Statistical Analysis Plan

A Phase 2a, Randomised, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy, Safety, and Pharmacokinetics of MEDI0382 in Subjects with Type 2 Diabetes Mellitus and Renal Impairment

Protocol Number: D5670C00013

Please note, the document header should be final, rather than draft. Version 2.0 is the first approved version. Version 1.0 was not approved or implemented.

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List of Abbreviations

Abbreviation or Specialized Term	Definition
ABPM	ambulatory blood pressure monitoring
ADA	anti-drug antibody(ies)
AE	Adverse event
AESI	Adverse event of special interest
ANCOVA	Analysis of covariance
AUC	area under the curve
AUC_{tau}	area under the curve during the dosing interval
[redacted]	[redacted]
BMI	Body mass index
CGM	continuous glucose monitoring
CI	Confidence interval
C_{max}	maximum observed concentration
C_{trough}	trough plasma concentration
ECG	Electrocardiogram
eCRF	electronic Case Report Form
ECG	Electrocardiogram
EDC	electronic data capture
eGFR	Estimated glomerular filtration rate
GLP-1	glucagon-like peptide-1
HbA1c	glycated hemoglobin
IM	Immunogenicity
ITT	intent-to-treat
IV	intravenous
IWRS	Interactive web response system
MedDRA	Medical Dictionary for Regulatory Activities
MMTT	mixed-meal tolerance test
PD	Pharmacodynamic(s)
PK	Pharmacokinetics
PT	MedDRA Preferred Term
SAE	Serious adverse event
SAP	Statistical analysis plan
SC	Subcutaneous
SID	Subject ID
SOC	MedDRA System Organ Class
SPP	Statistical programming plan
T2DM	Type 2 diabetes mellitus
T_{max}	time to maximum concentration
U	Units

Abbreviation or Specialized Term	Definition
ULN	upper limit of normal
WHO-DD	World Health Organization Drug Dictionary

1 INTRODUCTION

This document describes the statistical analysis methodology for protocol D5670C00013 (Amendment 2, 6Apr2018 and Local Amendment 1 [Germany], 4May2018), a phase 2a randomized, double-blind, parallel group study to evaluate the efficacy, safety, and pharmacokinetics of MEDI0382 and placebo during 32 days of treatment in T2DM subjects with renal impairment. 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 glucose control versus placebo after 32 days of treatment

2.1.2 Secondary Study Objectives

- To characterize the safety profile and tolerability of MEDI0382 titrated up to a dose level of [redacted] during dosing and follow-up in subjects with T2DM and renal impairment
- To assess the effects of MEDI0382 titrated up to a dose level of [redacted] on additional measures of glycemic control versus placebo after 32 days of treatment
- To assess the effects of MEDI0382 titrated up to a dose level of [redacted] on weight versus placebo after 32 days of treatment
- To characterize the PK profile and immunogenicity of MEDI0382

[redacted]

2.2 Study Design

This is a randomized, double-blind, placebo-controlled study to evaluate the safety, tolerability, efficacy, and PK profile of MEDI0382 titrated from [redacted]

administered once daily by subcutaneous (SC) injection for 32 days in subjects with T2DM and renal impairment (30 ≤ eGFR < 60 mL/min/1.73 m^2). The study has a 14-day run-in period of diet and exercise and continuous glucose monitoring (CGM), a 32-day treatment period and a 28-day follow-up. Forty (40) subjects across multiple study sites will be randomized in two strata (Insulin dose ≥20 U/day or Insulin dose < 20 U/day) [redacted]. In addition, at least 40% of randomized subjects will have screening eGFR values between 30 and 44 mL/min/1.73 m^2, inclusive and at least 40% of randomized subjects will have screening eGFR values between 45 and 59 mL/min/1.73 m^2, inclusive although there is no stratification based on screening eGFR to ensure balance within insulin strata or treatment groups.

Mixed-meal tolerance tests (MMTT) will be performed on Day -5 and Day 32. Subjects will wear a continuous glucose monitoring (CGM) sensor from the start of the run-in period until the first post-treatment follow-up visit. 24-hour ambulatory blood pressure monitoring (ABPM) will be performed 5 times during the study (pre-treatment and 4 during treatment evaluations). Vital signs, ECG, weight, [redacted] measurements will be collected during the study.

An interim analysis will be performed using data collected within 12 weeks after the first subject's first dose or after 20 subjects have completed 32 days of dosing, whichever occurs sooner. This interim analysis will be performed to plan Phase 3 studies and will not be used to modify the conduct of this study.

2.3 Treatment Assignment and Blinding

An IWRS will be used for randomization to a treatment group and assignment of blinded investigational product kit numbers. Forty (40) subjects will be randomized using a 1:1 ratio to receive either MEDI0382 or placebo with the randomization stratified [redacted]

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. Although not perfect, 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. An unblinded site monitor will interact with site unblinded personnel to maintain study blind.

2.4 Sample Size

Forty subjects (20 completers in the MEDI0382 group and 20 completers in placebo group) will provide > 85% power to detect 18.1% difference between the two treatment groups in percentage change in the MMTT glucose AUC from baseline (Day -5) to the end of 32 days of treatment (Day 32), with a two-sided significance level of 0.1 and assuming the standard deviation of 20%.

3 STATISTICAL METHODS

3.1 General Considerations

Data will be presented in data listings sorted by insulin strata, treatment, subject number and date collected, where appropriate. Tabular summaries will be presented for each treatment and for insulin strata within treatment. Categorical data will be summarized by treatment and for insulin strata within each treatment with the number and percentage of subjects within each category. In general, continuous variables will be summarized by treatment and insulin strata within treatment with descriptive statistics including mean, standard deviation, median, minimum, and maximum. Safety variables will generally be summarized by treatment across insulin strata.

All available data will be included in the analyses and missing data will not be imputed except as specified in the calculation of the AUC values. Unless specified otherwise, baseline values will be defined as the last valid assessment prior to the first administration of study medication.

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 9.3 or higher (SAS Institute Inc., Cary, NC) in a UNIX environment. 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 3.2-1.

Table 3.2-1 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.

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.
Pharmacokinetic (PK) population	The PK population includes all subjects who received at least 1 dose of investigational product and had at least one PK sample taken with a value above the lower limit of quantitation.

3.3 Study Subjects

3.3.1 Subject Disposition and Completion Status

A summary of subject eligibility and randomization (including summary of subjects randomized but not treated) as well as treatment administered and insulin strata will be provided. In addition, disposition of subjects throughout the study with respect to completion of treatment and follow-up 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 insulin strata and treatment group and for all subjects combined. A summary of baseline disease characteristics may include, but not be limited to screening eGFR, number (%) with $30 \leq eGFR < 45$ ml/min/1.73 m^2 and number (%) with $45 \leq eGFR < 60$ ml/min/1.73 m^2, HbA1c, and insulin dose (insulin strata), and oral anti-hyperglycemic medications.

3.3.3 Study Drug Exposure

The number of doses and total dose received will be summarized by insulin strata 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.

3.4 Efficacy Analyses

3.4.1 Primary Efficacy Endpoint(s) and Analyses

3.4.1.1 Primary Efficacy Endpoint(s)

Percentage change in glucose area under the curve (AUC) as measured by a standardized mixed-meal tolerance test (MMTT) from baseline (Day -5) to the end of 32 days of treatment.

3.4.1.2 Handling of Dropouts and Missing Data

Subjects who do not have a valid baseline evaluation or a valid Day 32 MMTT evaluation will not be included in the analysis.

3.4.1.3 Primary Efficacy Analysis

The primary efficacy analysis will be performed using the ITT population. The primary efficacy endpoint, percentage change in MMTT glucose AUC from baseline (Day -5) to the end of treatment evaluation (Day 32) will be analyzed using an analysis of covariance (ANCOVA) model. The model will include fixed effect for treatment (MEDI0382 or Placebo) with the baseline AUC used as a covariate. The treatment groups will be considered statistically significant if the two-sided significance level is less than 0.10.

3.4.1.4 Subgroup Analyses

Two subgroup analyses will be performed if there are at least 6 subjects in the smallest subgroup. The analysis will be an analysis of covariance with fixed effects for treatment (MEDI0382 or Placebo), subgroup, and treatment by subgroup interaction with the baseline AUC used as a covariate. The subgroups that will be included in the analysis are:

- Insulin strata (insulin dose ≥20 U/day and insulin dose < 20 U/day)
- Baseline HbA1c category (<8% and ≥8%)

3.4.2 Secondary Efficacy Endpoint(s) and Analyses

3.4.2.1 Secondary Efficacy Endpoint(s)

- Change in HbA1c from baseline (Day 1) to the end of 32 days of treatment (Day 32)
- Change in fasting glucose from baseline (Day 1) to the end of 32 days of treatment (Day 32)
- Change in percentage of time spent within a target glucose range of 70 mg/dL (3.9 mmol/L) to 180 mg/dL (10 mmol/L) over a 7-day period at baseline (Days -8 to - 2) to the final week of treatment (Days 26-32)

- Percentage and absolute change in body weight from baseline (Day 1) to the end of 32 days of treatment

3.4.2.2 Handling of Dropouts and Missing Data

If the end of treatment evaluation is missing for weight, the last post-baseline value will be used in the analysis (LOCF). Subjects who do not have a valid end of treatment evaluation for fasting plasma glucose, HbA1c, or percentage of time CGM glucose within target range will not be included in the analysis.

3.4.2.3 Secondary Efficacy Analyses

The secondary efficacy endpoints will be analyzed with ANCOVA, similar to that used for the primary endpoint.

3.4.3 Other Efficacy Analyses

3.5 Safety Analyses

3.5.1 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 insulin strata and treatment group as well as overall. The AEs summaries will include only treatment-emergent AEs, i.e., those occurring after administration of 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) will be presented in the listings.

3.5.2 Adverse Events of Special Interest

The following AESIs have been identified for this protocol: hepatic function abnormality meeting the definition of Hy's law, which is defined as any increase in alanine aminotransferase (ALT) or aspartate aminotransferase (AST) to greater than 3x ULN and concurrent increase in total bilirubin to greater than 2x ULN. Concurrent findings are those that derive from a single blood draw or from separate blood draws taken within 8 days of each other.

The AESIs will be summarized overall, as well as categorized by MedDRA system organ class and preferred term by insulin strata and treatment.

3.5.3 Deaths and Treatment Discontinuations due to Adverse Events

A listing of any deaths will be provided which will include the MedDRA SOC and PT. AEs resulting in permanent discontinuation of study drug will be summarized by insulin strata and

treatment. The summary will include results summarized overall and by MedDRA System Organ Class and Preferred Term.

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 calcitonin, lipase, and amylase) parameters as well as their changes from baseline will be summarized with descriptive statistics (number of subjects, mean, and standard deviation, median, minimum and maximum) by insulin strata and treatment group. Other laboratory parameters collected will be summarized in a similar manner. The hematology and serum chemistry results will also be classified as low, normal, or high. The urinalysis results will be classified as normal or abnormal. The shift from baseline hematology, serum chemistry, and urinalysis results will be summarized by insulin strata and 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 (mm Hg), temperature (^{o}C), and respiratory rate (breaths/min), as well as the change from baseline for each of those parameters, will be descriptively summarized by insulin strata and treatment at each time point. The change in blood pressure (systolic and diastolic (mm Hg) from supine to standing from Day 1 to Day 32 will be descriptively summarized by insulin strata and treatment.

3.5.5.2 Ambulatory Blood Pressure Measurements

Mean systolic blood pressure, mean diastolic blood pressure, and mean pulse rate over the 24-hour collection periods will be descriptively summarized by insulin strata and treatment at each visit.

3.5.5.3 Electrocardiogram

Electrocardiogram parameters will be assessed with a single ECG at each evaluation (Screening, Days 1, 5, 12, 19, 32 40 and 60) using a digitally recorded standard 12-lead electrocardiograph. The ECG parameters: Heart rate, RR, PR, QRS and QT intervals as well as derived parameter QT corrected interval QTcF (Fridericia's formula $\frac{QT}{\sqrt[3]{RR}}$) will be summarized. The results at each evaluation as well as the change from baseline (Day 1) for each post-baseline evaluation will be descriptively summarized by insulin strata and treatment. For the qualitative variable ECG interpretation, the ECG Interpretation results will be summarized with frequencies and percentages at each evaluation.

3.6 Immunogenicity

Analysis of immunogenicity will be based on the As-treated Population. The incidence and impact of ADA to MEDI0382 will be evaluated. The number and percentage of subjects with confirmed positive serum antibodies to MEDI0382 will be reported by insulin strata and treatment. Titer data and cross reactivity to GLP-1 and glucagon (if applicable) will be listed. If warranted by the data, the association of ADA-positive with observed PK data may be explored.

3.7 Pharmacokinetics

The analysis of the pharmacokinetic data is described below. However, the results of these analyses will be provided in the pharmacokinetic report that is prepared by the pharmacokineticist; therefore, no tables, figures or listings of pharmacokinetic data will be specified in the SPP.

- AUC over a dosing duration ($AUC_{0\text{-}24}$ on Day 32)
- maximum observed concentration (C_{max} on Day 32)
- time to C_{max} (T_{max} on Day 32)
- trough plasma concentration (C_{trough} on Days 5, 12, 19, 32, and 33)

3.8 Protocol Deviations

A summary of important protocol deviations (IPD) will be prepared by deviation category as well as overall. A listing of the important protocol deviations will also be provided.

4 INTERIM ANALYSIS

An interim analysis will be performed using data collected within 12 weeks after first subject first dose or when 20 subjects have completed 32 days of dosing, whichever occurs sooner. The purpose of this interim analysis is to plan Phase 3 studies and no changes to this study are anticipated. The interim analyses will use the available data to summarize primary and secondary endpoints and adverse event data.

All personnel involved with the conduct of the study will remain blinded to subjects' treatment assignments until final database lock. The interim analysis will be performed by a separate unblinded team, or alternatively any study team members who serve in the unblinded analysis group will stop day-to-day work on the study from the point of interim database lock and other pre-selected personnel will take over these roles for the remainder of the study.

Summary results will only be available to a restricted set of the project team who will use the results for the Phase 3 clinical plan and will not be provided to the investigator. There will be

no overlap between this project team and the study team. There will be an interim unblinding analysis plan that contains more details.

5 REFERENCES

None

6 VERSION HISTORY

Version	Date	Summary of Changes	Reason for Change
1.0	21May2018	Initial document	Initial document
2.0	08June2018	-MedDRA version -INTERIM ANALYSIS -The change in blood pressure (systolic and diastolic (mm Hg) from supine to standing from Day 1 to Day 32 will be descriptively summarized by insulin strata and treatment.	Incorporated Team Comments