

Statistical Analysis Plan

An Exploratory Phase 2a Randomized, Placebo-controlled, Double-blind Study to Evaluate the Efficacy and Safety of MEDI0382 versus Placebo in Overweight/Obese Subjects with Type 2 Diabetes Mellitus Treated with Dapagliflozin and Metformin

Protocol Number: D5670C00007

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List of Abbreviations

Abbreviation or Specialized Term	Definition
ABPM	Ambulatory blood pressure monitoring
████	████████████████
AE	Adverse event
AUC	Area under the concentration-time curve
CGM	Continuous glucose monitoring
C_{max}	Maximum observed concentration
ECG	Electrocardiogram
FFA	Free fatty acids
FPG	Fasting plasma glucose
GLP-1	Glucagon-like peptide-1
HbA1c	Hemoglobin A1c
ITT	Intent-to-Treat
IXRS	Interactive voice/web response system
LOCF	Last observation carried forward
MAGE	Mean amplitude of glucose excursion
MMTT	Mixed-meal tolerance test
PD	Pharmacodynamics
PK	Pharmacokinetics
SPP	Statistical Programming Plan
SC	Subcutaneous
SD	Standard deviation
T2DM	Type 2 diabetes mellitus

Abbreviation or Specialized Term	Definition
t_{\max}	Time to maximum-observed concentration
ULN	Upper limit of normal range

1 INTRODUCTION

This document describes the statistical analysis methodology for protocol D5670C00007, a Phase 2a exploratory randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of MEDI0382 versus placebo in overweight/obese subjects with type 2 diabetes mellitus (T2DM) treated with dapagliflozin and metformin. 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 compare the change in glucose area under the concentration-time curve (AUC) as measured by a standardized mixed meal tolerance test (MMTT) in subjects treated with dapagliflozin and metformin receiving MEDI0382 or placebo for 28 days

2.1.2 Secondary Study Objectives

- To compare the safety and tolerability profile of MEDI0382 (titrated up to a dose level of 300 µg subcutaneous [SC]) compared to placebo after 28 days of treatment in subjects treated with dapagliflozin and metformin
- To evaluate the pharmacokinetics (PK) profile of MEDI0382 and dapagliflozin (in subjects treated with dapagliflozin, metformin, and MEDI0382) and dapagliflozin (in subjects treated with dapagliflozin, metformin, and placebo)

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- To evaluate 24-hour glucose control as measured by continuous glucose monitoring (CGM) in subjects treated with dapagliflozin and metformin receiving MEDI0382 or placebo for 28 days

2.1.3 Exploratory Study Objectives

- To compare additional measures of glucose control (fasting plasma glucose [FPG] and hemoglobin A1c [HbA1c]) in subjects treated with dapagliflozin and metformin receiving MEDI0382 or placebo for 28 days

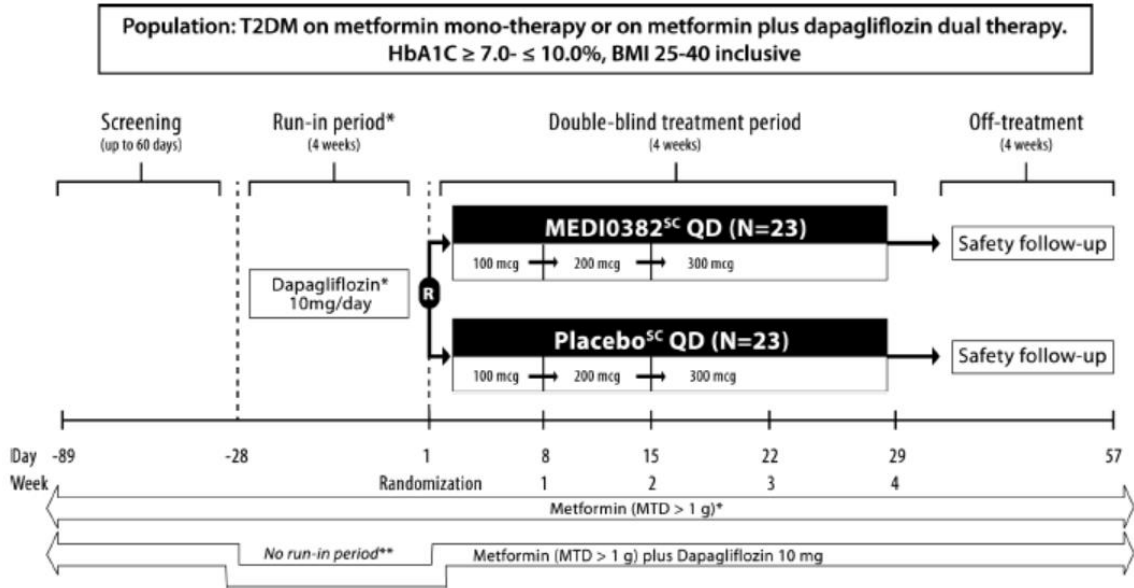
- To evaluate pancreatic and incretin hormone AUC profiles (ie, active glucagon-like peptide-1 [GLP-1], glucagon, insulin, and c-peptide) as measured by MMTT in subjects treated with dapagliflozin and metformin receiving MEDI0382 or placebo for 28 days
- To compare the fasting free fatty acid (FFA) levels in subjects treated with dapagliflozin and metformin receiving MEDI0382 or placebo for 28 days
- To compare plasma ketone profile (β -hydroxybutyrate) in subjects treated with dapagliflozin and metformin receiving MEDI0382 or placebo for 28 days
- To compare the change in body weight after 28 days of treatment with MEDI0382 or placebo in subjects treated with dapagliflozin and metformin
- To evaluate 24-hour urinary glucose excretion in subjects treated with dapagliflozin and metformin receiving MEDI0382 or placebo

2.2 Study Design

This is an exploratory randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of MEDI0382 versus placebo in overweight/obese subjects with T2DM treated with dapagliflozin and metformin dual therapy. Subjects will participate in the study for up to 20 weeks, including a screening period of up to 60 days, a 4-week run-in period (for subjects on metformin monotherapy only), a 4-week treatment period, and a 4-week post-treatment follow-up period.

The study will enroll subjects with T2DM treated either with metformin monotherapy or with metformin and dapagliflozin dual therapy. After the screening period of up to 60 days, subjects previously treated with metformin monotherapy only will enter an open-label, run-in period where subjects will be administered oral dapagliflozin 10 mg a day for 4 weeks. Enrolled subjects who are already treated with metformin and dapagliflozin dual therapy will continue this dual therapy throughout the study and can be randomized after the screening period without entering the run-in period. All subjects (ie, on monotherapy and dual therapy) entering the double-blind treatment period will receive dapagliflozin 10 mg a day. (Figure 2.2-1)

Figure 2.2-1 Study Flow Diagram



BMI = body mass index; HbA1c = hemoglobin A1c; MTD = maximum-tolerated dose; N = number of subjects; QD = once daily; SC = subcutaneous; T2DM = type 2 diabetes mellitus.

* Run-in period only for subjects on metformin monotherapy only at screening

** Subject on metformin and dapagliflozin dual therapy at screening move directly from screening to double blind treatment period

2.3 Treatment Assignment and Blinding

An Interactive voice/web response system (IXRS) will be used for assignment of dapagliflozin tablet bottles (where required), randomization to a treatment group, and assignment of blinded MEDI0382 or placebo investigational product kit numbers. A subject is considered randomized into the study when the investigator notifies the IXRS that the subject meets eligibility criteria, and the IXRS provides the assignment of investigational product kit number to the subject.

Eligible subjects will be randomized at a 1:1 ratio following screening to receive either MEDI0382 SC or placebo SC. The IXRS will assign a unique randomization code and treatment group to the subject at each randomization. Subjects who withdraw from the study may be replaced, if deemed necessary by the medical monitor, to ensure that safety data are collected on a sufficient number of subjects.

This is a double-blind study in which MEDI0382 and placebo are not identical in the prefilled syringe titration volumes. Neither the subject 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 (ICH E9).

The different fill volumes of investigational product (MEDI0382 and placebo) and the relative position of the plunger rods will be visually distinct during administration. To maintain the blind, investigational product (MEDI0382 and placebo) prefilled syringes will be handled by an unblinded investigational product manager or unblinded study personnel that will not be involved in the treatment or clinical evaluation of subjects. An unblinded qualified designee may administer investigational product to subjects during in-clinic visits.

An independent investigational product monitor will also be unblinded to perform investigational product accountability. In the event that a treatment allocation for a subject becomes known to the investigator or other study staff involved in the management of study subjects, the sponsor must be notified immediately. If the treatment allocation for a subject needs to be known to treat an individual subject for an adverse event (AE), the investigator must notify the sponsor immediately. The site will maintain a written plan detailing which staff members are blinded/unblinded and the process of investigational product administration used to maintain the blind.

2.4 Sample Size

A total of 46 subjects are planned for the study. Each of the 2 treatment groups will be randomized at a 1:1 ratio to receive (a) MEDI0382 with dapagliflozin and metformin administered simultaneously or (b) placebo with dapagliflozin and metformin administered simultaneously. A sample size of 23 subjects in each treatment group will provide a study power > 95% to detect a difference of 30% between treatment groups in relative change from baseline in glucose AUC_{0-4h} at a two-sided alpha of 5%, assuming a common standard deviation (SD) of 20%. This sample size will also provide a study power > 95% to detect a difference of 225 hr•mg/dL between treatment groups in absolute change from baseline in glucose AUC_{0-4h} at a two-sided alpha of 5%, assuming a common SD of 150 hr•mg/dL. The SD assumptions are based the result of 300 μ g cohorts in a prior study (D5670C00002).

3 STATISTICAL METHODS

3.1 General Considerations

Data will be presented in data listings sorted by treatment group, subject number, and date collected, where appropriate. Tabular summaries will be presented. Categorical data will be summarized by the number and percentage of subjects within each category. In general, continuous variables will be summarized by descriptive statistics including mean, standard deviation, median, minimum, and maximum. For some variables, the geometric mean and 95% CI will be presented.

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

3.3 Study Subjects

3.3.1 Subject Disposition and Completion Status

A summary of subject eligibility and randomization as well as treatment group received (including a summary of subjects randomized but not treated) 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, but not be limited to duration of T2DM, diabetes complications, HbA1c, fasting plasma glucose, eGFR, background therapy for diabetes (eg, metformin monotherapy or metformin + dapagliflozin).

3.3.3 Study Drug Exposure

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

3.3.4 Concomitant Medications

Concomitant medications will be coded using current World Health Organization Drug Dictionary. The number and percentage of subjects who took concomitant medications will be summarized by the highest anatomical therapeutic chemical class and preferred term by treatment group 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 study medication or any concomitant medication started prior to first dose study medication that continued beyond the date of first dose of study medication.

3.4 Efficacy Analyses

3.4.1 Primary Efficacy Endpoint(s) and Analyses

3.4.1.1 Primary Efficacy Endpoint(s)

- Change from baseline (Day -1) to the end of 28 days of treatment (Day 28) in glucose AUC from 0 to 4 hours (AUC_{0-4h}) as measured by a MMTT
- Percentage change from baseline (Day -1) to the end of 28 days of treatment (Day 28) in glucose AUC_{0-4h} as measured by a MMTT

3.4.1.2 Handling of Dropouts and Missing Data

No missing data imputation will be used for the primary efficacy analysis since there is only one post-baseline data collected for the primary efficacy endpoint. If any glucose values used in the calculation of the glucose AUC are missing, the AUC will be calculated as described in the SPP.

3.4.1.3 Primary Efficacy Analysis

The primary efficacy analysis will be based on the ITT population. The primary endpoints, change and % change from baseline to the end of 28 days of treatment in glucose AUC_{0-4h} as measured by a MMTT, will be summarized by treatment group. Statistical comparisons of these endpoints between MEDI0382 and placebo treatment groups will be performed using an analysis of covariance by adjusting baseline value and treatment group.

3.4.2 Secondary Efficacy Endpoint(s) and Analyses

3.4.2.1 Secondary Efficacy Endpoint(s)

- Change from baseline to the end of dosing at each dose level (Days 7, 14, and 28) in glucose AUC at 24 hours (AUC_{24h}) as measured by CGM
- Change from baseline to the end of dosing at each dose level (Days 7, 14, and 28) in 24-hour mean glucose as measured by CGM
- Change from baseline to the end of dosing at each dose level (Days 7, 14, and 28) in SD of 24-hour glucose readings as measured by CGM
- Change from baseline to Days 7, 14, and 28 in the coefficient of variation (CV) (ratio of SD:mean over 24 hours) of glucose readings as measured by CGM
- Change from baseline to Days 7, 14, and 28 in the mean amplitude of glucose excursion (MAGE) of 24-hour glucose readings as measured by CGM
- Change from baseline to Days 7, 14, and 28 in the percentage of 24-hour glucose readings obtained from CGM that fall within the euglycemic range of ≥ 70 mg/dL (≥ 3.9 mmol/L) and ≤ 180 mg/dL (≤ 10.0 mmol/L)
- Change from baseline to Days 7, 14, and 28 in the percentage of 24-hour glucose readings obtained from CGM that fall within hyperglycemic (high glucose) range of > 180 mg/dL (> 10.0 mmol/L)
- Change from baseline to Days 7, 14, and 28 in the percentage of 24-hour glucose readings obtained from CGM that fall within the hypoglycemic range of < 70 mg/dL (< 3.9 mmol/L)
- Change from baseline to Days 7, 14, and 28 in the percentage of 24-hour glucose readings obtained from CGM that fall within the clinically significant hypoglycemic range of < 54 mg/dL (3.0 mmol/L)

3.4.2.2 Handling of Dropouts and Missing Data

LOCF approach will be used to handle missing data for all secondary efficacy and pharmacodynamics (PD) analyses. If any values used in the calculation of the AUC are missing, the AUC will be calculated as described in the SPP.

3.4.2.3 Secondary Efficacy Analyses

Secondary efficacy analysis will be based on the ITT population. The secondary efficacy endpoints will be summarized by treatment group at each time point and analyzed similarly to the analysis of primary efficacy endpoint with LOCF approach to handle missing data.

3.4.3 Exploratory Efficacy Endpoint(s) and Analyses

3.4.3.1 Exploratory Efficacy Endpoint(s)

- Change from baseline (Day -1) to Day 28 in FPG
- Change from baseline (Day -2) to Day 28 in HbA1c
- Change from baseline (Day 1) to Day 29 in body weight (kg)
- Percentage change from baseline (Day 1) to Day 29 in body weight (kg)
- Proportion of subjects achieving $\geq 5\%$ body weight loss from baseline (Day 1) to Day 29

3.4.3.2 Exploratory Efficacy Analyses

Exploratory efficacy analyses will be based on the ITT population. The change from baseline endpoints will be summarized by treatment group at each time point and the final treatment evaluation time analyzed similar to the analysis of primary efficacy endpoint with LOCF approach to handle missing data.

The proportion of subjects achieving $\geq 5\%$ body weight loss from baseline (Day 1) to Day 29 will be analyzed using a logistic regression by adjusting baseline value and treatment group.

3.5 Pharmacodynamic Exploratory Endpoint(s) and Analyses

3.5.1.1 Pharmacodynamic Endpoint(s)

- Change from baseline (Day -1) to Day 28 in GLP-1, glucagon, insulin, and c-peptide AUC_{0-4h} as measured by MMTT
- Change from baseline (Day -1) to Days 7, 14, and 28 in fasting FFA level
- β -hydroxybutyrate profile to include AUC_{0-inf} , AUC_{0-last} , C_{max} , and t_{max}
- Total glucose excreted in urine collected for 24 hours on Days 1 and 28

3.5.1.2 Analysis of Pharmacodynamic Endpoint(s)

PD analysis will be based on the ITT population. The change from baseline endpoints for GLP-1, glucagon, insulin, and c-peptide AUC_{0-4h} and for fasting FFA levels will be summarized by treatment group at each time point and the final treatment evaluation time analyzed similar to the analysis of primary efficacy endpoint with LOCF approach to handle missing data.

Descriptive statistics will be provided for β -hydroxybutyrate parameters: AUC_{0-inf} , AUC_{0-last} , C_{max} , and t_{max} at each time point and total glucose urinary excretion (Days 1 and 28). The β -hydroxybutyrate parameters will be calculated by the Pharmacokinetics group following the calculations provided below in the Pharmacokinetics Section.

3.6 Safety Analyses

3.6.1 Adverse Events and Serious Adverse Events

Adverse events (AE) will be coded by MedDRA version 20.0 or higher. Analysis of adverse events will include the type, incidence, severity and relationship to study investigational product (MEDI0382 or dapagliflozin) summarized by MedDRA System Organ Class (SOC) and Preferred Term by treatment group as well as for overall treatments. The AEs summaries will include only treatment-emergent AEs; ie, those occurring after initial receipt of investigational product. Subjects will be counted once for specific PT or MedDRA SOC when calculating incidence. 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 will be presented in the listings.

3.6.2 Adverse Events of Special Interest

Hepatic function abnormality meeting the definition of Hy's law is considered an adverse event of special interest. Number and proportion of subjects who meet Hy's law criteria: aspartate transaminase or alanine transaminase $\geq 3 \times$ upper limit of normal range (ULN) together with total bilirubin $\geq 2 \times$ ULN will be summarized by treatment.

3.6.3 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.

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[REDACTED]

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3.8 Pharmacokinetics

For MEDI0382, Dapagliflozin and β -hydroxybutyrate, 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 plots. Missing PK parameters will not be imputed.

For subjects in each treatment group the following pharmacokinetic parameters will be determined from the plasma concentration-time data for MEDI0382, dapagliflozin and β -hydroxybutyrate if data allow. The pharmacokinetic parameters will be calculated by standard non-compartmental analysis according to current working practices and using Phoenix WinNonlin 6.3 or equivalent:

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 at the end of the dosing interval (i.e. 24 hours).
4. AUC_{τ} : Area under the plasma concentration time curve at the end of the dosage interval τ .
5. R_o : observed accumulation ratio will be calculated using both the AUC and C_{trough} methods, where data allows, as follows: $R_o = AUC_{\tau day i} / AUC_{\tau day 1}$ and $R_o = C_{\tau day i} / C_{\tau day 1}$.

If data allows additional parameters may be derived for MEDI0382 and Dapagliflozin such as $t_{1/2}$: the apparent terminal elimination half-life ($t_{1/2}$) 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; and CL/F : the apparent clearance calculated as $CL/F = Dose / AUC(0-\infty)$.

All the derived parameters described above will be listed. For each of these parameters, except for t_{max} , the following summary statistics will be calculated for each active treatment group: median, maximum, minimum, arithmetic mean, standard deviation, CV, geometric mean. For t_{max} , the following summary statistics will be calculated for each active treatment group: median, maximum, minimum, arithmetic mean.

Individual C_{trough} will be listed by treatment and day and will be summarized as maximum, minimum, arithmetic mean and geometric mean.

Subjects who have at least one measurable concentration time point of investigational product will be used for this analysis.

4 INTERIM ANALYSIS

No interim analysis is planned.

5 VERSION HISTORY

Version	Date	Summary of Changes	Reason for Change
1.0	03JUL2018	Initial document	Initial document

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Editor Delivery Events

Status

Timestamp

Agent Delivery Events	Status	Timestamp
Intermediary Delivery Events	Status	Timestamp
Certified Delivery Events	Status	Timestamp
Carbon Copy Events	Status	Timestamp
Notary Events	Signature	Timestamp
Envelope Summary Events	Status	Timestamps
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Certified Delivered	Security Checked	7/10/2018 6:12:32 PM
Signing Complete	Security Checked	7/10/2018 6:12:42 PM
Completed	Security Checked	7/10/2018 6:12:42 PM
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Required hardware and software

Operating Systems:	Windows2000? or WindowsXP?
Browsers (for SENDERS):	Internet Explorer 6.0? or above
Browsers (for SIGNERS):	Internet Explorer 6.0?, Mozilla FireFox 1.0, NetScape 7.2 (or above)
Email:	Access to a valid email account
Screen Resolution:	800 x 600 minimum
Enabled Security Settings:	<ul style="list-style-type: none"> •Allow per session cookies •Users accessing the internet behind a Proxy Server must enable HTTP 1.1 settings via proxy connection

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