Statistical Analysis Plan

A Phase 2a Randomized, Blinded, Placebo-controlled Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Efficacy of MEDI0382 in Overweight/Obese Subjects with Type 2 Diabetes Mellitus

Protocol Number: D5670C00030

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List of Abbreviations

Abbreviation or Specialized Term	Definition
ADA	anti-drug antibody
AE	adverse event
ANCOVA	analysis of covariance
AST	aspartate aminotransferase
AUC	area under the curve
BMI	body mass index
CI	confidence interval
[redacted]	[redacted]
C_{max}	maximum-observed plasma drug concentration
C_{trough}	trough concentrations from the pre-dose plasma concentration data
C_{τ}	trough concentrations (C_{trough}) from the pre-dose plasma drug concentration data
CV	coefficient of variation
DEC	dose escalation committee
ECG	electrocardiogram
GLP-1	glucagon-like peptide 1
HbA1c	hemoglobin A1c
HCTD	highest clinically tolerated dose
ITT	Intent-to-Treat
PK	pharmacokinetics
PR	ECG PR interval
PT	MedDRA preferred term or WHO-DDE preferred term
QRS	ECG QRS interval
QT	ECG QT interval
QTc	ECG QT interval corrected for heart rate
QTcF	ECG QT interval corrected for heart rate using Fridericia's formula
RR	ECG RR interval
SAE	serious adverse event
SD	standard deviation
SOC	MedDRA system organ class
SPP	statistical programming plan
$t_{1/2}$	apparent terminal elimination half-life
T2DM	type 2 diabetes mellitus
TEAE	treatment-emergent adverse event
WHO-DDE	World Health Organization drug dictionary enhanced

1 INTRODUCTION

This document describes the statistical analysis methodology for protocol D5670C00030, a randomized, blinded, placebo-controlled study designed to evaluate the safety, tolerability, pharmacokinetics (PK), and efficacy of ascending doses of MEDI0382 in overweight or obese subjects with type 2 diabetes mellitus (T2DM). 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)

Assess the safety and tolerability of MEDI0382 titrated up to a dose of [redacted] or to the highest clinically tolerated dose (HCTD) from a starting dose of [redacted]

2.1.2 Secondary Study Objectives

- To characterize the PK profile of MEDI0382 titrated up to a dose of [redacted] or to the highest clinically tolerated dose (HCTD)
- To characterize the immunogenicity of MEDI0382 titrated up to a dose of [redacted] or to the HCTD
- To assess the effects of MEDI0382, titrated up to a dose of [redacted] or to the HCTD, [redacted]
- To assess the effects of MEDI0382, titrated up to a dose of [redacted] or to the HCTD, on additional measures of glucose control
- To assess the effects of MEDI0382, titrated up to a dose of [redacted] or to the HCTD, on body weight

[redacted]

[redacted]

[redacted]

[redacted]

2.2 Study Design

This is a randomized, blinded, placebo-controlled study designed to evaluate the safety, tolerability, PK and efficacy of ascending doses of MEDI0382 in overweight or obese subjects with T2DM. This study will enroll subjects aged 18 to 74 years with a body mass index (BMI) 27 to 35 kg/m^2. Subjects will have a diagnosis of T2DM and inadequate blood glucose control as defined by a hemoglobin A1c (HbA1c) of 6.5% to 8.5% and will be on metformin monotherapy.

Twenty subjects will be enrolled to 2 cohorts: Cohort 1 (n = 8) and Cohort 2 (n = 12). For each cohort, subjects will be randomly assigned in a 3:1 ratio to receive MEDI0382 at doses titrated [redacted] or placebo. The study has a run-in period of 10 days and an up to 8-week up-titration treatment period (for the primary analysis) followed by a 3-week treatment extension period at the HCTD followed by a 28-day follow-up period.

In Cohort 1, MEDI0382 or matched placebo will be administered daily starting at [redacted] with the dose up-titrated weekly to [redacted], or until the HCTD is established (whichever occurs first). The dose escalation committee (DEC) will review 72-hour safety data when subjects reach the [redacted] dose levels to determine if the HCTD is established as these doses have not been previously studied in T2DM subjects and the safety profile is unknown. If the DEC determines that the current dose level is not being tolerated and does not approve progression to the next dose level, the preceding one will be declared as the HCTD.

Subjects in Cohort 2 will follow the up-titration schedule defined by Cohort 1, with the 3-week treatment extension period being conducted at the HCTD; thus, the duration of Cohort 2 subjects' participation in the study will be determined by the results obtained from Cohort 1. Dosing in Cohort 2 will occur ≥ 7 days after initiation of Cohort 1 (Figure 2.2-1).

Figure 2.2-1 Study Flow Diagram

2.3 Treatment Assignment and Blinding

Subjects will be randomized using a 3:1 ratio to receive either MEDI0382 or placebo via manual randomization.

This is a blinded study in which the subjects and investigator and staff performing evaluations are blinded to the identity of investigational product, while MedImmune staff involved in the study are unblinded. Investigational product and placebo are indistinguishable in appearance, identically labelled, and supplied as fully blinded kits.

2.4 Sample Size

The total study sample size is 20 subjects, who will be randomized by 2 cohorts: 8 subjects in Cohort 1 and 12 subjects in Cohort 2. For each cohort, subjects will be randomized in a 3:1 ratio to the MEDI0382 arm or the placebo arm. The sample size for this study was empirically determined to obtain adequate safety and tolerability evaluation.

3 STATISTICAL METHODS

3.1 General Considerations

Data will be presented in data listings sorted by treatment, dose, subject number, and date collected, where appropriate. Tabular summaries will be presented by treatment arm. Categorical data will be summarized by the number and percentage of subjects in each category. Continuous variables will be summarized with descriptive statistics (eg, n, mean, median, SD, minimum, and maximum).

Analyses will be conducted for each cohort and for the two cohorts combined. Formal statistical modeling analysis for the secondary efficacy endpoints will be conducted for the two-cohort combined analyses. In general, unless stated otherwise, baseline will be defined as the last value prior to dosing.

Two analyses are planned for this study as follows:

1 A primary analysis after the up-titration period for Cohort 2, and

2 A final analysis after the safety follow-up period for Cohort 2.

Data analyses will be conducted using the SAS® System Version 9.4 or higher (SAS Institute Inc., Cary, NC) in a UNIX platform.

3.2 Analysis Populations

The analysis populations are defined in Table 3.2-1.

Table 3.2-1 Analysis Populations

Population	Description
As-treated population	Subjects who receive any study investigational product will be included in the As-treated population and subjects will be analyzed according to the treatment they actually receive.
Intent-to-treat population (ITT)	Subjects who receive any study investigational product will be included in the ITT population and subjects will be analyzed according to the treatment they were randomized

Table 3.2-1 Analysis Populations

Population	Description
PK population	Subjects who have at least one measurable concentration time point of MEDI0382
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 randomized but not treated with investigational product as well as treatment administered) will be provided. In addition, disposition of subjects throughout the study with respect to dose administered and completion of treatment and follow-up will be provided. This summary will include the number of subjects who discontinued treatment.

3.3.2 Demographics and Baseline Characteristics

Demographic information related to sex, age, race, ethnicity, weight, height, and BMI will be summarized by treatment group and for all subjects for the As-treated population. A summary of baseline characteristics may include, but is not limited to, duration of diabetes, diabetes complications, baseline fasting plasma glucose, and baseline HbA1c.

3.3.3 Study Drug Exposure

The duration of exposure (number of days dosed) of MEDI0382 will be summarized by treatment group with descriptive statistics and frequencies.

3.3.4 Concomitant Medications

Concomitant medications will be coded using the current World Health Organization Drug Dictionary Enhanced (WHO-DDE). The number and percentage of subjects who took concomitant medications for the highest anatomical therapeutic chemical class and preferred term will be summarized by 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.

3.4 Efficacy Analyses

3.4.1 Primary Efficacy Endpoint(s) and Analyses

There are no primary efficacy endpoints in this study.

3.4.2 Secondary Efficacy Endpoint(s) and Analyses

3.4.2.1 Secondary Efficacy Endpoint(s)

- Change in estimated HbA1c (eA1c) from baseline to the end of each week of the up-titration period and the end of the treatment extension period
- Change in plasma fasting glucose from Day -1 versus each week of the up-titration period, the end of the up-titration period, and the end of the treatment extension period
- Change in HbA1c from Day -1 to the end of the treatment extension period

- Percentage and absolute change in body weight from baseline to the end of the up-titration period and the end of the treatment extension
- Percentage and absolute change in body weight from baseline to the end of each week of the up-titration period
- Proportion of subjects achieving > 5% body weight loss from baseline to the end of the treatment extension period.

3.4.2.2 Handling of Dropouts and Missing Data

Last observation carried forward approach will be used to handle missing data for all secondary efficacy analyses. [redacted]

3.4.2.3 Secondary Efficacy Analyses

The secondary efficacy analyses will be based on the ITT population. The continuous secondary efficacy endpoints for the two-cohort combined analysis will be compared between the MEDI0382 and placebo arms using an analysis of covariance (ANCOVA) model adjusting for baseline value and treatment arm. For the secondary proportion-related efficacy endpoints, a logistic regression model will be used adjusting for baseline value and treatment arm. For each cohort, the secondary efficacy endpoints will be summarized without formal statistical comparisons.

[redacted]

3.5 Safety Analyses

All safety analyses will be based on the As-treated population.

3.5.1 Adverse Events and Serious Adverse Events

Adverse events (AEs) will be coded with Medical Dictionary for Regulatory Activities (MedDRA) version 21.0 or later. Analysis of AEs will include the type, incidence, severity, and relationship to investigational product summarized by MedDRA system organ class (SOC) and preferred term (PT) by treatment group as well as overall. The AEs summarized will include only treatment-emergent AEs (TEAEs), ie, those starting after the first administration of investigational product. Subjects will be counted once for specific PT or MedDRA SOC when calculating incidence rates. If the same AE PT occurs multiple times within a subject, the highest severity and level of relationship observed will be reported. If any associations of interest between AEs and baseline characteristics are observed, additional stratified results may be presented. Non-TEAEs and serious adverse events (SAEs) will be presented in the listings.

The incidence and event rate of nausea, vomiting, and nausea/vomiting on each study day during the titration period [redacted] will be summarized. Note that this is not just onset of a new event but includes each day the subject experiences the event excluding the AE stop day. A similar analysis including event rates will be performed for each titration dosing periods: [redacted]

3.5.2 Adverse Events of Special Interest

No adverse events of special interest are identified in the protocol.

3.5.3 Deaths and Treatment Discontinuations due to Adverse Events

A listing of any death will be provided and will include the MedDRA SOC and PT. AEs resulting in permanent discontinuation of investigational product will be summarized by treatment. The summary will include results summarized overall and by MedDRA SOC and PT.

3.5.4 Clinical Laboratory Evaluation

Hematology, serum chemistry, and urinalysis laboratory evaluations will be performed during the study. The hematology and serum chemistry (including lipase and amylase) parameters as well as their changes from baseline and percent changes from baseline will be

summarized with descriptive statistics by treatment group. Other laboratory parameters collected will be summarized in a similar manner. The hematology and serum chemistry results (within reference range), or high (above upper limit of reference range). The urinalysis results will also be classified as low (below lower limit of reference range), and normal results will be classified as normal or abnormal. The shift from baseline for hematology, serum chemistry, and urinalysis results will be summarized by treatment at each evaluation time.

3.5.5 Other Safety Evaluations

3.5.5.1 Vital Signs

Vital signs including pulse rate (beats/min), systolic and diastolic blood pressure (mmHg), temperature (°C), and respiratory rate (breaths/min), as well as their change from baseline will be descriptively summarized by treatment at each visit.

3.5.5.2 Ambulatory Blood Pressure Measurements

Mean systolic blood pressure, diastolic blood pressure, and heart rate over the 24-hour collection for 3 periods (awake, asleep, and complete) will be descriptively summarized by treatment at each visit. Mean change from baseline of these parameters will be analyzed using an ANCOVA model adjusting for treatment and baseline value at end of dosing period and treatment extension.

3.5.5.3 Electrocardiogram

Triplicate electrocardiogram (ECG) will be performed using a digitally recorded standard 12-lead electrocardiograph. For each ECG parameter (heart rate, RR, PR, QRS, QT interval, and the derived parameter QT corrected interval QTcF (Fridericia's formula $\frac{QT}{\sqrt[3]{RR}}$), the average of the 3 values will be analyzed. The change from baseline (Day -1) to each post-baseline evaluation will be summarized with descriptive statistics. Results for the qualitative ECG interpretation (normal or abnormal) will be summarized with frequencies and percentages at each evaluation.

[redacted]

3.6 Immunogenicity

Analysis of immunogenicity will be based on the Immunogenicity population. The incidence and impact of anti-drug antibody (ADA) to MEDI0382 will be evaluated. The number and percentage of subjects with confirmed positive serum antibodies to MEDI0382 will be

reported by treatment. Titer data and cross-reactivity to glucagon-like peptide 1 (GLP-1) and glucagon (if applicable) will be listed.

The following categories will be utilized to describe the ADA response:

- ADA prevalence: subjects who are ADA positive at any visit (including baseline)
- Subjects who are ADA positive at baseline only
- Subjects who are ADA positive at baseline and positive post baseline
- Subjects who are ADA positive post-baseline only (treatment-induced ADA)
- Proportion of subjects who are treatment-boosted ADA; treatment-boosted ADA is defined as baseline ADA titer that was boosted to a 4-fold or higher level following drug administration
- ADA incidence (treatment-emergent ADA), defined as the sum of treatment-induced ADA (post-baseline positive only) and treatment-boosted ADA

A similar summary will be performed for ADA cross-reactivity to GLP-1 and/or glucagon (as data allows and if applicable).

3.7 Pharmacokinetics

PK parameters will be calculated from plasma drug concentration-time data for MEDI0382 for subjects in the PK population. Descriptive statistics will be generated for PK parameters. However, the results of these analyses will be provided in the bioanalytical report that is prepared by the bioanalyst and pharmacokineticist; therefore, no tables, figures, or listings of PK data will be specified in the SPP.

Actual time of sampling, rather than nominal (planned) sampling time, will be used to derive PK parameters. Nominal sampling time will be used for the summary of PK concentrations and will be utilized in the descriptive summaries in mean and median plots. Missing PK parameters will not be imputed.

The PK parameters will be calculated by standard non-compartmental analysis according to current working practices and using Phoenix 64 or equivalent. All calculations of non-compartmental parameters will be based on actual sampling times.

The following PK parameters of MEDI0382 will be determined, if data allow, for each subject from the plasma concentration-time data:

1. C_{max}: The first occurrence of the maximum observed plasma concentration determined directly from the raw concentration-time data.
2. t_{max}: The first time at which C_{max} is observed will be determined directly from the raw concentration-time data.

3. C_τ: trough concentrations from the plasma concentration-time data defined as pre-dose samples.
4. $t_{1/2}$: The apparent terminal elimination half-life obtained as the ratio of $\ln 2/\lambda_z$, where λ_z is the terminal phase rate constant estimated by linear regression analysis of the log transformed concentration-time data.
5. AUC following the last dose until the last measurable concentration ($AUC_{0\text{-last}}$).
6. AUC_τ: AUC at the end of the dosage interval τ.
7. Ro: observed accumulation ratio will be calculated using both the AUC and C_{trough} methods, where data allows, as follows: $Ro = AUC_{\tau dayi}/AUC_{\tau day1}$ and $Ro = C_{\tau dayi}/C_{\tau day1}$.

All derived parameters described above will be listed. For each of these parameters, except t_{max}, the following summary statistics will be calculated for each dose group: median, maximum, minimum, arithmetic mean, standard deviation, coefficient of variation (CV), geometric mean. For t_{max} the following summary statistics will be calculated: median, maximum, minimum, arithmetic mean and geometric mean. Individual C_{trough} will be listed by day and will be summarized as maximum, minimum, arithmetic mean, median, and geometric mean.

[redacted]

3.8 Protocol Deviations

A listing of important protocol deviations will be provided.

4 INTERIM ANALYSIS

No interim analyses are planned; however, the DEC will be evaluating the data periodically to determine whether to escalate the dose.

5 REFERENCES

None

6 VERSION HISTORY

Version	Date	Summary of Changes	Reason for Change
1.0	19JAN2019	Initial document	Initial document

SIGNATURE PAGE

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