# Statistical Analysis Plan

## An Exploratory Phase 2, Randomised, Double-blind, Placebo-controlled, and Open-label Active Comparator Study to Evaluate the Effect of MEDI0382 on Hepatic Glycogen Metabolism in Overweight and Obese Subjects with Type 2 Diabetes Mellitus

**Protocol Number:** D5670C00022

# TABLE OF CONTENTS

## LIST OF TABLES

# List of Abbreviations

| Abbreviation or Specialized Term | Definition |
|---|---|
| AE | Adverse event |
| ANCOVA | Analysis of covariance |
| ATC | Anatomical Therapeutic Chemical |
| AUC | Area under the concentration-time curve |
| BMI | Body mass index |
| C2 | Carbon atom number 2 in glucose molecule (used to assess $^{2}H$ enrichment) |
| C6 | Carbon atom number 6 in glucose molecule (used to assess $^{2}H$ enrichment) |
| CI | Confidence interval |
| $C_{trough}$ | Trough plasma concentration, measured at the end of a dosing interval, taken directly before next administration |
| eCRF | Electronic Case Report Form |
| eGFR | Estimated glomerular filtration rate |
| ECG | Electrocardiogram |
| GLP-1 | glucagon-like peptide-1 |
| $^{2}H$ | deuterium |
| 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 |
| MRI | Magnetic resonance imaging |
| MRS | Magnetic resonance spectroscopy |
| P | Probability |
| PD | Pharmacodynamic(s) |
| PK | Pharmacokinetic(s) |
| PR | ECG PR interval |
| PT | MedDRA preferred term |
| QRS | ECG QRS interval |
| QT | ECG QT interval |
| QTcF | ECG QT interval corrected for heart rate using Fridericia's formula |
| RR | ECG RR interval |
| SAE | Serious adverse event |
| SAP | Statistical analysis plan |
| SPP | Statistical Programming Plan |

| Abbreviation or Specialized Term | Definition |
|---|---|
| SC | Subcutaneous |
| SID | Subject ID |
| SOC | MedDRA system organ class |
| T | Time |
| T2DM | Type 2 Diabetes Mellitus |
| ULN | upper limit of normal |
| WHO-DD | WHO Drug Dictionary enhanced |

# 1 INTRODUCTION

This document describes the statistical analysis methodology for protocol D5670C00022 (Amendment 6, 15Jul2020), a Phase 2 study to evaluate the effect of MEDI0382 on hepatic glycogen levels post prandially versus placebo in Part A and to compare the effect of MEDI0382 on hepatic glycogen levels versus placebo and liraglutide in Part B in overweight or obese subjects with T2DM. This document details the statistical summaries relating to each study objective and describes the general conventions and definitions that will be used. In addition, a set of table templates and specifications will be included in a statistical programming plan (SPP) to complement this document.

# 2 STUDY OVERVIEW

## 2.1 Study Objectives

### 2.1.1 Primary Study Objective(s)

- To assess the effect of MEDI0382 on hepatic glycogen levels post prandially versus placebo after 28 days (Part A) and 35 days (Part B) of treatment

### 2.1.2 Secondary Study Objectives

- To assess the effect of MEDI0382 on hepatic glycogen levels post prandially versus liraglutide after 35 days of treatment (Part B only)
- To assess the effect of MEDI0382 on hepatic fat fraction versus placebo after 35 days of treatment (Part B only)
- To evaluate the safety and tolerability of MEDI0382 [redacted]
- To characterize the immunogenicity profile of MEDI0382 [redacted]

### 2.1.3 Exploratory Study Objectives

- [redacted]

- [redacted]

[redacted]

s

[redacted]

## 2.2 Study Design

This exploratory Phase 2 study has 2 parts (Part A and Part B).

Part A is a randomized, double-blind, placebo-controlled sub-study to evaluate the effect of MEDI0382 ([redacted] administered once daily SC for 28 days on hepatic glycogen metabolism in overweight or obese subjects with T2DM. Part A is planned to randomize up to 20 subjects. Subjects will be consented, screened for suitability, and randomized within 60 days if eligible. Subjects from Part A will not be re-enrolled in Part B.

Part B is contingent on the results from Part A such that the combined sample size of two parts will ensure at least 80% power to detect the treatment effect observed from Part A using the standard deviation information also observed from Part A. If the minimal required sample size for Part B is less than or equal to 10 subjects per arm, Part B will be conducted.

Part B is an exploratory Phase 2 randomized, double-blind, placebo-controlled and open label active comparator sub-study to evaluate the effect of MEDI0382 on hepatic glycogen metabolism in overweight and obese subjects with T2DM subjects with the exact sample size determined by the results from Part A. Subjects in Part B will be randomized to receive double-blind MEDI0382 ([redacted] or placebo or open label liraglutide (titrated from 0.6 to 1.8 mg) once daily SC for 35 days.

Part A:

The study will involve measurement of hepatic glycogen content using a carbon (C)-13 MRS based technique before and after 28 days of treatment. Subjects will undergo a 5-day washout

period where metformin therapy will be suspended at the beginning of the study starting from Day -4 (metformin dosing to resume on Day 2) and the end of the study starting from Day 25 (metformin dosing to resume on Day 30). Across the course of the study (up to 126 days in total including screening) subjects will have a total of 6 study visits, 6 nights of inpatient stay and will undergo a total of 10 MRS scans alongside additional assessments and blood sampling.

Part B:

In Part B a comparison will be made between MEDI0382, [redacted] placebo and liraglutide once daily titrated from 0.6 to 1.8 mg in 7-day intervals. The treatment duration will be 35 days in each treatment group, with subjects randomized to liraglutide spending 21 days at 1.8 mg, in contrast subjects randomized to MEDI0382 will spend 14 days at top dose of 300 μg.

The procedures for subjects who go through to the completion of the visit on Day 8, are identical to Part A; aside from the MRS scanning and related activities that will occur at baseline prior to treatment, then at T = 0, 5, 14 and 24 hours and at the end of the 35 day treatment period as detailed in the schedule of events. The duration of MRS scans will be approximately 40 minutes with the exception of the baseline and end of treatment scans used for liver fat evaluation which will be prolonged and up to 1 hour 45 minutes in duration.

## 2.3 Treatment Assignment and Blinding

An IWRS will be used for randomization to a treatment group and assignment of investigational product kit numbers. A subject is considered randomized into the study when the IWRS provides the assignment of the subject's investigational product kit number.

Eligible subjects will be randomized at a 1:1 ratio following screening to receive either blinded MEDI0382 SC or placebo SC (Part A) or randomized at a 1:1:1 ratio following screening to receive either blinded MEDI0382 SC or placebo SC or open-label liraglutide SC (Part B). The IWRS will assign a unique randomization code and treatment group to the subject at the time of 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.

In Part A only, this is a double-blind study in which MEDI0382 and placebo [redacted] Neither the subject nor any of the investigator or sponsor staff who are involved in the treatment or clinical evaluation of subjects will be aware of treatment received.

[redacted] To maintain the blind in Part A of the study, investigational product (MEDI0382 and placebo) prefilled syringes will be handled by an unblinded investigational product manager or unblinded study personnel who will not be involved in the treatment or clinical evaluation of subjects. An unblinded site monitor will perform investigational product accountability, and this will be a different person from the blinded site monitor who will oversee other aspects of the study at the clinical site.

[redacted]. Each subject will know the volume of investigational product they have been instructed to select and administer, the subject and site staff are blinded with respect to whether they are receiving MEDI0382 or placebo. Liraglutide used in Part B will be open-label.

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

CCI [redacted]

[redacted]

# 3 STATISTICAL METHODS

## 3.1 General Considerations

In the event that there is a delay in data delivery or the full set of results is not expected to be available in timely manner (for example; follow-up of positive ADA results at 3 and 6

months after the follow-up visit) an initial database lock in Part B for the purpose of clinical study analysis and reporting will be performed when the last randomized subject completes the final visit or is discontinued prior to that visit. Final database lock will occur once all results have been received in the database.

In the event that an initial DBL is required, results received after this point may be reported in the clinical study report addendum.

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

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.

The study objectives will be evaluated with analyses that include data from both Part A and Part B, if Part B is conducted. Analyses will also be performed separately for each study part. In general, the efficacy analyses will be analyzed with the ITT population and all other analyses will be performed with the As-treated population.

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) in a UNIX environment.

## 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 and subjects will be analyzed according to the treatment they actually received. |
| Pharmacokinetic population | The PK population includes all subjects who received at least one dose of investigational product and had at least one PK blood sample taken that is 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 as well as treatment group received (including summary of subjects randomized but not treated) will be provided by study part. 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 study part and by treatment. 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, baseline medication use, HbA1c, glucose, blood pressure, and pulse rate.

### 3.3.3 Study Drug Exposure

The number of doses and total dose received will be summarized by study part for each investigational product (MEDI0382 or placebo or liraglutide) 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. 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)

Change in hepatic glycogen concentration adjusted for liver volume as measured by MRS at T = 4 hours post standardized morning meal from baseline (Day -1) to the end of 28 days of treatment (Part A only)

Percentage change in fasting glycogen concentration adjusted for liver volume as measured by MRS at T = 24 hours post standardized morning meal from baseline (Day 1) to the end of 35 days of treatment (Part B only)

#### 3.4.1.2 Handling of Dropouts and Missing Data

Since there is only one post-baseline measurement MRS, subjects who do not have a valid baseline evaluation or a valid Day 28 (Part A) and Day 35 (Part B) MRS evaluation at 4 hours (Part A) and 24 hours (Part B) post standardized morning meal will not contribute to the analysis.

#### 3.4.1.3 Primary Efficacy Analysis

The primary efficacy analysis will be performed using the ITT population.

The primary endpoint, change in hepatic glycogen concentration (measured by MRS, adjusted for liver volume) at T = 4 hours post standardized morning meal from baseline (Day -1) to the end of 28 days of treatment will be analyzed using an analysis of covariance (ANCOVA) model with baseline covariate and treatment group. Pairwise comparisons between MEDI0382 and placebo will be performed within this analysis (Part A only).

The primary endpoint, percentage change in fasting hepatic glycogen concentration (adjusted for liver volume) as measured by MRS at T=24 hours post standardized morning meal from baseline (Day 1) to the end of 35 days of treatment (Day 36), will be compared between the MEDI0382 and placebo groups using an analysis of covariance (ANCOVA) model adjusting for baseline value and treatment group (Part B only).

### 3.4.2 Secondary Efficacy Endpoint(s) and Analyses

#### 3.4.2.1 Secondary Efficacy Endpoint(s)

- Percentage change in fasting hepatic glycogen concentration adjusted for liver volume as measured by MRS at T = 24 hours post standardized morning meal from baseline (Day -1) to the end of 28 days of treatment (versus placebo, Part A only)
- Percentage change in fasting hepatic glycogen concentration adjusted for liver volume as measured by MRS at T = 24 hours post standardized morning meal from baseline (Day 1) to the end of 35 days of treatment (versus liraglutide, Part B only)
- Change in hepatic fat fraction from baseline as measured by magnetic resonance imaging (Day -1) to the end of 28 days of treatment (Part A only)
- Change in hepatic fat fraction from baseline as measured by magnetic resonance imaging (Day 1) to the end of 35 days of treatment (Part B only)
- Measures of safety and tolerability (vital signs, ECGs, laboratory test results, AEs)
- Development of ADA and titre (if confirmed positive)

#### 3.4.2.2 Secondary Efficacy Analyses

The secondary efficacy analyses will be performed using the ITT population.

The percentage change in fasting hepatic glycogen concentration (measured by MRS, adjusted for liver volume) at T = 24 hours post standardized morning meal from baseline (Day 1) to the end of 35 days of treatment, will be compared between MEDI0382 and liraglutide groups only in Part B of the study. This will be done using the ANCOVA model adjusting for baseline value and treatment group. A similar analysis will be applied to measure change in hepatic fat fraction from baseline (Day -1 or Day 1) to the end of 35 days of treatment (Day 35 or 36) versus placebo (Part B only).

The percentage change in fasting glycogen concentration (measured by MRS, adjusted for liver volume) at T = 24 hours post standardized morning meal from baseline (Day -1) to the end of 28 days of treatment, will be compared between MEDI0382 and placebo groups only in Part A of the study. This will be done using the ANCOVA model adjusting for baseline value and treatment group. A similar analysis will be applied to measure change in hepatic fat fraction from baseline (Day -1) to the end of 28 days of treatment versus placebo (Part A only).

### 3.4.3 Exploratory Efficacy Endpoint(s) and Analyses

#### 3.4.3.1 Exploratory Efficacy Endpoint(s)

- [redacted]

#### 3.4.3.2 Exploratory Efficacy Analyses

The exploratory efficacy analyses with the ITT population will be performed using an analysis of covariance (ANCOVA) model adjusting for baseline value and treatment group. The analyses will be performed as well as analyzed separately for each part.

## 3.5 Pharmacodynamic Analyses

### 3.5.1 Exploratory Pharmacodynamic Endpoint(s) and Analyses

#### 3.5.1.1 Exploratory Pharmacodynamic Endpoint(s)

- [redacted]

- [redacted]

#### 3.5.1.2 Exploratory Pharmacodynamic Analysis

The exploratory efficacy analyses will be performed using an analysis of covariance (ANCOVA) model adjusting for baseline value and treatment group. The analyses will be performed only separately for each part.

## 3.6 Safety Analyses

### 3.6.1 Adverse Events and Serious Adverse Events

Adverse events will be coded with MedDRA version 21.0 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 study part treatment group as well as for combined study parts. The AEs summaries will include only treatment-emergent AEs, ie, those occurring after initial 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.

### 3.6.2 Deaths and Treatment Discontinuations due to Adverse Events

A listing of any deaths will be provided which will include the MedDRA system organ class and preferred term. AEs resulting in permanent discontinuation from study drug will be summarized by study part and treatment. The summary will include results summarized overall and by MedDRA System Organ Class and Preferred Term.

### 3.6.3 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 study part 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 study part and treatment at each evaluation time.

### 3.6.4 Other Safety Evaluations

#### 3.6.4.1 Vital Signs

Vital signs including pulse rate (beats/min), systolic and diastolic blood pressure (mmHg), temperature (oC), and respiratory rate (breaths/min), as well as the change from baseline for each of those parameters, will be descriptively summarized study part and treatment.

#### 3.6.4.2 Electrocardiogram

Electrocardiogram parameters will be assessed with a single ECG at each evaluation (Screening, Day 1, and Day 26) 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 Day 26 as well as the change from baseline (Day 1) will be descriptively summarized by study part and treatment. For the qualitative variable ECG interpretation, the ECG Interpretation results will be summarized with frequencies and percentages at each evaluation.

## 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 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.

Plasma $C_{trough}$ concentrations of MEDI0382 at steady state (Part A Day 15 and Day 28; Part B Day 35) will be summarized with descriptive statistics.

### 3.9 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 be also provided.

## 4 INTERIM ANALYSIS

An interim analysis (ie, Part A analysis) was performed after Part A subjects have completed the study.

## 5 REFERENCES

None

## 6 VERSION HISTORY

| Version | Date | Summary of Changes | Reason for Change |
|---|---|---|---|
| 1.0 | 14May2018 | Initial document | Initial document |
| 2.0 | 04Jun2018 | - Updated Protocol D5670C00022 (Amendment 3, 8May2018).<br>- Add subsection 3.9 – Protocol Deviations A summary of important protocol deviation (IPD) will be prepared by deviation category as well as overall, A listing of the important protocol deviations will be also provided. | Incorporated Team Review Comments |
| 3.0 | 31May2021 | - Updated Protocol D5670C00022 (Amendment 6, 15July2020).<br>- Amend for potential 2 DBLs of Part B | Incorporated Team Review Comments |

# SIGNATURE PAGE

*This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature*

| **Document Name:** d5670c00022-sap-ed-3 | | |
|---|---|---|
| **Document Title:** | Statistical Analysis Plan Edition 3 | |
| **Document ID:** | Doc ID-004586895 | |
| **Version Label:** | 1.0 CURRENT LATEST APPROVED | |
| **Server Date** **(dd-MMM-yyyy HH:mm 'UTC'Z)** | **Signed by** | **Meaning of Signature** |
| 04-Jun-2021 14:02 UTC | [redacted] | [redacted] |
| [redacted] | [redacted] | [redacted] |

Notes: (1) Document details as stored in ANGEL, an AstraZeneca document management system.