Statistical Analysis Plan

A Phase 2, Randomised, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy, Safety, Tolerability, and Pharmacokinetics of Different Doses of MEDI0382 in Overweight and Obese Subjects with Type 2 Diabetes Mellitus

Protocol Number: D5670C00011

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List of Abbreviations

Abbreviation or Specialized Term	Definition
ABPM	Ambulatory blood pressure monitoring
ADA	Anti-drug antibody
AE	Adverse event
ANCOVA	Analysis of covariance
ATC	Anatomical Therapeutic Chemical
AUC	Area under the concentration-time curve
BMI	Body mass index
CGM	Continuous glucose monitoring
[redacted]	[redacted]
CV	Coefficient of variation (standard deviation/mean)
eCRF	electronic Case Report Form
ECG	Electrocardiogram
FFA	free fatty acids
[redacted]	[redacted]
GLP-1	Glucagon-like peptide-1
hr	hours
IM	Immunogenicity
ITT	Intent-to-Treat
IWRS	Interactive web response system
LOCF	Last observation carried forward
MMTT	Mixed-meal tolerance test
msec	milliseconds
PD	Pharmacodynamics
PK	Pharmacokinetics
PT	Preferred Term
SAE	Serious adverse event
SAP	Statistical analysis plan
SC	Subcutaneous
SID	Subject identification number
SOC	System Organ Class
SPP	Statistical programming plan
T2DM	Type 2 diabetes mellitus
ULN	Upper limit of normal reference range

1 INTRODUCTION

This document describes the statistical analysis methodology for protocol D5670C00011, a phase 2a study to evaluate the efficacy, safety, tolerability, and pharmacokinetics (PK) of different doses of MEDI0382 in overweight and obese subjects with Type 2 Diabetes Mellitus. The main portion of 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 effects of MEDI0382 titrated up to a dose level of 300 µg on glucose control and body weight versus placebo after 49 days of treatment (Cohort 1 only).

2.1.2 Secondary Study Objectives

- To assess the effects of MEDI0382 titrated up to a dose level of 300 µg on additional measures of glucose control and body weight versus placebo after 49 days of treatment (Cohort 1 only).
- To characterize the safety profile and tolerability of MEDI0382 titrated up to a dose level of 300 µg during dosing and follow-up (Cohorts 1 and 2).
- To characterize the PK profile and immunogenicity of 50 and 300 µg of MEDI0382 (Cohorts 1 and 2).
- To characterize the effect of 50 µg of MEDI0382 on glucose lowering versus placebo after 7 days (Cohorts 1 and 2).

2.1.3 Exploratory Study Objectives

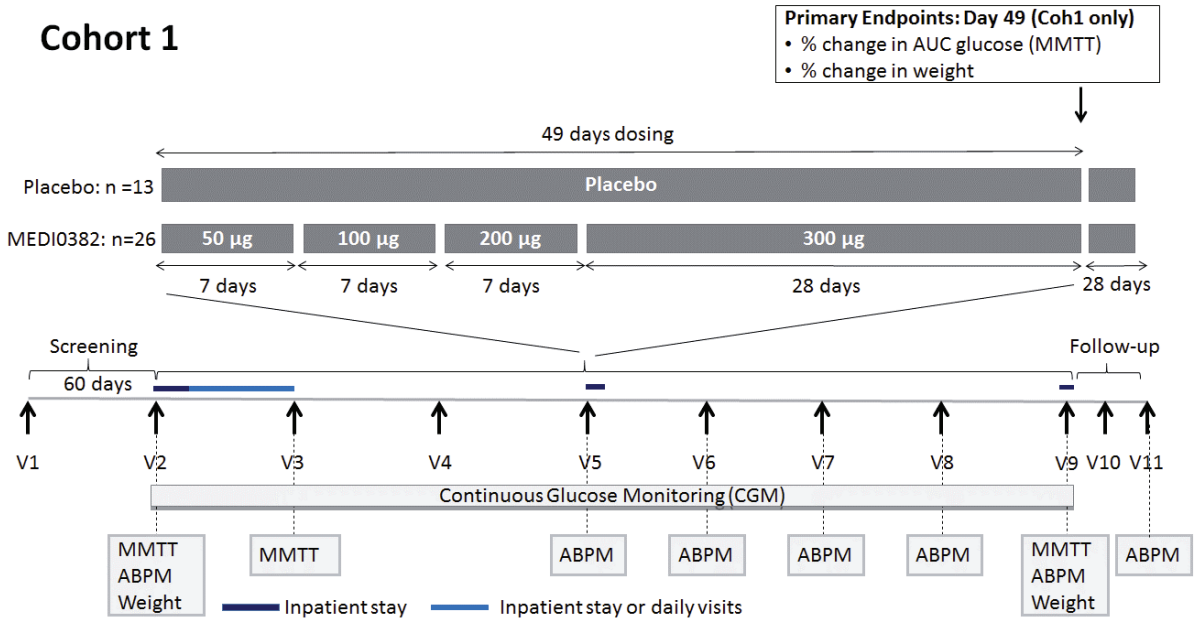
- [redacted]
- To assess gastrointestinal tolerability across different titration schedules (Cohorts 1 and 2).
- To assess the effect of MEDI0382 on glucose lowering during different meals and times of the day as measured by continuous glucose monitoring (CGM) (Cohort 1 only).
- To characterize the effect of MEDI0382 on glucose lowering and weight versus placebo after 7, 14 and 49 days (Cohort 2 only).
- To assess the effect of MEDI0382 on pancreatic and incretin hormone profiles at baseline and during the mixed-meal tolerance test (MMTT) (Cohorts 1 and 2).
- To assess the effect of MEDI0382 on ketone bodies, amino acids, and free fatty acid (FFA) levels over 49 days of treatment (Cohort 1 only).

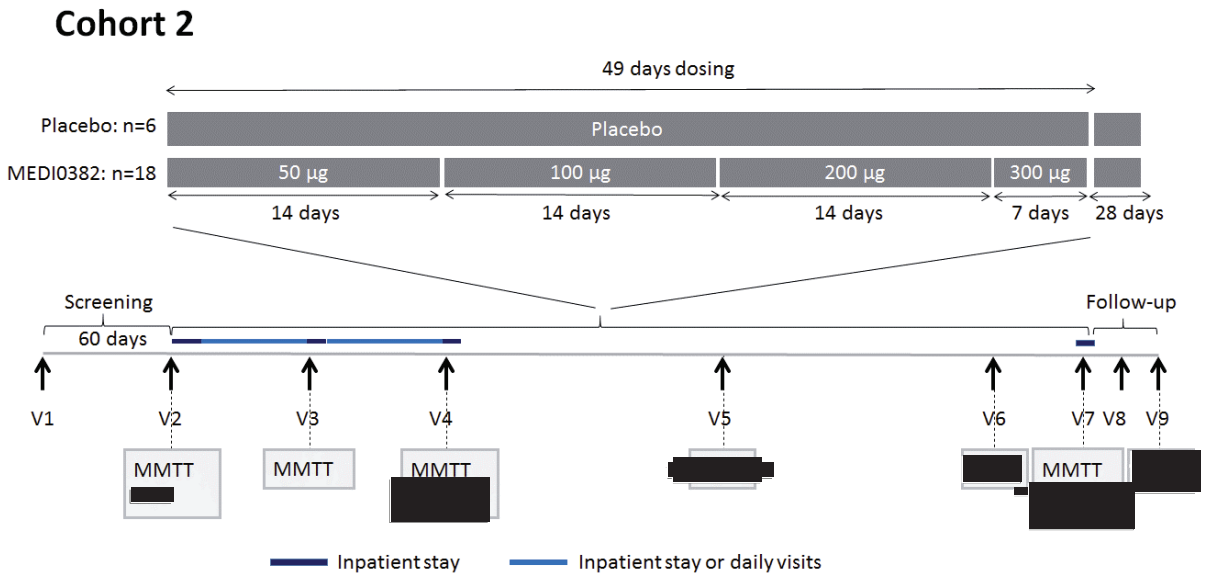
- To assess the effect of MEDI0382 on uric acid [redacted] (Cohort 1 only).

2.2 Study Design

This is a randomized, double-blind, placebo-controlled study to evaluate the efficacy, safety, tolerability, and PK profile of 50 and 300 µg of MEDI0382 in overweight and obese subjects with T2DM. Up to 63 subjects are planned to be enrolled across multiple study sites. The study is divided into 2 cohorts that will be recruited in parallel; for both cohorts, subjects will be consented, screened for suitability, and randomized within 60 days if eligible. A total of 39 subjects will be randomized to Cohort 1, and 24 subjects will be randomized to Cohort 2. Cohort 1 will evaluate the efficacy, safety, tolerability, and PK of MEDI0382 when titrated up in weekly intervals from 50 to 300 µg and administered over 49 days. Cohort 2 will explore an alternative 2-week titration schedule, and will provide additional information on the PK profile and glucose-lowering efficacy of 50 µg MEDI0382 [redacted]. Each dose is administered as an SC injection each morning according to the dosing schedule is presented below:

Figure 2.2-1 Study Flow Diagram





2.3 Treatment Assignment and Blinding

An interactive web response system (IWRS) will be used for randomization to a treatment group and assignment of blinded investigational product kit numbers. A subject is considered randomized when the IWRS provides the assignment of blinded investigational product kit numbers for the subject.

In Cohort 1, subjects will be randomized using a ratio of 2:1 to one of 2 treatment arms to receive either MEDI0382, titrated from 50 µg up to 300 µg according to a fixed schedule, or placebo for 49 days.

In Cohort 2, subjects will be randomized using a ratio of 3:1 to receive either MEDI0382, titrated from 50 µg up to 300 µg according to a different fixed schedule, or placebo for 49 days.

This is a double-blind study in which MEDI0382 and placebo are identically labeled and indistinguishable in appearance so that neither the subject nor any of the investigator or sponsor staff who are involved in the treatment or clinical evaluation of the subjects or data analysis will be aware of the treatment received (ICH E9).

2.4 Sample Size

For Cohort 1, 26 subjects in the MEDI0382 arm and 13 subjects in the placebo arm will provide 97% power to detect 28% glucose AUC change-from-baseline difference between MEDI0382 300 µg and placebo, assuming a standard deviation of 20%. It will also provide 85% power to detect 2.3% difference of percentage change of body weight versus placebo, assuming a standard deviation of 2.2%. From the two cohorts, the combined 44 subjects in

the MEDI0382 arms and 19 subjects in the placebo arms can also provide 80% power to detect 12% glucose AUC change-from-baseline difference between MEDI0382 50 μg and placebo at Day 7.

3 STATISTICAL METHODS

3.1 General Considerations

Data will be presented in data listings sorted by cohort and treatment, subject number and date collected, where appropriate. Tabular summaries will be presented by cohort and treatment group. 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.

The last observation carried forward (LOCF) will be used in efficacy and pharmacodynamics (PD) endpoints analyses unless otherwise specified. Baseline values will be defined as the last valid assessment prior to the first administration of study treatment unless otherwise specified.

All statistical tests will be 2-sided at an alpha = 0.1 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).

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.
As-treated population	Subjects who receive any study investigational product will be included in the as-treated population will be analyzed according to the treatment they received.
PK population	The PK population includes all subjects who received at least one dose of MEDI0382 and had at least one post-baseline MEDI0382 PK sample with a value above the lower limit of quantitation.
PD population	The PD population includes all subjects who received at least one dose of investigational product and had at least one post-baseline PD sample or PD evaluation [redacted]

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 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 follow-up will be provided.

3.3.2 Demographics and Baseline Characteristics

Demographic information and baseline characteristics will be summarized by cohort and by treatment group. Demographic information will include: gender, age (years), ethnicity, race, weight (kg), height (cm), and body mass index (BMI) (kg/m^2). A summary of baseline characteristics may include but not limited to eGFR, HbA1c, glucose, insulin, blood pressure, and pulse rate etc.

BMI= weight (kg) / $[height\ (m)]^2$

All summaries of continuous characteristics will be based on non-missing observations. For categorical characteristics, percentage will be calculated, and the denominator for each percentage is the number of subjects with non-missing data for that demographic or baseline parameter.

No statistical test will be performed for comparison of any baseline measurement among treatment groups.

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 by frequency.

3.3.4 Concomitant Medications

Concomitant medications will be coded using current WHO Drug Dictionary. The number and percentage of subjects who took concomitant medications will be summarized by the highest anatomical therapeutic chemical (ATC) class and preferred term by treatment group for each cohort 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)

The co-primary endpoints for this trial are:

1. Percentage change in plasma glucose $AUC_{0\text{-}4hr}$ as measured by a standardized MMTT from baseline (Day -1) to the end of 49 days of treatment (Day 49)
2. Percentage change in body weight from baseline (Day 1) to the end of 49 days of treatment (Day 50)

3.4.1.2 Primary Efficacy Analysis

The percent change in the MMTT plasma glucose $AUC_{0\text{-}4mmtt}$ from the baseline (Day -1) evaluation to the Day 49 evaluation will be analyzed with an analysis of covariance (ANCOVA) with an effect for treatment (MED0382 or Placebo) and the baseline MMTT glucose $AUC_{0\text{-}4hr}$ value used as a covariate (Cohort 1).

The percent change in body weight from baseline (Day 1) to the Day 50 evaluation will also be analyzed with an ANCOVA with an effect for treatment (MED0382 or Placebo) and the baseline body weight used as a covariate (Cohort 1).

Both comparisons will be performed at the 0.05 significance level (2-sided).

3.4.2 Secondary Efficacy Endpoint(s) and Analyses

3.4.2.1 Secondary Efficacy Endpoint(s)

1. Change in HbA1c from baseline (Day -1) to the end of 49 days of treatment (Day 49) (Cohort 1)
2. Change in fasting plasma glucose (Day -1) from baseline to the end of 49 days of treatment (Day 49) (Cohort 1)
3. Change in body weight (kg) from baseline (Day 1) to the end of 49 days of treatment (Day 50) (Cohort 1)
4. Proportion of subjects achieving > 5% body weight loss from baseline (Day 1) after 49 days of treatment (Day 50) (Cohort 1)
5. Percent change in MMTT plasma glucose $AUC_{0\text{-}4hr}$ from baseline (Day -1) to Day 7 (Cohorts 1 and 2 combined)

3.4.2.2 Secondary Efficacy Analyses

All analyses will be performed at the 0.05 (2-tailed) significance level unless otherwise specified.

The changes from baseline in HbA1c, fasting plasma glucose, and body weight will be analyzed using an ANCOVA with an effect for treatment and the corresponding baseline measure as a covariate. The pre-meal plasma glucose values from the MMTT are used for the fasting plasma glucose values. The proportion of subjects who have a >5% decrease in body weight will be analyzed with logistic regression with treatment effect and the baseline weight as a covariate.

The percent change in MMTT glucose AUC from baseline to Day 7, including data from both cohorts, will be analyzed with an ANCOVA with treatment effect and the baseline value used as a covariate.

3.4.3 Other Efficacy Analyses

For Cohort 2 data, the percent change in the MMTT plasma glucose $AUC_{0\text{-}4hr}$ from the baseline (Day -1) evaluation to the Day 7, Day 14, and Day 49 evaluations will be summarized by visit and analyzed for the end-of-treatment measure at Day 49 only with a similar ANCOVA model as that in the primary analysis.

Similar summary and analysis will be also applied to the change in fasting plasma glucose from baseline (Day -1) to the Day 7, Day 14, and Day 49 evaluations (Cohort 2 only), the change and percent change in body weight from baseline (Day 1) to the Day 8, Day 15, and Day 50 evaluations (Cohort 2 only), and the change in HbA1c from baseline (Day -1) to the Day 49 evaluations.

3.5 Exploratory Pharmacodynamic Endpoint(s) and Analyses

3.5.1.1 Pharmacodynamic Endpoint(s)

- [redacted]
- Change in CGM glucose $AUC_{0\text{-}24h}$ from baseline (Day -1) to the end of each dosing level for titration and treatment (Cohort 1 only)
- Change in coefficient of variation (CV) (ratio of standard deviation: mean) of CGM glucose values over 24 hours from baseline (Day -1) to the end of each dosing level for titration and treatment (Cohort 1 only)
- CV of CGM glucose values over 7 days at each dose level (Days 1 to 7, Days 8 to 14, Days 15 to 21, and Days 22 to 28) (Cohort 1 only)
- Change in percentage of time in hyperglycemia (defined as > 7.8 mmol/l or > 140 mg/dl as measured by CGM) over 24 hours from baseline (Day -1) to the end of each dosing level for titration and treatment periods (Cohort 1 only)
- Change in percentage of time in hypoglycemia (defined as < 3 mmol/l or < 54 mg/dl as measured by CGM) over 24 hours from baseline (Day -1) to the end of each dosing level for titration and treatment periods (Cohort 1 only)

- Percentage of time in hyperglycemia (defined as > 7.8 mmol/l or > 140 mg/dl as measured by CGM) over 7 days at each dose level (Days 1 to 7, Days 8 to 14, Days 15 to 21, and Days 22 to 28) (Cohort 1 only)
- Percentage of time in hypoglycemia (defined as < 3 mmol/l or < 54 mg/dl as measured by CGM) over 7 days at each dose level (Days 1 to 7, Days 8 to 14, Days 15 to 21, and Days 22 to 28) (Cohort 1 only)
- CGM glucose $AUC_{0\text{-}4hr}$ during MMTT (type A) on baseline (Day -1) and Day 49 and during MMTT (type B) on Day 7 (Cohort 1 only)
- CGM glucose $AUC_{0\text{-}2hr}$ during morning MMTT (type A) on baseline (Day -1) and Day 49 (Cohort 1 only)
- CGM glucose $AUC_{0\text{-}2hr}$ during evening MMTT (type C) on baseline (Day -1) and Day 49 (Cohort 1 only)
- The change in insulin $AUC_{0\text{-}4hr}$, glucagon $AUC_{0\text{-}4hr}$, and active and total (the sum of active and inactive GLP-1) GLP-1 $AUC_{0\text{-}4hr}$ from baseline (Day -1) to Day 49 (Cohort 1 and 2)
- The change in pre-meal (i.e., time 0 basal/fasting) values of insulin, glucagon, and active and total (the sum of active and inactive GLP-1) GLP-1 from baseline (Day -1) to Day 49 (Cohort 1 and 2)
  For Cohort 1 only, the fasting plasma insulin value on Day 7 will also be summarized
- The change in fasting C-peptide from baseline (Day -1) to Day 7 and Day 49 (Cohort 1 only)
- The change in serum beta-hydroxybutyrate concentration from baseline (Day -1) to Days 22 and 49 (pre-dose and 4 hr post-dose) (Cohort 1 only)
- The change in capillary blood ketone concentration from baseline (Day -1) to Days 22 and 49 (pre-dose and 4 hr post-dose) (Cohort 1 only)
- The change in free fatty acids from baseline (Day -1) to Day 49 (Cohort 1 only)
- The change in fasting amino acids from baseline (Day -1) to Day 49 (Cohort 1 only)
- The change in uric acid from baseline (Day -1) to Day 49 (Cohort 1 only)
- [redacted]

3.5.1.2 Analysis of Pharmacodynamic Endpoint(s)

All of the PD measures will be summarized by scheduled visits. Except for the analyses specified in the following of this section, all of the other PD endpoints will be analyzed for the end-of-treatment measure only using similar ANCOVA model as that in the primary analysis. Treatment effect and baseline value (if available) will be added in the model.

[redacted]

The CV of CGM glucose values over 7 days at each dose level will be analyzed with a 2-sample t-test (assuming equal variance).

The change in percentage of time in hyperglycemia and hypoglycemia over 24 hours from baseline (Day -1) to Day 49 will be analyzed with the Wilcoxon rank sum test.

The percentage of time in hyperglycemia and hypoglycemia over 7 days at each dose level will be analyzed with the Wilcoxon rank sum test.

The morning (type A) and evening (type C) MMTT CGM glucose $AUC_{0\text{-}2hr}$ on baseline (Day -1) and Day 49, will be summarized. Their difference and agreement will be analyzed by the paired t-test and the concordance correlation coefficient, respectively. The CGM glucose $AUC_{0\text{-}4hr}$ during MMTT on baseline (Day -1), Day 7, and Day 49, and the corresponding plasma glucose $AUC_{0\text{-}4hr}$ will be summarized and analyzed in a similar manner.

3.6 Safety Analyses

The analyses will be based on the As-treated population. All safety summaries will be presented by treatment group for each cohort, unless otherwise specified.

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 summarized by MedDRA System Organ Class (SOC) and Preferred Term (PT) by treatment group for each cohort as well as for overall treatments. The AEs summaries will include only treatment-emergent AEs, i.e., 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 (SAEs) will be presented in the listings.

The number and percentage of subjects with nausea, vomiting, and either nausea or vomiting will be summarized daily for first 7 days of treatment. For MEDI0382 only, the above three endpoints over the first 7 days for two cohorts combined will be summarized. In addition, two-sided 80% confidence intervals of the percentages will also be reported using exact method.

3.6.2 Adverse Events of Special Interest

Hepatic function abnormality meeting the definition of Hy's law is considered an adverse events of special interest. Number and proportion of subjects who meet Hy's law criteria: AST or ALT ≥ 3 × ULN together with total bilirubin ≥ 2 × ULN will be summarized by treatment and cohort.

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 and cohort. The summary includes overall, categorized by MedDRA system organ class, and preferred term.

3.6.4 Clinical Laboratory Evaluations

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 treatment group at each of the time points specified in Treatment and Follow-up Period Study Procedures in the protocol. The urinalysis results will be listed. 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 treatment group at each of specified time points.

3.6.5 Vital Signs

Vital signs including pulse rate (beats/min), systolic and diastolic blood pressure (mmHg), temperature (ºC), weight (kg), and respiratory rate (breaths/min), as well as the change from baseline for each of those parameters will be descriptively summarized by treatment group at each of the specified time points in the protocol.

The 24-hour average ambulatory blood pressure monitoring (ABPM) pulse rate (beats/min) and systolic and diastolic blood pressure (mm Hg) from the ABPM will be summarized by treatment group at each visit (Days -2, 22, 29, 36, 43, and 49) performed. The change from baseline (Day -2) for the 24-hour average pulse rate and systolic and diastolic blood pressure at each post-baseline visit will be analyzed with an ANCOVA with an effect for treatment and the baseline value as the covariate. The above summary and analyses will also be conducted for PR, SBP and DBP during asleep and awake periods.

3.6.6 Electrocardiogram

Electrocardiogram parameters will be assessed using standard 12-lead electrocardiography. The following 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. A listing of subjects will be produced which will display all ECG findings in subjects with abnormal ECGs.

3.7 Immunogenicity

All subjects in the safety analysis set with reported anti-drug antibody (ADA) results (ADA positive or ADA negative, titer, cross-reactivity to GLP1 (positive or negative), cross-reactivity to glucagon (positive or negative) will be shown in the data listing.

ADA status (positive vs. negative) will be summarized by treatment group according to the following categories:

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)

Subjects who are persistently positive; persistently positive is defined as at least 2 post-baseline ADA positive measurements (with >=16 weeks apart) or an ADA positive result at the last available assessment

Proportion of subjects who are transiently positive; transiently positive is defined as at least one post-baseline ADA positive measurement and not fulfilling the conditions for persistently positive.

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

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

The association of ADA status with PK, PD endpoints, efficacy, and safety may be evaluated if data allows and if applicable.

3.8 Pharmacokinetics

The analysis of the PK data is described below. 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.

For subjects in each active treatment group the following pharmacokinetic parameters will be determined from the plasma concentration-time data for MEDI0382 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. 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. $C\tau$: trough concentrations from the plasma concentration-time data at the end of the dosing interval (i.e. 24 hours).
4. t half: 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
5. AUCτ: Area under the plasma concentration time curve at the end of the dosage interval τ.
6. Ro: observed accumulation ratio will be calculated using both the AUC and Ctrough methods, where data allows, as follows: Ro = AUCτdayi/AUCτday1 and Ro = Cτdayi/Cτday1.

All the derived parameters described above will be listed. For each of these parameters, except 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} median, maximum, minimum, arithmetic mean.

Individual Ctrough will be listed by cohort, treatment and day and will be summarized as maximum, minimum, arithmetic mean and geometric mean.

4 INTERIM ANALYSIS

The analysis of the PK data will be conducted after the last subject has completed his/her last dose and all pharmacokinetic samples have been collected. The PK scientist will be unblinded and create descriptive summaries of the PK data, and once being unblinded the PK scientist will not be involved in the day-to-day study work until the final data base lock.

5 VERSION HISTORY

Version	Date	Summary of Changes	Reason for Change
1.0	08Sep2017	Initial document	Initial document