summarized by treatment at each time point.

3.7.5.2 Electrocardiogram

Electrocardiogram parameters will be assessed using standard 12-lead electrocardiography. The following Electrocardiogram (ECG) parameters as well as the change from baseline for each of those parameters will be reported and descriptively summarized by treatment group at each of the specified time points: Heart rate (beats/min), RR (msec), PR (msec), QRS (msec), and QT (msec) intervals and the QT corrected interval.

The normality/abnormality of the ECG evaluation will be summarized using frequency tables of the number of subjects with a normal/abnormal ECG evaluation at each scheduled visit.

3.8 Immunogenicity

[redacted]

3.9 Pharmacokinetics

[redacted]

3.10 Protocol Deviations

A listing and table of important protocol deviations (IPD) will be provided. The summary of IPD may be prepared by deviation category as well as overall.

4 INTERIM ANALYSIS

No interim analyses are planned.

5 REFERENCES

None

6 VERSION HISTORY

Version	Date	Summary of Changes	Reason for Change
1.0	10DEC2018	Initial document	Initial document
2.0	23FEB2019	Updates on certain endpoints and analysis populations	Updates needed following protocol amendment