MedImmune

A member of the AstraZeneca Group

Statistical Analysis Plan Approval

Date: *20MAR2019*
To: Study File
From: Redacted
Re: Statistical Analysis Plan Approval for Study *D5670C00004*

The Statistical Analysis Plan, version 3.0, for Study *D5670C00004* has been reviewed and approved.

Name:	Redacted	Signature:	DocuSigned by: Redacted ABA51CA6345B455...
Role:	Statistician	Date:	Redacted
Name:	Redacted	Signature:	DocuSigned by: Redacted 98BDDC6A80F2403...
Role:	Statistical Programmer	Date:	Redacted
Name:	Redacted	Signature:	DocuSigned by: Redacted B3821AB4F9C64E5...
Role:	Clinical Development Lead	Date:	Redacted
Name:	Redacted	Signature:	DocuSigned by: Redacted 1D71949A44A548A...
Role:	Clinical Biostatistics Therapeutic Area Head	Date:	Redacted
Name:	Redacted	Signature:	DocuSigned by: Redacted 0D76271E895C434...
Role:	Head of Clinical Biostatistics & Data Management	Date:	Redacted

Statistical Analysis Plan

A Phase IIb, Randomized, Parallel, Double-Blind Placebo-Controlled and Open-Label Active Comparator Study to Evaluate the Efficacy and Safety of MEDI0382 in the Treatment of Overweight and Obese Subjects with Type 2 Diabetes Mellitus

Protocol Number: D5670C00004

TABLE OF CONTENTS

LIST OF TABLES AND FIGURES

List of Abbreviations

Abbreviation or Specialized Term	Definition
ADA	Anti-drug antibodies
AE	Adverse event
ALT	Alanine transaminase
ANCOVA	Analysis of covariance
ANOVA	Analysis of variance
AST	Aspartate transaminase
ATC	Anatomical therapeutic chemical
BMI	Body mass index
CSR	Clinical study report
[redacted]	[redacted]
ECG	Electrocardiogram
eGFR	Estimated glomerular filtration rate
[redacted]	[redacted]
[redacted]	[redacted]
FPG	Fasting plasma glucose
HbA1c	Hemoglobin A1c
[redacted]	[redacted]
[redacted]	[redacted]
IM	Immunogenicity
ITT	Intent-to-Treat
IP	Investigational product
IVRS	Interactive voice response system
IWRS	Interactive web response system
[redacted]	[redacted]
LOCF	Last observation carried forward
MedDRA	Medical Dictionary for Regulatory Activities
[redacted]	[redacted]
PK	Pharmacokinetics
PP	Per protocol
SAE	Serious adverse event
SAP	Statistical analysis plan
T2DM	Type 2 diabetes mellitus
TBL	Total bilirubin level
ULN	Upper limit of normal
URC	Unblind Review Committee

1 INTRODUCTION

This document describes the statistical analysis for protocol *D5670C00004*, a phase IIb study to evaluate the efficacy and safety of MEDI0382 in the treatment of overweight and obese Subjects with type 2 diabetes mellitus (T2DM). In addition, a set of table templates and specifications will be included in a statistical programming plan to complement this document.

2 STUDY OVERVIEW

2.1 Study Objectives

2.1.1 Primary Study Objective(s)

Primary objective:	**Outcome measure:**
To assess the effect of 100 µg, 200 µg and 300 µg of MEDI0382 on haemoglobin A1c (HbA1c) and body weight versus placebo	Change in HbA1c from baseline to 14 weeks Percent change in body weight from baseline to 14 weeks

2.1.2 Secondary Study Objectives

Secondary objective:	**Outcome measure:**
To assess the effect of 100 µg, 200 µg and 300 µg of MEDI0382 on additional measures of glycaemic control and body weight versus placebo	Change in HbA1c from baseline to 26 weeks, and 54 weeks Percentage of subjects achieving an HbA1c target of <7.0% at 14 weeks, 26 weeks, and 54 weeks Percent change in body weight from baseline to 26 weeks, and 54 weeks Absolute change in body weight from baseline to 14 weeks, 26 weeks, and 54 weeks Percentage of subjects achieving weight loss of ≥5% and ≥10% after 14 weeks, 26 weeks, and 54 weeks
To assess the effect of 100 µg, 200 µg and 300 µg of MEDI0382 on the requirement for additional blood glucose lowering therapies versus placebo	Proportion of subjects rescued or discontinued for lack of glycaemic control at 14 weeks, 26 weeks, and 54 weeks
To assess the effect of 100 µg, 200 µg and 300 µg of MEDI0382 on weight versus liraglutide 1.8 mg once daily	Percent and absolute change in body weight from baseline to 14 weeks, 26 weeks, and 54 weeks
To characterise the PK profile and immunogenicity of 100 µg, 200 µg and 300 µg of MEDI0382	PK endpoints (trough plasma concentration, C_{min}) Development of anti-drug antibodies and titre (if positive) during dosing and follow-up

2.1.3 [redacted]

[redacted]	[redacted]
Redacted	[redacted]
[redacted]	Redacted
[redacted]	[redacted]
[redacted]	Redacted
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

2.2 Study Design

This is a randomized, double-blind, placebo-controlled study with an open-label active comparator (liraglutide) arm, designed to evaluate the efficacy and safety of MEDI0382 in overweight and obese subjects with T2DM. This study will enroll male and female subjects aged ≥18 years, with a BMI ≥25 and ≤45 kg/m2. Subjects will have a diagnosis of T2DM, and inadequate blood glucose control as defined by an HbA1c of 7.0% to 10.5%, and are on metformin monotherapy. Approximately 750 subjects will be randomized and it is anticipated that approximately 542 subjects will complete the study, taking into account a projected annual study drop-out rate of 15%. The study has a run in period of 2 weeks, a 14-week treatment period, followed by a minimum 40-week treatment extension.

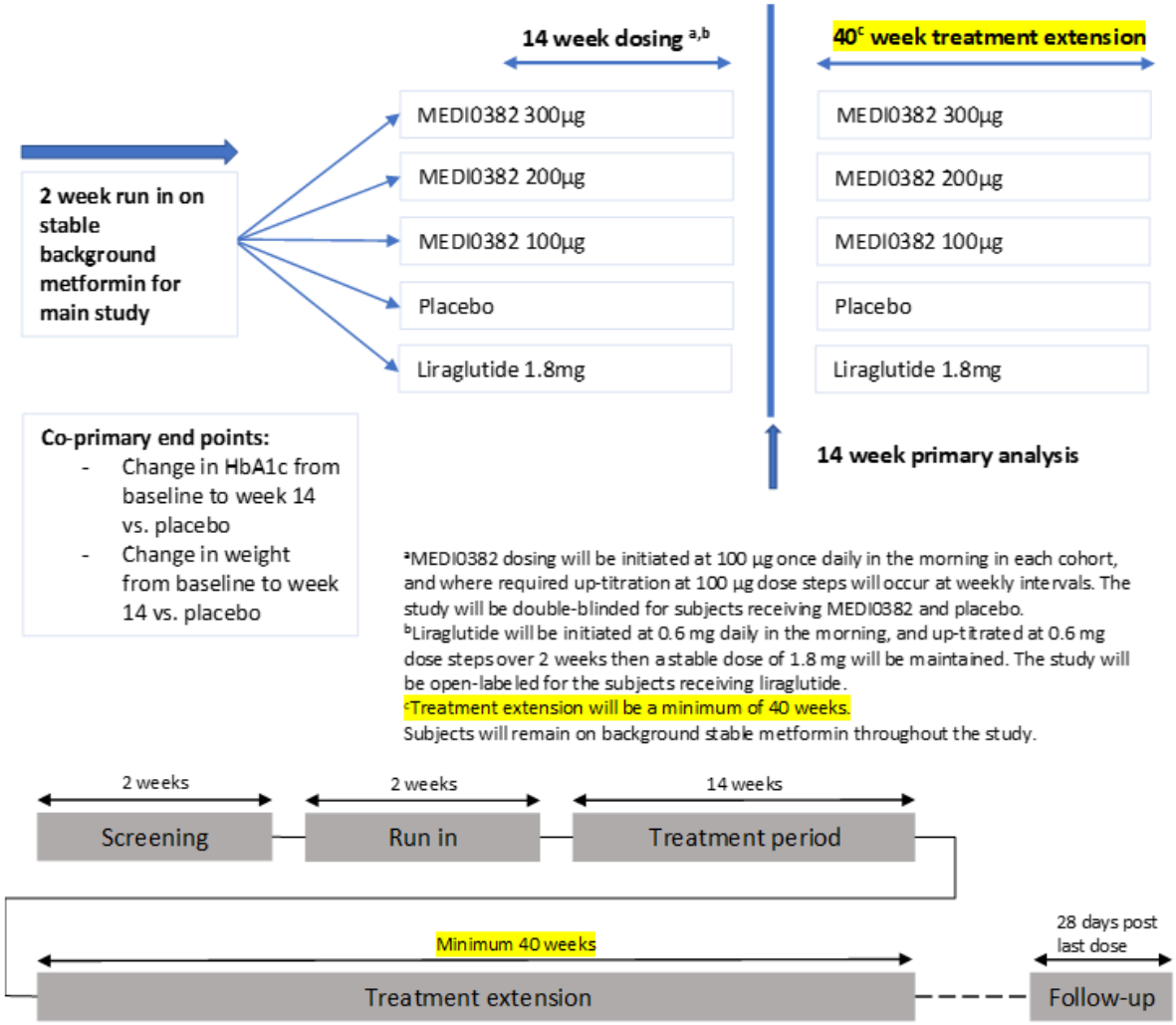
Prior to the run-in period, subjects will be consented and screened for suitability. During the run-in period, subjects will refrain from taking prohibited medications, but will continue to take their prescribed stable dose of metformin for the remainder of the study. After completion of run-in, subjects who are still eligible will be randomized within 1 week. Diet and exercise counselling will be provided from the beginning and throughout the duration of the study. Only subjects who are treated with metformin monotherapy will be enrolled; this will ensure that subjects with an early stage of T2DM are treated in this study.

To achieve the enrolment goal for the initially planned interim analysis, subjects will be randomly assigned with a ratio of 2:2:2:1:1 to 1 of 5 treatment arms to receive MEDI0382 at dose level of 300 μg, 200 μg, or 100 μg, placebo or liraglutide respectively. After approximately the first 400 subjects have been enrolled, the randomization ratio will be changed to 5:5:0:2:2 to fully enroll the remaining 350 subjects. Randomization will be stratified with respect to screening HbA1c (≤8% or >8%).

For subjects randomized to MEDI0382 or placebo, MEDI0382 will be initiated at 100 μg, and dose increments may occur in 100 μg steps every week until the predefined maintenance dose is reached. Subjects and Investigators will be advised that there may be dose increments. During the 14-week treatment period, open-label liraglutide will be initiated at 0.6 mg and up titrated by an additional 0.6 mg weekly until a stable daily dose of 1.8 mg is reached. After the 14-week treatment period, subjects will continue with the allocated treatment for a further minimum of 40 weeks of extension treatment, after which study treatment will end. An Early Termination visit will be performed for subjects who discontinue treatment prematurely at any time and for any reason as soon as possible, but not later than 7 days from last investigational product (IP) dose. A follow-up visit will be performed for final safety assessments 4 weeks after the last dose of IP.

See Figure 2.2-1 for a summary of the study design. Details of assessments at each visit are summarized in the study protocol.

Figure 2.2-1 Study flow diagram



2.3 Treatment Assignment and Blinding

Assignment to treatment groups will be determined by a computer-generated random sequence using an IVRS/IWRS.

The study will be conducted in a double-blind fashion for MEDI0382 and placebo. The treatment code should not be broken except in medical emergencies when the appropriate management of the subject requires knowledge of the treatment randomization. The Investigator documents and reports the action to AstraZeneca, without revealing the treatment given to the subject to the AstraZeneca staff.

AstraZeneca retains the right to break the code for serious adverse events (SAEs) that are unexpected and are suspected to be causally related to an IP and that potentially require expedited reporting to regulatory authorities. Treatment codes will not be broken for the planned analyses of data until all decisions on the evaluability of the data from each individual subject have been made and documented.

The exception to the above is for those personnel analyzing the PK samples. The randomization code will be provided to ensure that only samples from subjects who were on active study treatment are analysed. Samples from subjects not dosed with the relevant active study treatment will only be analysed on a 'for cause' basis, for example, if there is suspicion that a subject has been dosed incorrectly. The treatment allocation information will be kept in a secure location until the end of the study.

For the purpose of the primary analysis and the 26-week analysis, any study team members who serve in the unblinded analysis group will stop day-to-day work on the study and other pre-selected personnel will take over these roles for the remainder of the trial. The study team members will remain blinded to treatment assignment until the data base lock after the treatment extension is finished.

2.4 [redacted]

[redacted]

3 STATISTICAL METHODS

3.1 General Considerations

Data will be provided in data listings sorted by treatment group and subject number. Tabular summaries will be presented by treatment group and by visit. Categorical data will be summarized by the number and percentage of subjects in each category. Continuous variables will be summarized by descriptive statistics, including mean, standard deviation, median, minimum, and maximum.

Baseline values will be defined as the last measurements prior to the first administration of IP at the randomization visit.

Unless otherwise specified, efficacy analyses will be based on ITT population (Section 3.2) and include post IP-discontinuation and post rescue data. Last observation carried forward (LOCF) method will be applied for efficacy endpoints to handle missing data, that is, a missing endpoint will be replaced with the last available post-baseline measurement prior to the missing endpoint.

Data analyses will be conducted using the SAS® System Version 9.3 or higher (SAS Institute Inc., Cary, NC).

The following analyses are planned for this study:

- A primary analysis when all subjects reach 14 weeks treatment.
- An analysis when all subjects reach 26 weeks treatment
- A final analysis at the end of the study.

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 IP will be included in the ITT population and subjects will be analyzed according to their randomized treatment group. The analysis will include the post IP-discontinuation data and post rescue data for those subjects who discontinue from study treatments or are rescued, but are still followed up for their scheduled visits.
As-treated population	Subjects who receive any study IP will be included in the as-treated population and subjects will be analyzed according to the treatment they actually receive.
Per-protocol population	The Per Protocol (PP) analysis set includes only subjects who didn't discontinue study IP during the relevant treatment period and excludes those with important protocol violation(s) during the relevant treatment period that lead to complete data exclusion. Important protocol violations are those that have the potential to affect the result of the primary efficacy results. Partial data will be excluded for PP subjects who meet those important protocol violation(s) during the relevant treatment period that lead to partial data exclusion. PP population will be analyzed according to the treatment they actually receive.
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 taken that is above the lower limit of quantitation.

3.2.1 Important Protocol Violations

Protocol deviations that are determined to affect the primary efficacy results are deemed important protocol violations. The list of important protocol violations and data exclusion rules are described in Table 3.2.1-1. Since some important protocol deviations include unblinding information and data are subject to clean before data base lock, the important protocol deviations will be reviewed and confirmed as much as possible before data base lock, and will be finalized by the unblinded study physician based on pre-specified criteria below after data base locks for the primary, the 26-week, and the final analyses.

Table 3.2.1-1 List of Important Protocol Violations

Number	Important Protocol violation criteria	Complete/Partial data exclusion
1	Randomized patients without Type 2 Diabetes at screening	Complete data exclusion
2	Has HbA1c of [<7%, or >10.5%] at screening	Complete data exclusion
3	Receipt of wrong study medication during the study	Complete data exclusion
4	IP compliance <80% or >120% during the treatment period	Complete data exclusion
5	Hemolytic anemia, or chronic anemia (hemoglobin concentration <11.5 g/dL [115 g/L] for males, <10.5 g/dL [105 g/L] for females) prior to V3	Complete data exclusion
6	Systemic corticosteroids within 3 months prior to Screening (Visit 1) by oral, intravenous, intra-articular, or intramuscular route	Complete data exclusion
7	Concurrent or previous use of drugs approved for weight loss (orlistat, bupropion -naltrexone, phentermine-topiramate, phentermine, lorcaserin) within the last 30 days, prior to screening (V1)	Complete data exclusion
8	Same subject randomized to current study more than once	Complete data exclusion; Note: the identification of subjects who meet this criteria will be based on study and site monitoring
9	Randomized patients who received no study medication for ≥1 week (7 consecutive days) during the 14 week treatment period, or > 2 consecutive weeks in the treatment extension period	Partial data exclusion: exclude data on or after the first violation date (violation date is defined as the date when any rules becomes violated; e.g. the 7th day without receiving study medication during the 14 week treatment period)
10	Receipt of glucose lowering medication, (other than IP, metformin, or protocol allowed rescue therapy) for ≥ 14 consecutive days during the double blind treatment period	Partial data exclusion: exclude data on or after the first violation date

3.3 Study Subjects

3.3.1 Subject Disposition and Completion Status

A summary of subjects treated at each treatment group will be provided. In addition, disposition of subjects throughout the study with respect to completion of treatment and study and the reasons for discontinuation will be provided.

3.3.2 Demographics and Baseline Characteristics

Demographic information related to gender, age, race, ethnicity, weight, height, body mass index (BMI= weight (kg) / [height (m)]^2), and BMI categories (< 25, ≥ 25 to < 30, or ≥30) will be presented by treatment group and for all subjects combined. A summary of baseline disease characteristics will include but may not be limited to: baseline HbA1c, the strata of screening HbA1c (≤8% or >8%), duration of diabetes, duration of diabetes category (<3 years, ≥3 to ≤10 years, >10 years), FPG, blood pressure, pulse rate, smoking history, alcohol history, eGFR, and eGFR categories (< 30, ≥ 30 to <60, ≥ 60 to <90, and ≥ 90).

3.3.3 Study Drug Exposure

The number of doses of study drug (investigational product) received will be summarized. In addition, the duration of drug exposure and the percent of compliance (the ratio of the number of actual dose received to the number of planned doses) will also be summarized by treatment group. The percent of compliance will then be categorized to <80%, 80% to <120%, and ≥120%. The total number of doses received will be calculated based on the drug exposure data. Extent of exposure will be calculated for each patient using the last study medication date minus the first study medication date plus 1 and excluding the off-treatment days. Extent of exposure will also be categorized into fixed intervals. In addition, the extent of exposure will also be summarized by country.

3.3.4 Concomitant Medications

Concomitant medications will be coded using WHO Drug Dictionary (March 2017 or higher version). Concomitant medications will be summarized using frequency count and percentage by the highest anatomical therapeutic chemical (ATC) class and preferred term. The following three situations will be summarized separately: the concomitant medications with stop date prior to the first randomized dose; the concomitant medications with start date prior to the first randomized dose and continued afterwards; the concomitant medications with start date on or after the first randomized dose. All concomitant medications will also be presented in a data listing.

Rescue medications will be summarized and listed separately.

3.4 Efficacy Analyses

3.4.1 Primary Efficacy Endpoint(s) and Analyses

3.4.1.1 Primary Efficacy Endpoint(s)

1. Change in HbA1c from baseline to 14 weeks

2. Percent change in body weight from baseline to 14 weeks

3.4.1.2 Primary Efficacy Analysis

HbA1c change and weight percent change from baseline to 14 weeks will be compared between MEDI0382 and placebo arms. For these endpoints, an analysis of covariance (ANCOVA) model will be used and adjusted for treatment and measurement at baseline. For weight loss, the strata of screening HbA1c (≤8% or >8%) will be added into the model as a covariate. Analyses will be based on the ITT population. The comparisons will be performed at the 0.05 significance level (2-sided). HbA1c change and weight percent change from baseline for all scheduled visits will also be summarized descriptively by treatment.

3.4.1.3 Additional Analyses of the Primary Efficacy Endpoint(s)

For the primary endpoints, three sensitivity analyses will be performed. First, an ANCOVA analysis that only contains data before subjects discontinue study treatments and before subjects receive rescue therapy will be performed. Second, an ANCOVA analysis based on PP population will be done. Third, a multiple imputation based ANCOVA model will be done. Missing endpoints for subjects from a specific treatment group will be imputed based on only those subjects who are from the same treatment group and discontinued study IP but still remain in the study and have endpoint measures. After the imputed datasets are obtained, they will be analyzed by ANCOVA model and then the analysis results from ANCOVA models will be combined by considering both within and between imputation variabilities. If the “MI” procedure does not converge, then the missing endpoints will be imputed based on all subjects from the placebo group with non-missing endpoint measures.

3.4.2 Secondary Efficacy Endpoint(s) and Analyses

3.4.2.1 Secondary Efficacy Endpoint(s)

- Change in HbA1c from baseline to 26 weeks, and 54 weeks.

- Percentage of subjects achieving an HbA1c target of <7.0% at 14 weeks, 26 weeks, and 54 weeks.
- Percent change in body weight from baseline to 14 weeks (MEDI0382 vs Lira), 26 weeks, and 54 weeks (MEDI0382 vs Placebo; MEDI0382 vs Lira).
- Absolute change in body weight from baseline to 14 weeks, 26 weeks, and 54 weeks (MEDI0382 vs Placebo; MEDI0382 vs Lira).
- Percentage of subjects achieving weight loss of ≥5% and ≥10% after 14 weeks, 26 weeks, and 54 weeks (MEDI0382 vs Placebo; MEDI0382 vs Lira).
- Proportion of subjects rescued or discontinued for lack of glycemic control at 14 weeks, 26 weeks, and 54 weeks.

3.4.2.2 Secondary Efficacy Analyses

Secondary efficacy endpoints will be summarized by treatment and by visit. Body weight (percent) change and HbA1c change at 26 weeks and 54 weeks will be analysed by ANCOVA model with LOCF, including fixed effect of treatment and covariates of treatment, baseline measurement, strata of screening HbA1c (≤8% or >8%). Strata of screening HbA1c will not be included in HbA1c related analyses, as baseline HbA1c will be included as a covariate. For the secondary proportion-related endpoints, a logistic regression model will be used with similar fixed effect and covariates. These analyses will be performed based on the ITT population. In addition, repeated measures modeling or generalized estimation equation modeling may be performed.

3.4.3 Subgroup Analyses

Subgroup analyses will be conducted for the following subgroup factors and for HbA1c and body weight related primary and secondary endpoints. The data will be presented by subgroups and by treatments. The statistical analysis will be based on similar models as those for primary and secondary endpoints with the addition of the interaction between subgroup and treatment, and the p-value for the subgroup effect (interaction effect) will be reported. The statistical testing on treatment effect within each of the subgroup categories will also be conducted, and p-value and confidence interval will be reported. Subgroup Identification based on Differential Effect Search (SIDES) analysis may be performed if deemed appropriate. Subgroup factors to be analyzed are:

1. Whether a subject received rescue therapy;
2. Baseline BMI: ≥ 25 to < 30 or ≥ 30;

3. Baseline HbA1c: < 8%, ≥ 8% to < 9%, or ≥ 9%;
4. Diabetes duration: < 3 years, ≥ 3 to ≤ 10 years or > 10 years;
5. eGFR: < 30, ≥ 30 to <60, ≥ 60 to <90, or ≥ 90;
6. Age group: < 65 years, ≥ 65 to <75 years, or ≥ 75 years;
7. Region: US or the rest of the world.

3.5 Other Additional Analyses

Redacted

Redacted

3.6 Safety Analyses

3.6.1 Adverse Events and Serious Adverse Events

All safety analyses will be based on the As-treated population. Only AEs/SAEs that are collected on or after the randomization visit will be summarized. Adverse events and SAEs will be coded by the most updated version of the MedDRA and be summarized by System Organ Class and Preferred Term and by treatment. Additionally, AEs with ≥5% incidence

rate in any treatment group will be summarized. Study IP related AEs and SAEs, and AEs leading to treatment discontinuations or death will also be summarized. Specific AEs will be counted once for each subject for calculating percentages. In addition, if the same AE occurs multiple times within a particular subject, the highest severity and level of relationship observed will be reported. Subject level data listings of all AEs will be presented.

Additionally, the incidence and event rate of nausea and vomiting will be summarized for the time intervals of interest: e.g. for the first 3 weeks, 4-14 weeks and the first 14 weeks. The incidence and percentage of subjects that meet Hy's law criteria (AST or ALT >3x ULN and TBL >2x ULN) will also be summarized for the time intervals of interest.

No formal statistical testing will be performed for safety analyses; only descriptive summaries will be provided.

3.6.2 Deaths

All deaths recorded on the AE page of the CRF will be listed and summarized. Any deaths that occur during the study will be described in depth as narrative in the CSR.

3.6.3 Clinical Laboratory Evaluation

Redacted

, the hematology and serum chemistry parameters (including serum Amylase, Lipase, and Calcitonin) as well as their changes from baseline will be listed and summarized with descriptive statistics by treatment group at each of the time points specified in the study schedule. The urinalysis results will also be listed. The hematology and serum chemistry results will also be classified into low, normal, and high. The urinalysis results will be classified into normal and abnormal. The shift from baseline hematology, serum chemistry, and urinalysis results will be summarized by treatment group.

Additionally, for liver safety, a summary of the incidence and proportion of patients with elevated liver tests that meet the following criteria by visit will be provided:

- ALT and/or AST are >5 × ULN
- ALT and /or AST are >8 × ULN.

3.6.4 Other Safety Evaluations

3.6.4.1 Vital Signs

In addition to blood pressure that are already included in the exploratory objectives, values and changes from baseline for pulse rate will be summarized by treatment group at each scheduled visit.

3.6.4.2 Electrocardiogram

The normality/abnormality of the ECG tracing (as determined by the investigator or qualified designee) will be summarized using frequency tables on number of patients with a normal/abnormal ECG tracing at each scheduled visit. A listing of patients will be produced which will display all ECG findings in patients with abnormal ECGs.

3.7 Immunogenicity

All subjects in the safety analysis set with reported 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 GLP1 and/or glucagon (as data allows and if applicable).

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

3.8 Pharmacokinetics

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.

Individual MEDI0382 plasma concentrations will be summarized by treatment and visit. MEDI0382 plasma concentration at trough (Cmin) may be summarized by treatment and visit using descriptive statistics for the MEDI0382 treatment arms.

A population PK analysis may be performed to further evaluate the PK properties of MEDI0382, but will not be reported in the CSR.

4 VERSION HISTORY

Version	Date	Summary of Changes	Reason for Change
1	24Aug2017	Initial document	Initial document
2	21May2018	Removed the section of Interim Analysis; Removed or adjusted “interim analysis” or “26-week analysis for 296 subjects” related languages in Section 2.2, 2.3, and 3.1; Added “26-week analysis when all subjects reach 26 weeks” related languages; Revised Per-protocol population definition in Section 3.2;	According to study protocol amendment, Interim and 26-week analysis based partial data were removed, and 26-week analysis based on all subjects was added; Revised Per-protocol population definition in Section 3.2 to take into account the complete and partial data exclusions; The important protocol violations contain unblinding information and data are subject to clean before data base lock, so cannot be finalized before data base lock; BMI subgroup typos corrected;

		Revised language about how to finalize the important protocol violation review in Section 3.2.1; Revised in Section 3.2.2 the BMI subgroups; Revised in Section 3.3.3 how to calculate the dose received; [redacted] Add general description in Section 3.6.1 for time intervals to be more accurate. Corrected typo in Section 3.7 for "Reactivity".	Drug accountability data didn't contain information if a syringe is broken or has other pre-existing issues, so cannot be used as the source for calculating the actual received doses; [redacted]
3	20Mar2019	Revised in Sections 2.1.2 and 2.1.3 removing Week 106 in endpoints. Revised treatment extension from 92 weeks to minimum of 40 weeks throughout the document.	According to study protocol amendment 5, the length of the treatment extension period was reduced from 92 to 40 weeks. Week 54 (Visit 14) will be the minimum required time point for treatment comparisons. Study duration will now be a minimum of 62 weeks, including a 2-week screening period, a 2-week run-in period, a 14-week treatment period, a minimum 40-week treatment extension, and a 4-week follow-up. The rationale for this change is to allow subjects adequate time to transition to other therapies and allow continued collection of safety and efficacy data to inform further decisions regarding MEDI0382 doses.

Certificate Of Completion

Envelope Id: Redacted
Status: Completed
Subject: Please DocuSign: Statistical Analysis Plan MEDI0382 D5670C00004_V3.0 signature page.docx
iSave Workspace ID:
Source Envelope:
Document Pages: 1
Signatures: 5
Envelope Originator:
Certificate Pages: 5
Initials: 0
Redacted
AutoNav: Enabled
Puerta de Hierro
EnvelopeId Stamping: Disabled
Guadalajara, Jalisco 45116
Time Zone: (UTC) Dublin, Edinburgh, Lisbon, London
Redacted
IP Address: Redacted

Record Tracking

Status: Original
Holder: Redacted
Location: DocuSign
Redact 5:53:32 PM
Redacted

Signer Events	Signature	Timestamp
Redact ed AstraZeneca Security Level: Email, Account Authentication (None)	DocuSigned by: Redacted 98BDDC6A80F2403...	Sent: Redact 5:55:30 PM Viewed: Redacte 5:56:15 PM Signed: Redacte 5:56:23 PM
	Signature Adoption: Pre-selected Style Using IP Address: Redacted	
Electronic Record and Signature Disclosure: Not Offered via DocuSign		
Redacte Redacted Security Level: Email, Account Authentication (None)	DocuSigned by: Redacted 0D76271E895C434...	Sent: Redact 5:55:30 PM Viewed: Redacte 6:12:55 PM Signed: Redacte 6:58:48 PM
	Signature Adoption: Pre-selected Style Using IP Address: Redacted F	
Electronic Record and Signature Disclosure: Accepted: Redact 6:12:55 PM ID: Redacted		
Redacted Redacted Security Level: Email, Account Authentication (None)	DocuSigned by: Redacted 1D71949A44A548A...	Sent: Redacte 5:55:30 PM Viewed: Redact 8:53:48 PM Signed: Redact 8:54:17 PM
	Signature Adoption: Pre-selected Style Using IP Address: Redacted	
Electronic Record and Signature Disclosure: Accepted: 3/20/2019 8:53:48 PM ID: Redacted		
Redacte Redacted Security Level: Email, Account Authentication (None)	DocuSigned by: Redacted B3821AB4F9C64E5...	Sent: Redact 5:55:30 PM Viewed: Redact 10:57:12 AM Signed: Redact 10:57:23 AM
	Signature Adoption: Pre-selected Style Using IP Address: Redacted	
Electronic Record and Signature Disclosure: Accepted: Redact 10:57:12 AM ID: Redacted		

Signer Events	Signature	Timestamp
Redacted Sr. Prin. Statistician AstraZeneca Security Level: Email, Account Authentication (None)	DocuSigned by: Redacted ABA51CA6345B455...	Sent: Redact 5:55:30 PM Viewed: Redact 5:55:44 PM Signed: Redact 5:55:49 PM
	Signature Adoption: Pre-selected Style Using IP Address: Redacted	

Electronic Record and Signature Disclosure:
Not Offered via DocuSign

In Person Signer Events	Signature	Timestamp

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
Envelope Sent	Hashed/Encrypted	Redact 5:55:32 PM
Certified Delivered	Security Checked	Redact 10:57:13 AM
Signing Complete	Security Checked	Redact 10:57:23 AM
Completed	Security Checked	Redact 10:57:23 AM

Payment Events	Status	Timestamps

Electronic Record and Signature Disclosure

ELECTRONIC RECORD AND SIGNATURE DISCLOSURE

From time to time, AstraZeneca (we, us or Company) may be required by law to provide to you certain written notices or disclosures. Described below are the terms and conditions for providing to you such notices and disclosures electronically through your DocuSign, Inc. (DocuSign) Express user account. Please read the information below carefully and thoroughly, and if you can access this information electronically to your satisfaction and agree to these terms and conditions, please confirm your agreement by clicking the 'I agree' button at the bottom of this document.

Getting paper copies

At any time, you may request from us a paper copy of any record provided or made available electronically to you by us. For such copies, as long as you are an authorized user of the DocuSign system you will have the ability to download and print any documents we send to you through your DocuSign user account for a limited period of time (usually 30 days) after such documents are first sent to you. After such time, if you wish for us to send you paper copies of any such documents from our office to you, you will be charged a $0.00 per-page fee. You may request delivery of such paper copies from us by following the procedure described below.

Withdrawing your consent

If you decide to receive notices and disclosures from us electronically, you may at any time change your mind and tell us that thereafter you want to receive required notices and disclosures only in paper format. How you must inform us of your decision to receive future notices and disclosure in paper format and withdraw your consent to receive notices and disclosures electronically is described below.

Consequences of changing your mind

If you elect to receive required notices and disclosures only in paper format, it will slow the speed at which we can complete certain steps in transactions with you and delivering services to you because we will need first to send the required notices or disclosures to you in paper format, and then wait until we receive back from you your acknowledgment of your receipt of such paper notices or disclosures. To indicate to us that you are changing your mind, you must withdraw your consent using the DocuSign 'Withdraw Consent' form on the signing page of your DocuSign account. This will indicate to us that you have withdrawn your consent to receive required notices and disclosures electronically from us and you will no longer be able to use your DocuSign Express user account to receive required notices and consents electronically from us or to sign electronically documents from us.

All notices and disclosures will be sent to you electronically

Unless you tell us otherwise in accordance with the procedures described herein, we will provide electronically to you through your DocuSign user account all required notices, disclosures, authorizations, acknowledgements, and other documents that are required to be provided or made available to you during the course of our relationship with you. To reduce the chance of you inadvertently not receiving any notice or disclosure, we prefer to provide all of the required notices and disclosures to you by the same method and to the same address that you have given us. Thus, you can receive all the disclosures and notices electronically or in paper format through the paper mail delivery system. If you do not agree with this process, please let us know as described below. Please also see the paragraph immediately above that describes the consequences of your electing not to receive delivery of the notices and disclosures electronically from us.

How to contact AstraZeneca:
You may contact us to let us know of your changes as to how we may contact you electronically, to request paper copies of certain information from us, and to withdraw your prior consent to receive notices and disclosures electronically as follows:
To contact us by email send messages to: Redacted

To advise AstraZeneca of your new e-mail address
To let us know of a change in your e-mail address where we should send notices and disclosures electronically to you, you must send an email message to us at Redacted and in the body of such request you must state: your previous e-mail address, your new e-mail address. We do not require any other information from you to change your email address..
In addition, you must notify DocuSign, Inc to arrange for your new email address to be reflected in your DocuSign account by following the process for changing e-mail in DocuSign.

To request paper copies from AstraZeneca
To request delivery from us of paper copies of the notices and disclosures previously provided by us to you electronically, you must send us an e-mail to Redacted and in the body of such request you must state your e-mail address, full name, US Postal address, and telephone number. We will bill you for any fees at that time, if any.

To withdraw your consent with AstraZeneca
To inform us that you no longer want to receive future notices and disclosures in electronic format you may:

i. decline to sign a document from within your DocuSign account, and on the subsequent page, select the check-box indicating you wish to withdraw your consent, or you may;
ii. send us an e-mail to Redacted and in the body of such request you must state your e-mail, full name, IS Postal Address, telephone number, and account number. We do not need any other information from you to withdraw consent.. The consequences of your withdrawing consent for online documents will be that transactions may take a longer time to process..

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:	•Allow per session cookies •Users accessing the internet behind a Proxy Server must enable HTTP 1.1 settings via proxy connection

** These minimum requirements are subject to change. If these requirements change, we will provide you with an email message at the email address we have on file for you at that time

providing you with the revised hardware and software requirements, at which time you will have the right to withdraw your consent.

Acknowledging your access and consent to receive materials electronically

To confirm to us that you can access this information electronically, which will be similar to other electronic notices and disclosures that we will provide to you, please verify that you were able to read this electronic disclosure and that you also were able to print on paper or electronically save this page for your future reference and access or that you were able to e-mail this disclosure and consent to an address where you will be able to print on paper or save it for your future reference and access. Further, if you consent to receiving notices and disclosures exclusively in electronic format on the terms and conditions described above, please let us know by clicking the 'I agree' button below.

By checking the 'I Agree' box, I confirm that:

- I can access and read this Electronic CONSENT TO ELECTRONIC RECEIPT OF ELECTRONIC RECORD AND SIGNATURE DISCLOSURES document; and

- I can print on paper the disclosure or save or send the disclosure to a place where I can print it, for future reference and access; and

- Until or unless I notify AstraZeneca as described above, I consent to receive from exclusively through electronic means all notices, disclosures, authorizations, acknowledgements, and other documents that are required to be provided or made available to me by AstraZeneca during the course of my relationship with you.