Statistical Analysis Plan	
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A Phase IIa, Randomised, Parallel, Double-Blind, Placebo-Controlled Study to Evaluate the Safety, Efficacy, and Pharmacokinetics of MEDI0382 in Japanese Preobese or Obese Subjects with Type 2 Diabetes Who Have Inadequate Glycemic Control with Diet and Exercise

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[redacted]

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

Abbreviation or special term	Explanation
ADA	antidrug antibody
AE	adverse event
ABPM	ambulatory blood pressure monitoring
ALP	alkaline phosphatise
ALT	alanine transaminase
ANCOVA	analysis of covariate
AST	aspartate transaminase
AUC	area under the curve
AZ	AstraZeneca
BMI	body mass index
BP	blood pressure
CGM	continuous glucose monitoring
CI	confidence interval
CRF	case report form
CSR	clinical study report
C_{trough}	trough plasma concentration
DAE	adverse events leading to discontinuation of study drug
DBP	diastolic blood pressure
ECG	electrocardiogram
eCRF	electronic case report form
eGFR	estimated glomerular filtration rate
FAS	full analysis set
FWER	family wise error rate
FPG	fasting plasma glucose
GCP	Good Clinical Practice
GI	gastrointestinal
GLP-1	glucagon-like peptide-1
HbA1c	glycated hemoglobin
HOMA	Homeostatic Model Assessment
HR	heart rate
ICF	informed consent form
ICH	International Conference on Harmonisation
IP	investigational product

Abbreviation or special term	Explanation
LSMean	least squares mean
MedDRA	Medical Dictionary for Regulatory Activities
MMT	mixed-meal test
PD	Pharmacodynamics
PK	Pharmacokinetics
PT	preferred term
QTcF	QT interval corrected for heart rate using Fridericia's formula
SAE	serious adverse event
SAP	statistical analysis plan
SBP	systolic blood pressure
SC	subcutaneous
SOC	system organ class
TBL	total bilirubin
$t_{1/2}$	terminal half-life
T2DM	Type 2 diabetes mellitus
ULN	upper limit of normal
Q1	1st quartile (25 percentile)
Q3	3rd quartile (75 percentile)

AMENDMENT HISTORY

Date	Brief description of change
	N/A
19-Dec-2018	Update to reflect change for protocol • Change of secondary variable Glycoalbumin to Fructosamine • Correction of CGM interval for alignment • Change of baseline definition to appropriately reflect the planned study schedule • Added derivation for HOMA-beta and HOMA-R

1 STUDY DETAILS

1.1 Study objectives

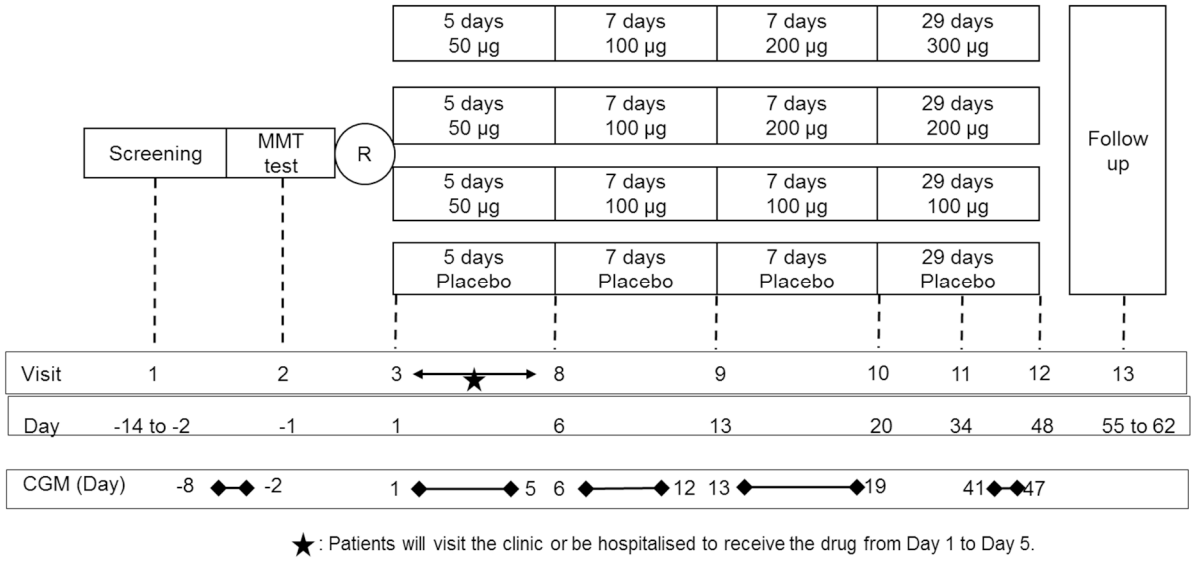
Objectives and Endpoints

Primary objective:	Endpoint/variable:
To characterise the safety profile and tolerability of MEDI0382 titrated up to a dose level of 100, 200 or 300 µg during dosing and follow-up	Measures of safety and tolerability (24-hour heart rate and blood pressure, other vital signs, electrocardiogram [ECG], laboratory test results, and adverse event [AE]s)
To assess the effects of MEDI0382 titrated up to a dose level of 100, 200 and 300 µg on glucose control and body weight versus placebo after 48-day treatment	• Percentage change in glucose area under the curve (AUC) $_{0\text{-}4h}$ as measured by a standardised MMT from baseline to the end of 48-day treatment • Percentage change in body weight from baseline to the end of 48-day treatment
Secondary objective:	**Endpoint/variable:**
To assess the effects of MEDI0382 titrated up to a dose level of 100, 200 or 300 µg on additional measures of glucose control versus placebo after 48-day treatment	• Change in glycated hemoglobin (HbA1c) from baseline to the end of 48-day treatment • Change in fasting plasma glucose from baseline to the end of 48-day treatment • Change in fructosamine from baseline to the end of 48-day treatment
To assess the effect of MEDI0382 on glucose lowering during different meals and times of the day as measured by continuous glucose monitoring (CGM)	• Change in percentage of time in hyperglycaemia (defined as > 7.8 mmol/L or > 140 mg/dL) and hypoglycaemia (defined as < 3 mmol/L or < 54 mg/dL) from the last day of baseline CGM over 24 hours to the end of dosing at each dose level (Days 5, 12, 19, and 47) • Change in percentage of time in hyperglycaemia and hypoglycaemia at each dose level over 5 days for 50 µg and 7 days for other dose levels (Days 1 to 5, Days 6 to 12, Days 13 to 19, and Days 41 to 47)
To characterise the PK profile of 50, 100, 200 and 300 µg of MEDI0382	PK endpoints: Trough plasma concentration (C_{trough})
To characterise immunogenicity of 100, 200 and 300 µg of MEDI0382	Development of anti-drug antibodies and titre (if confirmed positive)
Exploratory Objective:	**Endpoint/variable:**
To assess the effect of MEDI0382 on pancreatic and incretin hormone profiles at baseline and during the MMT	• Change in insulin, GLP-1, and glucagon (AUC and levels) from baseline after 48-day treatment. • Change in pro-insulin, c-peptide levels, pro-insulin/c-peptide ratio from baseline after 48-day treatment.
To assess the effects of MEDI0382 in insulin resistance and beta cell function.	• Change in percentage of Homeostatic model assessments (HOMA)-Beta and HOMA-R from baseline after 48-day treatment.

1.2 Study design

This is a randomized, parallel-group, placebo-controlled, double-blind, multicenter Phase IIa study to evaluate the safety, efficacy, and pharmacokinetics of MEDI0382 in Japanese preobese and obese subjects with type 2 diabetes who have inadequate glycemic control with diet and exercise. Subject fulfilling all of the inclusion criteria and none of the exclusion criteria will be randomised in a 1:1:1:1 ratio to four treatment arms (MEDI0382 100ug, 200ug, 300ug or Placebo). MEDI0382 dose will be up-titrated from 50ug to the randomized target dose of MEDI0382 100ug, 200ug or 300ug, respectively, as shown in Figure 1.

Figure 1 Study Diagram



1.3 Number of subjects

Approximately 60 patients are to be randomized to Placebo, MEDI0382 100 µg, MEDI0382 200 µg, and MEDI0382 300 µg in a ratio 1:1:1:1.

Anticipating approximately 10% drop out during the 48-day treatment period, approximately 13 subjects are expected to be evaluable per treatment group.

Assuming standard deviation of percent change in MMT glucose $AUC_{(0\text{-}4h)}$ for 20%, approximately 13 patients per arm would provide more than 80% power to detect 23% difference in percent change of MMT glucose $AUC_{(0\text{-}4h)}$ for pairwise comparison between each of MEDI0382 dose group and Placebo each at two-sided alpha = 0.05, without formal multiplicity adjustment.

Assuming standard deviation of percent change from baseline in body weight for 2.5%, the same number of subjects would provide approximately 68% power to detect mean difference of 2.5% at two-sided alpha =0.05.

2 ANALYSIS SETS

2.1 Definition of analysis sets

2.1.1 Enrolled (All patients)

All patients who signed the ICF.

2.1.2 Randomized Set (All randomized patients)

All subjects who received randomization number.

2.1.3 Full Analysis Set

The full analysis set (FAS) for the efficacy evaluation will be the primary analysis set and will include all randomized subjects who received at least one dose of Investigational Product (IP), and will be analysed according to their randomised treatment group.

2.1.4 Safety analysis set

The Safety analysis set, which includes all subjects receiving at least one dose of any study IP, will be analysed according to the treatment they actually received.

2.1.5 PK analysis set

The PK analysis set includes all subjects who received at least one dose of MEDI0382 and had at least one post-baseline MEDI0382 PK sample taken that is above the lower limit of quantification.

2.2 Violations and deviations

Protocol deviations will be identified programmatically or manually and reviewed in a blinded fashion and documented prior to the un-blinding the study.

Important protocol deviations would include but not limited to:

- Patients who were randomised but did not meet inclusion and exclusion criteria
- Patients who developed withdrawal from study criteria but were not withdrawn
- Patients who received incorrect treatment or dose
- Patients who were randomised but took no study medication
- Patients who received prohibited concomitant medication

3 PRIMARY AND SECONDARY VARIABLES

3.1 Primary Efficacy Variables

Primary efficacy variables are

- Percentage change in glucose area under the curve (AUC) $_{0\text{-}4h}$ as measured by a standardised MMT from baseline to the end of 48-day treatment
- Percentage change in body weight from baseline to the end of 48-day treatment

3.2 Secondary Efficacy Variables

Following secondary efficacy variables will be evaluated :

- Change in glycated hemoglobin (HbA1c) from baseline to the end of 48-day treatment
- Change in fasting plasma glucose from baseline to the end of 48-day treatment
- Change in fructosamine from baseline to the end of 48-day treatment
- Change in percentage of time in hyperglycaemia (defined as > 7.8 mmol/L or > 140 mg/dL) and hypoglycaemia (defined as < 3 mmol/L or < 54 mg/dL) from the last day of baseline CGM over 24 hours to the end of dosing at each dose level (Days 5, 12, 19, and 47)
- Change in percentage of time in hyperglycaemia and hypoglycaemia at each dose level over 5 days for 50 µg and 7 days for other dose levels (Days 1 to 5, Days 6 to 12, Days 13 to 19, and Days 41 to 47)

3.2.1 PK/ADA

- PK : Trough plasma concentration (C_{trough})
- ADA : Development of anti-drug antibodies and titre (if confirmed positive)

3.3 Exploratory Variables

- Change in insulin, GLP-1, and glucagon (AUC and levels) from baseline after 48-day treatment.
- Change in pro-insulin, c-peptide levels, pro-insulin/c-peptide ratio from baseline after 48-day treatment.
- Change in percentage of Homeostatic model assessments (HOMA)-Beta and HOMA-R from baseline after 48-day treatment

3.4 Safety Variables (Primary)

Safety evaluation will be done with the following variables.

- Adverse Events (including SAEs)
- 24-hour ABPM (Heart Rate and Systolic/Diastolic Blood Pressure)
- Other Vital Signs
- Electrocardiogram [ECG]
- Safety Laboratory parameters

4 ANALYSIS METHODS

4.1 General principles

The SAS® software, version 9.2 or higher, will be used in order to generate all the statistical outputs.

Unless otherwise specified, all efficacy analyses will be carried out on the FAS and all safety analyses will be based on the Safety analysis set. Efficacy summary results during the treatment phase will be presented based on randomized treatment group (MEDI0382 100ug, MEDI0382 200ug, MEDI0382 300ug and Placebo). Safety summary results will be presented based on treatment they actually received. For Safety analysis, patients who discontinued before reaching target dose would be included in their randomized treatment group. Patients who wrongly took higher dose of MEDI0382 than randomized target dose will be analysed according to the highest dose of study medication received.

4.1.1 Objectives and hypotheses

The one of primary objectives of this study is to characterize the safety profile of MEDI0382 100ug ,200ug and 300ug up-titration regimens compared with Placebo, measured by the Adverse Events (including SAEs), 24-hr ABPM heart rate and blood pressures, other vital sings, safety laboratory tests, and ECGs. The safety evaluation will be conducted through descriptive manner and no statistical testing will be performed for safety analysis.

The other primary objective is to assess the efficacy of MEDI0382 doses, as measured by percent change from baseline in MMT glucose $AUC_{(0\text{-}4h)}$ to Day 48 and by percent change in body weight from baseline to Day 48. Statistical hypotheses testing will be conducted by pair-wise comparisons between MEDI0382 each dose group vs. Placebo each at two-sided alpha of 0.05. Strong control of Family Wise Error Rate (FWER) will not be pursuit.

4.1.2 Definitions

4.1.2.1 Last Observation Carried Forward (LOCF)

In the analysis of change (or percent change) from baseline, as well as response endpoint at Day *t* LOCF, the Day *t* measurement will be used. If no Day *t* measurement is available (subject has discontinued before Day *t,* or the subject has not discontinued, but the measurement was not taken at Day *t*), the last post-baseline measurement prior to Day t will be used. Unless specified otherwise, all data, regardless of rescue medication, will be used for the calculation of LOCF values.

4.1.2.2 Mixed Meal Test glucose $AUC_{(0\text{-}4h)}$

MMT will be conducted at baseline (Day -1) and Day 48. Following a minimum 8-hour fast, blood samples for the tests indicated will be taken 15 minutes before the subject drinking 1 entire can of Ensure H as a standardised meal. After consumption of the standardised meal, blood samples will additionally be taken at 15, 30, 45, 60, 90, 120, 180, and 240 minutes for glucose and insulin; 15, 45, 90, 180, and 240 minutes (± 5 min) for pro-insulin, c-peptide, GLP-1 and glucagon.

MMT glucose $AUC_{(0\text{-}4h)}$ will be derived by the trapezoidal method.

$$\sum_{i=1}^{n}\left(\frac{\left(M_i + M_{i+1}\right)}{2}\cdot\left(T_{i+1} - T_i\right)\right)$$

Where M_i is the glucose test at time T_i and M_{i+1} is the subsequent non-missing glucose measured at time T_{i+1}. T_1 and T_n are the time of the first (0 min) and last (240 min) glucose measurement. $AUC_{(0\text{-}4h)}$ for other parameters will be derived in a similar manner.

4.1.2.3 Percentage of time in certain glucose range as measured by CGM

Percent of CGM readings falling within a range over a 24-hour period will be calculated as the number of readings during a 24-hour period within the corresponding range divided by the total number of available readings during the same 24-hour period.

4.1.2.4 Homeostatic model assessments (HOMA)-Beta and HOMA-R

Beta cell function (HOMA beta) and insulin sensitivity (HOMA-IR, Matsuda index) will be derived by Glucose (in mg/dL) and insulin (in mU/L) taken during MMT.

- Beta cell function: HOMA-beta (%) (based on fasting glucose and insulin from MMT data for each visit)

$$\text{HOMA-}\beta[\%] = \frac{360 \times \text{Insulin[mU/L]}}{\text{Glucose[mg/dL]} - 63}$$

- Insulin sensitivity: HOMA-IR (%) (based on fasting glucose and insulin from MMT data for each visit)

$$\text{HOMA-IR}[\%] = \frac{\text{Glucose[mg/dL]} \times \text{Insulin[mU/L]}}{405}$$

- Insulin sensitivity: Matsuda Index (no unit) (based on glucose and insulin from MMT data at 0, 30, 60, 90, and 120 minutes for each visit)

$$\frac{10000}{\sqrt{g_0 \times i_0 \times \frac{(g_0 \cdot 15 + g_{30} \cdot 30 + g_{60} \cdot 30 + g_{90} \cdot 30 + g_{120} \cdot 15)}{120} \times \frac{(i_0 \cdot 15 + i_{30} \cdot 30 + i_{60} \cdot 30 + i_{90} \cdot 30 + i_{120} \cdot 15)}{120}}}$$

Here, g_t indicates glucose [mg/dL] value at time *t* [min] and i_t indicates insulin[mU/L] value at time *t* [min] during MMT.

4.1.2.5 Use Rescue Medication

Start date of rescue medication is defined as the earliest of the dates of first insulin or injectable or oral antidiabetic drugs initiated as rescue medication. Treatment intensification starting on the first or last day of study medication will not be defined as rescue medication.

4.1.2.6 Analysis of covariance model (ANCOVA)

In summaries of efficacy endpoints examining changes from baseline at Day t or Day t LOCF, ANCOVA of the differences between post-baseline and baseline measurements will be performed, with treatment group as a factor and the baseline measurement as a covariate. The following ANCOVA model will be used:

$D_{t,ij}$ = intercept + β [$Y_{0,ij}$] + τ_i + $error_{ij}$

where

- $D_{t,ij} = Y_{t,ijk} - Y_{0,ijk}$ = the Week *t* or Week *t* LOCF (percent) change from baseline of subject *j* in treatment group *i*),
- $Y_{0,ijk}$ is the baseline measurement of subject *j* in treatment group *i*,
- $Y_{t,ijk}$ is the Week *t* or Week *t* LOCF measurement of subject *j* in treatment group *i*,
- β is the slope of $D_{t,ij}$ regressing on the baseline measurement and,
- τ_i is the mean effect of treatment group *i*.
- *Intercept*, β and τ_i are unknown parameters to be estimated from the data.

The model will provide least squares mean estimates and 2-sided 95% confidence intervals (CIs) for mean changes from baseline within and (when warranted) differences in mean change from baseline between treatments.

4.2 Analysis methods

4.2.1 Study Population

4.2.1.1 Subject disposition

Subject disposition will be described including information on number and percentage of subjects enrolled, randomized, not randomized, reason for not randomized, started treatment,

not started treatment, reason for not started treatment, completed treatment, not completed treatment, reason for not completed treatment, completed study, not completed study and reason for not completed the study. This summary will include all enrolled subjects, i.e. all subjects who signed informed consent, and be done by randomized treatment group and in total.

4.2.1.2 Important protocol deviations

Patients with important protocol deviations will be summarized by treatment and in total using all randomized patients. Important protocol deviations will be collected as described in section 2.2.

4.2.1.3 Demographic and other subject characteristics

Demographic and other subject characteristics, including diabetes-related characteristics will be summarized by treatment and in total using the FAS.

All summaries of continuous characteristics will be based on non-missing observations. For categorical characteristics, percentages should be calculated based on the number of patients in the analysis set (i.e., each denominator includes the number of subjects with missing/unknown values for the characteristic).

Age will be calculated as (date of informed consent – birth date + 1)/365.25.

The duration of type 2 diabetes will be calculated as (date of informed consent - date of Diabetes Mellitus Type II First Diagnosed + 1)/365.25. If the birth date, or the date of type II DM diagnosis is partially missing, the following rules will be implemented:

- If year is missing: No imputation will occur to neither year, month or day.
- If month and day is missing: -06-30 will be imputed.
- If day is missing: -15 will be imputed

Table 1 Demographic Characteristics

Characteristic	Summarized as	Categories
Gender	Categorical	Male Female
Age (years)	Categorical and continuous	< 50 ≥ 50 and <65 ≥ 65 and <75 ≥ 75

Table 1 Demographic Characteristics

Characteristic	Summarized as	Categories
Race	Categorical	White Black or African American Asian Native Hawaiian or Other Pacific Islander American Indian or Alaska Native Other
Region	Categorical	Asia/Pacific Europe North America South America
Country	Categorical	Japan
Ethnicity	Categorical	Hispanic/Latino Non Hispanic/Latino

Table 2 Patient Characteristics

Characteristic	Summarized as	Categories
Height (cm)	Continuous	
Body Weight (kg)	Continuous	
Body Mass Index (kg/m^2)	Categorical and continuous	< 25 ≥ 25 and <30 ≥ 30 and <35 ≥ 35 and <40 ≥ 40

Table 3 Diabetes-Related Characteristics

Characteristic	Summarized as	Categories
Duration of Type 2 Diabetes (years)	Categorical and continuous	< 3 ≥ 3 and < 10 ≥ 10
Baseline HbA1c (%)	Categorical and continuous	< 8.0 ≥ 8.0 and < 9.0 ≥ 9.0
Baseline fasting plasma glucose (mg/dl)	Continuous	
Baseline fasting c-peptide (ng/ml)	Continuous	
Baseline Systolic and Diastolic BP, pulse (mmHg)	Continuous	

Table 3 Diabetes-Related Characteristics

Characteristic	Summarized as	Categories
eGFR (mL/min/1.73m2)*	Categorical and continuous	< 20 ≥ 20 and <30 ≥ 30 and <60 ≥ 60 and <90 ≥ 90

*eGFR is derive based on formula provided by JSN (Japan Society of Nephrology).

$$\mathrm{eGFR[mL/min/1.73m^2]} = 194 \times \mathrm{SCr[mg/\,dL]}^{-1.094} \times \mathrm{Age[years]}^{-0.287} \left(\times 0.739 \,\text{for female}\right)$$

4.2.1.4 Medical and surgical history

The number and percentage of subjects with medical and surgical history findings will be summarized per SOC/PT by treatment and in total using the FAS. In addition, specific DM complications will be summarized.

Table 4 DM Complications

Characteristic	Summarized as	Categories
Diabetes Mellitus Complications	Categorical	Retinopathy Neuropathy Autonomic Neuropathy Peripheral Nephropathy Angiopathy Other

4.2.1.5 Pre-study, concomitant, and post-study treatment(s)

The number and percentage of subjects with the following will be summarized according to ATC code and generic name, by treatment and in total using FAS:

- Medication used prior to study treatment
- Concomitant medication

Concomitant medications is defined as medications taken on or at least one day after the study drug start date and before or on the last day on study drug.

4.2.1.6 Measurements of treatment compliance

For each subject receiving at least one dose of study treatment percent compliance will be calculated as: 100 x number of injections/(day of last dose in study period – day of first dose + 1). Treatment compliance will be described using Q1, Median and Q3 by treatment and in

total using the FAS. Number and percent of subjects with compliance <80%, ≥80% will be summarized.

4.2.2 Efficacy

Efficacy analyses will be carried out for FAS.

4.2.2.1 Primary Efficacy Variables

Percent Change from baseline in MMT glucose $AUC_{(0-4h)}$

MMT will be conducted at baseline (Day -1) and Day 48.

Percent change from baseline in MMT Glucose $AUC_{(0-4h)}$ to Day 48 will be analysed with ANCOVA model with treatment group as a factor and baseline as a covariate. Least squares mean (LSMean)s and their 95%CIs for percent changes from baseline for each treatment group, as well as difference in LSMeans, 95%CI and nominal p-values will be provided for pair-wise comparison of each MEDI0382 dose vs. Placebo group.

Due to lack of intermediate visit assessment, it is assumed patients will have at most one post-baseline MMT assessment regardless of their completion of discontinuation of study drug. Primary analysis will include all on-treatment assessment regardless of rescue.

Percent change from baseline in body weight

Body weight will be collected at selected visits.

Percent change from baseline in body weight to Day 48 will be analysed with ANCOVA model with treatment group as a factor and baseline as a covariate. LSMeans and their 95%CIs for percent changes from baseline for each treatment group, as well as difference in LSMeans, 95%CI and nominal p-values will be provided for pair-wise comparison of each MEDI0382 dose vs. Placebo group. For subjects who prematurely discontinued study drug, the last on-treatment measurement regardless of rescue will be used for this analysis (LOCF).

The similar analyses will be also conducted by each post-baseline visit, without LOCF. Absolute change from baseline in body weight to Day 48 will be also analysed in the same way.

4.2.2.2 Analysis of Secondary Efficacy variables

Change in glycated hemoglobin (HbA1c) from baseline to the end of 48-day treatment

HbA1c will be measured at baseline and Day 48.

Change from baseline in HbA1c to Day 48 will be analysed with ANCOVA model with treatment group as a factor and baseline as a covariate. LSMeans and their 95%CIs for

changes from baseline for each treatment group, as well as difference in LSMeans, 95%CI and nominal p-values will be provided for pair-wise comparison of each MEDI0382 dose vs. Placebo group.

Due to lack of intermediate visit assessment, it is assumed patients will have at most one post-baseline HbA1c assessment regardless of completion or discontinuation of study drug. All available on-treatment measurement regardless of rescue will be included in the analyses.

Change in fasting plasma glucose (FPG) from baseline to the end of 48-day treatment

FPG will be measured at baseline and Day 48.

Change from baseline in FPG to Day 48 will be analysed with ANCOVA model with treatment group as a factor and baseline as a covariate. LSMeans and their 95%CIs for changes from baseline for each treatment group, as well as difference in LSMeans, 95%CI and nominal p-values will be provided for pair-wise comparison of each MEDI0382 dose vs. Placebo group.

Due to lack of intermediate visit assessment, it is assumed patients will have at most one post-baseline FPG assessment. All available on-treatment measurement regardless of rescue will be included in the analyses.

Change in fructosamine from baseline to the end of 48-day treatment

Fructosamine will be measured at baseline and Day 20 and 48.

Change from baseline in fructosamine to Day 48 will be analysed with ANCOVA model with treatment group as a factor and baseline as a covariate. LSMeans and their 95%CIs for percent changes from baseline for each treatment group, as well as difference in LSMeans, 95%CI and nominal p-values will be provided for pair-wise comparison of each MEDI0382 dose vs. Placebo group. For subjects who prematurely discontinued study drug, the last on-treatment measurement regardless of rescue will be used for this analysis.

The similar analyses will be also conducted by each post-baseline visit, without LOCF.

Change from baseline in continuous glucose monitoring (CGM) parameters

A CGM sensor will be inserted subcutaneously on protocol specified study days to allow the collection of information on subject's interstitial glucose level over specified intervals: From Day -8 ~ -2, Day 1~5, Day 6~12, Day 13~19 and Day 41~47. The system records data approximately every 15 minutes. The data will remain blinded to the subject and to the investigators during the recording and will be downloaded into a data file.

All analysis endpoints will be based on the 24-hour readings for every subject. The 24-hour period is defined based on the first available time point with a valid CGM glucose reading. The last 24-hour readings within each dose intervals will be the last 24-hour intervals within that dosing intervals.

Descriptive summary at baseline and each post-baseline visit (the last day or all intervals) as changes from baseline for percentage of time in hyperglycemia/hypoglycaemia will be provided by treatment group.

Descriptive summary for 24-hour average glucose readings will be also summarized for the last day of each dosing intervals as well as average over each dosing interval.

The glucose reading over 24-hour during baseline (average over Day -8 to Day -2) and during last dosing interval (average over Day 41-47) will be plotted for each treatment group .

Coefficient of Variation(CV) of glucose readings over each dose intervals will also be summarized with descriptive statistics and will be plotted.

Pharmacokinetics/ADA

The plasma concentrations/ADA will be summarized descriptively at each time point for the MEDI0382 treatment groups excluding values after IP discontinuation. Additional pharmacokinetic analyses and/or modelling may be conducted separately, outside of this SAP.

4.2.2.3 Analyses of exploratory efficacy variables

Change in insulin, GLP-1 and glucagon from baseline after 48-day treatment

Change in fasting measurement from baseline (Day -1) and percent change in 4-hour AUC from baseline will be compared between MEDI0382 and placebo as measured by a standardised MMT from baseline to the end of 48-day treatment. The above parameters will be analysed by ANCOVA model including respective baseline as a covariate and treatment as a factor. The last on-treatment measurements regardless of rescue use will be included in response variable.

Change in pro-insulin, c-peptide levels, pro-insulin/c-peptide ratio from baseline after 48-day treatment

Change in fasting measurement from baseline and percent change in 4-hour AUC (except for pro-insulin/c-peptide ratio) from baseline will be compared between MEDI0382 and placebo as measured by a standardised MMT from baseline to the end of 48-day. The above parameters will be analysed by ANCOVA model including respective baseline as a covariate and treatment as a factor. The last on-treatment measurements regardless of rescue use will be included in response variable.

Change in percentage of Homeostatic model assessments (HOMA)-Beta and HOMA-R from baseline after 48-day treatment

Beta cell function will be derived using the HOMA calculation from fasting glucose and insulin data, and insulin sensitivity will be derived from MMT data using the HOMA-IR algorithm and the modified Matsuda index calculation (4.1.2.4).

The above parameters will be analysed by ANCOVA model including respective baseline as a covariate and treatment as a factor. The last on-treatment measurements regardless of rescue use will be included in response variable.

4.2.2.4 Other supplemental tables

- Number and percentage of subjects on rescue medication will be presented by treatment group.
- For all efficacy parameters, descriptive summary at each visit and changes from base will be provided by treatment group.

4.2.3 Safety

Unless otherwise specified, all safety analysis will be performed for the safety set and the safety data will be presented using descriptive statistics and no statistical test will be performed.

4.2.3.1 Extent of exposure

The duration of exposure, day of last dose – day of first dose + 1, will be summarized using descriptive statistics by treatment and in total using FAS. Also, the cumulative duration of exposure will be given for ≥1, ≥5, ≥12, ≥19, and ≥48 days and illustrated with a cumulative distribution plot. In addition, the duration of exposure in terms of total patient-years will be calculated by treatment.

A listing of patients experience at least one overdose will be provided.

4.2.3.2 Adverse events

Adverse Events (AEs) will be classified by Primary System Organ Class (SOC) and Preferred Term (PT) according to the Medical Dictionary for Regulatory Activities (MedDRA) version at the time of database lock for each study.

Each AE will be assigned to one or more of the following periods;

- Run-in period: Time prior to randomization date.
- Baseline period: Time from randomization date until the day prior to first dose date.
- On treatment period: Time from first dose date of IP until 3 days after last dose of IP.

- Follow up period: Time from last IP dose + more than 3 days .

AEs will be assigned to the period where they started. For AEs assigned to the on treatment period, the number of subject included in safety set and with any of the following will be tabulated:

- AEs per category (Any AE, Any AE with outcome of death, Any SAE, Any AE leading to discontinuation (DAE))
- AEs per SOC and PT
- AEs by PT, most common with frequency of at least 2 subjects
- AEs by PT and maximum reported intensity
- AEs by PT and causality as judged by investigator
- AEs with outcome of death by SOC and PT
- SAEs by SOC and PT
- AEs leading to discontinuation of IP by SOC and PT

In summaries by SOC and PT, AEs will be sorted by decreasing frequency within each SOC and PT according to the highest MEDI0382 dose group. In summaries by PT, AEs will be sorted by decreasing frequency within PT according to the highest MEDI0382 dose group.

For AEs assigned to the on treatment period key subject information for patients included in safety set will be presented for:

- Adverse events with outcome of death
- SAEs
- Adverse events leading to discontinuation of IP

Following listings of AEs will be produced:

- Listing of SAEs during the run-in period (All patients)
- Listing of AEs during of the baseline period (All randomised patients)
- Listing of AEs during on treatment period (safety set)
- Listing of AEs during the follow up period (safety set)

Narratives will be generated for all deaths, DAEs and SAEs.

4.2.3.3 Nausea and vomiting

The number and percent of patients and the event rate with nausea and vomiting per person-days will be summarized by treatment. The event rate per person-days over each dosing intervals will be tabulated and plotted.

4.2.4 Clinical Safety Laboratory Values

Laboratory values reported at each scheduled visit and the change from baseline will be summarized by treatment using descriptive statistics.

Number and percent of subjects with baseline laboratory value within the reference limit but with any post-baseline value outside the reference limit will be summarized per treatment.

Number and percent of subjects with liver enzyme abnormalities (including potential Hy's Law criteria) will be produced by treatment.

Shift table of the eGFR from baseline to post-baseline will be created. Classification is as follows : renal function groups ≥ 90, ≥ 60 to <90, ≥ 30 to < 60, and < 30 mL/min/1.73 m2.

4.2.5 Electrocardiograms

Electrocardiogram(ECG) per visit and change from baseline will be summarized by treatment at each scheduled visit using descriptive statistics. This will include heart rate (HR), PR, QRS, QT and QTcF.

Here QTcF will be derived by below formula.

$$QTcF = \frac{QT}{(60 / \mathrm{HR})^{1/3}}$$

where, QT is in msec and HR is in bpm.

A shift table for ECG in categories of Normal and Abnormal will be summarized by treatment from baseline to post baseline.

Abnormal prolongation of QTcF will be summarized based on criteria specified in the table below. The most extreme (highest) value for a subject during on-treatment will be used in this summary.

Table 5 Categorical evaluation of QT prolongation

Parameter	Criterion
QTcF	>450 msec >480 msec >500 msec

Table 5 Categorical evaluation of QT prolongation

Parameter	Criterion
Change from baseline in QTcF	>30 msec >60 msec

4.2.6 24-hr ABPM

Value at visit and change from baseline in 24-hour ABPM (Heart Rate, SBP and DBP) will be summarized by treatment group. The similar summary for Daytime average and Nighttime average will also be provided by treatment.

4.2.7 Vital Signs (other than 24hr ABPM)

Vital sign measurements at each visit and change from baseline will be summarized by treatment at each scheduled visit using descriptive statistics.

4.2.8 Pregnancy Test

A listing of subjects with positive pregnancy test results will be provided.

5 INTERIM ANALYSES (NOT APPLICABLE)

6 CHANGES OF ANALYSIS FROM PROTOCOL (NOT APPLICABLE)

7 REFERENCES (NOT APPLICABLE)

8 APPENDIX

8.1 Conventions

8.1.1 Baseline Measurements

Unless specified otherwise, a baseline value should be the last assessment taken prior to the 1st dose of study medication. When there is a missing baseline assessment, it should not be imputed, thus, subjects should be excluded from any changes from baseline analysis for which they have a missing baseline value.

8.1.2 Change and Percent Change from Baseline

Change from baseline to any Time *t* in correction phase double-blind treatment period is defined as follows:

$C_{Time\ t} = M_{Time\ t} - M_{baseline}$,

where:

- $C_{Time\ t}$ is the change from baseline at Time *t*,
- $M_{Time\ t}$ is the measurement at Time *t*,
- $M_{baseline}$ is the measurement at baseline.

Percent change from baseline to any Time *t* in correction phase double-blind treatment period is defined as follows:

$$P_{Time\ t} = 100 \times (M_{Time\ t} - M_{baseline}) / M_{baseline}.$$

Where $P_{Time\ t}$ is the percent change from baseline at Time *t*, and $M_{Time\ t}$ and $M_{baseline}$ are defined as above.

8.1.3 Analysis Visit Mapping

In principle, CRF nominal visits will be utilized for by-visit summary presentation.

For subjects who discontinued study drug prematurely, the measurements obtained at or before premature discontinuation visit are considered as "on-treatment" and would be included in the efficacy analyses, if appropriate. Efficacy measurements obtained after Day 48 visit/premature discontinuation visit will be considered as "off-treatment" and will be separated in data presentation.

Unscheduled visits will be included in summary of abnormality using most extreme values and also for LOCF (if applicable).

8.1.4 Fasting status

For FPG, fasting insulin, fasting c-peptide and fasting lipids, only assessment confirmed as measured during fasting state will be included in the analysis.

8.1.5 Descriptive statistics

Summaries of continuous characteristics will be based on non-missing observations.

Continuous variables will be summarised using descriptive statistics including the number of patients included in analysis, mean, standard deviation (SD), minimum, 1st quartile, median, 3rd quartile and maximum.

Categorical variable will be based on number and proportions in each category.