MedImmune

A member of the AstraZeneca Group

[redacted]

[redacted]

[redacted]

[redacted]	[redacted]	[redacted]	[redacted] 06 July 2018
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted] 06 July 2018
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted] 06 July 2018
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted] 7F1AD1C2097D4CD...
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted] 7F1AD1C2097D4CD...
[redacted]	[redacted]	[redacted]	[redacted]

Statistical Analysis Plan

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

Protocol Number: D5670C00007

TABLE OF CONTENTS

1 INTRODUCTION 6
2 STUDY OVERVIEW 6
2.1 Study Objectives 6
2.1.1 Primary Study Objective(s) 6
2.1.2 Secondary Study Objectives 6
2.1.3 Exploratory Study Objectives 6
2.2 Study Design 7
2.3 Treatment Assignment and Blinding 8
2.4 Sample Size 9
3 STATISTICAL METHODS 9
3.1 General Considerations 9
3.2 Analysis Populations 10
3.3 Study Subjects 11
3.3.1 Subject Disposition and Completion Status 11
3.3.2 Demographics and Baseline Characteristics 11
3.3.3 Study Drug Exposure 11
3.3.4 Concomitant Medications 11
3.4 Efficacy Analyses 11
3.4.1 Primary Efficacy Endpoint(s) and Analyses 11
3.4.1.1 Primary Efficacy Endpoint(s) 11
3.4.1.2 Handling of Dropouts and Missing Data 12
3.4.1.3 Primary Efficacy Analysis 12
3.4.2 Secondary Efficacy Endpoint(s) and Analyses 12
3.4.2.1 Secondary Efficacy Endpoint(s) 12
3.4.2.2 Handling of Dropouts and Missing Data 13
3.4.2.3 Secondary Efficacy Analyses 13
3.4.3 Exploratory Efficacy Endpoint(s) and Analyses 13
3.4.3.1 Exploratory Efficacy Endpoint(s) 13
3.4.3.2 Exploratory Efficacy Analyses 13
3.5 Pharmacodynamic Exploratory Endpoint(s) and Analyses 13
3.5.1.1 Pharmacodynamic Endpoint(s) 13
3.5.1.2 Analysis of Pharmacodynamic Endpoint(s) 14
3.6 Safety Analyses 14
3.6.1 Adverse Events and Serious Adverse Events 14
3.6.2 Adverse Events of Special Interest 14
3.6.3 Deaths and Treatment Discontinuations due to Adverse Events 14

3.6.4Clinical Laboratory Evaluation....15
3.6.5Other Safety Evaluations....15
3.6.5.1 Vital Signs....15
3.6.5.2 Electrocardiogram....15
[redacted]
3.8 Pharmacokinetics....16
4 INTERIM ANALYSIS....17
5 VERSION HISTORY....17

LIST OF TABLES

Table 3.2-1 Analysis Populations....10

List of Abbreviations

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

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

1 INTRODUCTION

This document describes the statistical analysis methodology for protocol D5670C00007, a Phase 2a exploratory randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of MEDI0382 versus placebo in overweight/obese subjects with type 2 diabetes mellitus (T2DM) treated with dapagliflozin and metformin. This document details the statistical summaries relating to each study objective and describes the general conventions and definitions that will be used. In addition, a set of table templates and specifications will be included in a statistical programming plan (SPP) to complement this document.

2 STUDY OVERVIEW

2.1 Study Objectives

2.1.1 Primary Study Objective(s)

To compare the change in glucose area under the concentration-time curve (AUC) as measured by a standardized mixed meal tolerance test (MMTT) in subjects treated with dapagliflozin and metformin receiving MEDI0382 or placebo for 28 days

2.1.2 Secondary Study Objectives

- To compare the safety and tolerability profile of MEDI0382 (titrated up to a dose level of 300 μg subcutaneous [SC]) compared to placebo after 28 days of treatment in subjects treated with dapagliflozin and metformin
- To evaluate the pharmacokinetics (PK) profile of MEDI0382 and dapagliflozin (in subjects treated with dapagliflozin, metformin, and MEDI0382) and dapagliflozin (in subjects treated with dapagliflozin, metformin, and placebo)
- [redacted]
- To evaluate 24-hour glucose control as measured by continuous glucose monitoring (CGM) in subjects treated with dapagliflozin and metformin receiving MEDI0382 or placebo for 28 days

2.1.3 Exploratory Study Objectives

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

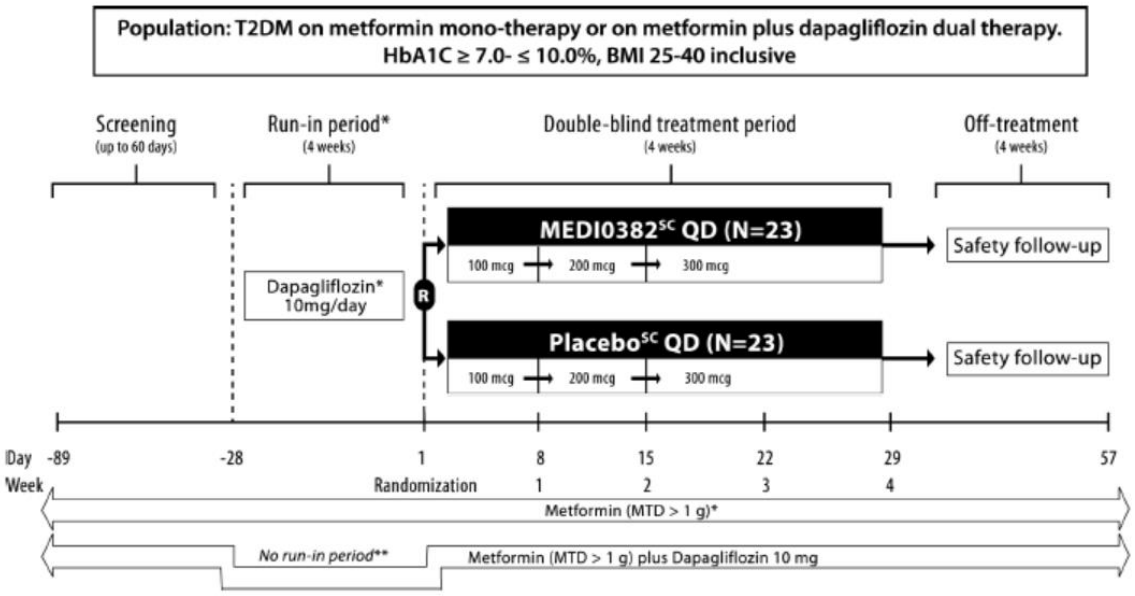
- To evaluate pancreatic and incretin hormone AUC profiles (ie, active glucagon-like peptide-1 [GLP-1], glucagon, insulin, and c-peptide) as measured by MMTT in subjects treated with dapagliflozin and metformin receiving MEDI0382 or placebo for 28 days
- To compare the fasting free fatty acid (FFA) levels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

2.2 Study Design

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

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

Figure 2.2-1 Study Flow Diagram



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

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

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

2.3 Treatment Assignment and Blinding

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

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

This is a double-blind study in which MEDI0382 and placebo are not identical in the prefilled syringe titration volumes. Neither the subject nor any of the investigator or sponsor staff who are involved in the treatment or clinical evaluation of the subjects will be aware of the treatment received (ICH E9).

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

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

2.4 Sample Size

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

3 STATISTICAL METHODS

3.1 General Considerations

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

All available data will be included in the analyses and missing data will not be imputed, except in a last observation carried forward (LOCF) analysis and as specified in the

calculation of the AUC values. When LOCF is used to impute for missing post-baseline data, only post-baseline data will be carried forward (eg, baseline data will not be carried forward). Unless otherwise specified, baseline values will be defined as the last valid assessment prior to the first administration of study medication (MEDI0382 or placebo).

All statistical tests will be 2-sided at an alpha level of 5% 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). The analytical results generated from SAS programs will follow MedImmune SAS programming standards and will be validated according to MedImmune SAS validation procedures.

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	Randomized subjects who receive any investigational product (MEDI0382 or placebo) analyzed according to their randomized treatment group.
As-treated Population	Subjects who receive any investigation product (MEDI0382 or placebo) analyzed according to the treatment they actually receive.
MEDI0382 PK Population	Subjects who receive at least 1 dose of investigational product (MEDI0382 or placebo) and have at least 1 MEDI0382 PK sample taken that is above the lower limit of quantitation.
Dapagliflozin PK Population	Subjects who receive at least 1 dose of investigational product (dapagliflozin or placebo) and have at least 1 dapagliflozin PK sample for dapagliflozin taken that is above the lower limit of quantitation.
Ketone PK Population	Subjects who receive at least 1 dose of investigational product (MEDI0382 or dapagliflozin or placebo) and have at least 1 ketone PK sample taken that is above the lower limit of quantitation.
[redacted]	[redacted]

3.3 Study Subjects

3.3.1 Subject Disposition and Completion Status

A summary of subject eligibility and randomization as well as treatment group received (including a summary of subjects randomized but not treated) will be provided. In addition, disposition of subjects throughout the study with respect to completion of treatment and end of study will be provided.

3.3.2 Demographics and Baseline Characteristics

Demographic information related to sex, age, race, weight, height, and body mass index (BMI) will be presented by treatment group and for all subjects combined. A summary of baseline disease characteristics may include, but not be limited to duration of T2DM, diabetes complications, HbA1c, fasting plasma glucose, eGFR, background therapy for diabetes (eg, metformin monotherapy or metformin + dapagliflozin).

3.3.3 Study Drug Exposure

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

3.3.4 Concomitant Medications

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

3.4 Efficacy Analyses

3.4.1 Primary Efficacy Endpoint(s) and Analyses

3.4.1.1 Primary Efficacy Endpoint(s)

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

3.4.1.2 Handling of Dropouts and Missing Data

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

3.4.1.3 Primary Efficacy Analysis

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

3.4.2 Secondary Efficacy Endpoint(s) and Analyses

3.4.2.1 Secondary Efficacy Endpoint(s)

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

3.4.2.2 Handling of Dropouts and Missing Data

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

3.4.2.3 Secondary Efficacy Analyses

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

3.4.3 Exploratory Efficacy Endpoint(s) and Analyses

3.4.3.1 Exploratory Efficacy Endpoint(s)

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

3.4.3.2 Exploratory Efficacy Analyses

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

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

3.5 Pharmacodynamic Exploratory Endpoint(s) and Analyses

3.5.1.1 Pharmacodynamic Endpoint(s)

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

3.5.1.2 Analysis of Pharmacodynamic Endpoint(s)

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

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

3.6 Safety Analyses

3.6.1 Adverse Events and Serious Adverse Events

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

3.6.2 Adverse Events of Special Interest

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

3.6.3 Deaths and Treatment Discontinuations due to Adverse Events

Death and AEs resulting in permanent discontinuation from the study drug will be summarized by treatment. The summary includes overall, categorized by MedDRA system organ class, and preferred term.

3.6.4 Clinical Laboratory Evaluation

Hematology, serum chemistry, and urinalysis laboratory evaluations will be performed during the study. The hematology and serum chemistry (including amylase, lipase, lactate, and calcitonin) parameters as well as their changes from baseline will be summarized with descriptive statistics (number of subjects, mean, and standard deviation, median, minimum and maximum) by treatment group at each time point. The urinalysis results will be listed. The hematology and serum chemistry results will also be classified as low, normal, or high. The urinalysis results will be classified as normal or abnormal. The shift from baseline hematology, serum chemistry, and urinalysis results will be summarized by treatment group at each time point.

3.6.5 Other Safety Evaluations

3.6.5.1 Vital Signs

Vital signs including pulse rate (beats/min), blood pressure (mm Hg), temperature (^{o}C), and respiratory rate (breaths/min), as well as the change from baseline for each of those parameters will be descriptively summarized by treatment group at each time point.

The 24-hour average ambulatory blood pressure monitoring (ABPM) pulse rate (beats/min) and systolic and diastolic blood pressure (mm Hg) from the ABPM will be summarized by treatment group at each time point. The change from baseline (Day -2) for the 24-hour average pulse rate and systolic and diastolic blood pressure at each post-baseline visit will be analyzed with an analysis of covariance with an effect for treatment and the baseline value as the covariate. The above summary and analyses will also be conducted for pulse rate, systolic blood pressure, and diastolic blood pressure during asleep and awake periods.

3.6.5.2 Electrocardiogram

Electrocardiogram parameters will be assessed using standard 12-lead electrocardiography. The following Electrocardiogram (ECG) parameters as well as the change from baseline for each of those parameters will be reported and descriptively summarized by treatment group at each of the specified time points: Heart rate (beats/min), RR (msec), PR (msec), QRS (msec), and QT (msec) intervals and the QT corrected interval.

The normality/abnormality of the ECG evaluation will be summarized using frequency tables of the number of subjects with a normal/abnormal ECG evaluation at each scheduled visit.

[redacted]

[redacted]

3.8 Pharmacokinetics

For MEDI0382, Dapagliflozin and β-hydroxybutyrate, actual time of sampling, rather than nominal (planned) sampling time, will be used to derive PK parameters. Nominal sampling time will be used for the summary of PK concentrations and will be utilized in the descriptive summaries in mean plots. Missing PK parameters will not be imputed.

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

1. C_{max}: The first occurrence of the maximum observed plasma concentration determined directly from the raw concentration-time data

2. t_{max}: The first time at which C_{max} is observed will be determined directly from the raw concentration-time data.
3. $C\tau$: trough concentrations from the plasma concentration-time data at the end of the dosing interval (i.e. 24 hours).
4. $AUC\tau$: Area under the plasma concentration time curve at the end of the dosage interval τ.
5. Ro: observed accumulation ratio will be calculated using both the AUC and Ctrough methods, where data allows, as follows: Ro = $AUC\tau dayi/AUC\tau day1$ and Ro = $C\tau dayi/C\tau day1$.

If data allows additional parameters may be derived for MEDI0382 and Dapagliflozin such as t half: the apparent terminal elimination half-life ($t_{1/2}$) obtained as the ratio of $\ln 2/\lambda_z$, where λ_z is the terminal phase rate constant estimated by linear regression analysis of the log transformed concentration-time data; and Cl/F: the apparent clearance calculated as $CL/F=Dose/AUC(0-\infty)$.

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

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

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

4 INTERIM ANALYSIS

No interim analysis is planned.

5 VERSION HISTORY

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

Certificate Of Completion

Envelope Id: E9F8709D1D674C5FA0E4FE714672C609 Status: Completed

Subject: Please DocuSign: MEDI0382 D5670C00007 SAP Final v1.0 signature page.docx, D5670C00007 Statistic...

iSave Workspace ID:

Source Envelope:

Document Pages: 18 Signatures: 5 Envelope Originator:

Certificate Pages: 5 Initials: 0 [redacted]

[redacted]

IP Address: 104.129.194.134

Record Tracking

Status: Original Holder: [redacted] Location: DocuSign

7/6/2018 2:29:14 PM [redacted]

Signer Events	Signature	Timestamp
[redacted]	[redacted]	Sent: 7/6/2018 2:32:29 PM Viewed: 7/6/2018 2:39:39 PM Signed: 7/6/2018 6:32:20 PM
Electronic Record and Signature Disclosure: Not Offered via DocuSign		
[redacted] Security Level: Email, Account Authentication (None)	[redacted] Using IP Address: 104.129.194.127	Sent: 7/6/2018 2:32:29 PM Viewed: 7/6/2018 3:28:16 PM Signed: 7/6/2018 3:28:35 PM
Electronic Record and Signature Disclosure: Accepted: 7/6/2018 3:28:16 PM ID: 1d2851a7-0b74-4af4-857c-4991781b941b		
[redacted] AstraZeneca Security Level: Email, Account Authentication (None)	[redacted] Using IP Address: 104.129.194.134	Sent: 7/6/2018 2:32:30 PM Viewed: 7/6/2018 2:32:41 PM Signed: 7/6/2018 2:32:47 PM
Electronic Record and Signature Disclosure: Not Offered via DocuSign		
[redacted] (None)	[redacted] Using IP Address: 104.129.194.70	Sent: 7/6/2018 2:32:30 PM Viewed: 7/10/2018 6:12:31 PM Signed: 7/10/2018 6:12:42 PM
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	7/6/2018 2:32:31 PM
Certified Delivered	Security Checked	7/10/2018 6:12:32 PM
Signing Complete	Security Checked	7/10/2018 6:12:42 PM
Completed	Security Checked	7/10/2018 6:12:42 PM

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.