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

Sponsor Protocol Number: D5670C00007

Application Number: 2017-002817-78

Investigational Product: MEDI0382

Sponsor: MedImmune Limited, a wholly owned subsidiary of AstraZeneca, Milstein Building, Granta Park, Cambridge, CB21 6GH, UK

Medical Monitor: [redacted], MedImmune

Contract Research Organization: Covance Clinical and Periapproval Services Limited Osprey House, Westacott Way, Maidenhead, SL6 3QH, UK

Protocol History, Date: **Original Protocol, 19Sep2017**

PROTOCOL SYNOPSIS

TITLE

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.

HYPOTHESES

Primary Hypothesis:

- The administration of MEDI0382 subcutaneously (SC) once daily will improve glycemic control in overweight/obese subjects with type 2 diabetes mellitus (T2DM) treated concurrently with dapagliflozin and metformin.
- **Secondary Hypotheses:**
- The administration of MEDI0382 SC will have an acceptable safety profile and be well tolerated when coadministrated with dapagliflozin and metformin
- The pharmacokinetic (PK) profile of MEDI0382 will remain unchanged in the presence of coadministered dapagliflozin and metformin.
- [redacted]
- The administration of MEDI0382 decreases 24-hour glycemic variation when coadministered with dapagliflozin and metformin.

OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary	
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	• Change from baseline (Day -1) to the end of 28 days of treatment (Day 28) in glucose AUC from 0 to 4 hours (AUC_{0-4h}) as measured by a MMTT • Percentage change from baseline (Day -1) to the end of 28 days of treatment (Day 28) in glucose AUC_{0-4h} as measured by a MMTT
Secondary	
To compare the safety and tolerability profile of MEDI0382 given SC (titrated up to a dose level of 300 µg) compared to placebo after 28 days of treatment in subjects treated with dapagliflozin and metformin	Measures of safety and tolerability include: • Incidence of treatment-emergent adverse events (TEAEs) and treatment-emergent serious adverse events (TESAEs) • Clinically important changes in 12-lead electrocardiogram (ECG), vital signs (including 24-hour heart rate and blood pressure), physical examination, and clinical laboratory evaluations
To evaluate the PK profile of MEDI0382 and dapagliflozin (in subjects treated with dapagliflozin, metformin, and MEDI0382) and dapagliflozin (in subjects treated with dapagliflozin, metformin, and placebo)	PK profile of both MEDI0382 and dapagliflozin administered simultaneously and dapagliflozin administered with placebo include: • Plasma AUC from zero to infinity (AUC_{0-inf}), from zero to last observation (AUC_{0-last}) and over the dosing duration (AUC_{tau}) • Maximum-observed serum drug concentration (C_{max})

	• Time to maximum-observed serum drug concentration (t_{max}) • Terminal elimination half-life ($t_{1/2}$) • Apparent clearance (Cl/F)
[redacted]	[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	• 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 standard deviation (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)
Exploratory	
To compare additional measures of glucose control (fasting plasma glucose [FPG] and hemoglobin A1c [HbA1c]) in subjects treated with dapagliflozin and	• Change from baseline (Day -1) to Day 28 in FPG

metformin receiving MEDI0382 or placebo for 28 days	• Change from baseline (Day -2) to Day 28 in HbA1c
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	• Change from baseline (Day -1) to Day 28 in GLP-1, glucagon, insulin, and c-peptide $AUC_{0\text{-}4h}$ as measured by MMTT
To compare the fasting free fatty acid (FFA) levels in subjects treated with dapagliflozin and metformin receiving MEDI0382 or placebo for 28 days	• Change from baseline (Day -1) to Days 7, 14, and 28 in fasting FFA level
To compare plasma ketone profile (β-hydroxybutyrate) in subjects treated with dapagliflozin and metformin receiving MEDI0382 or placebo for 28 days	• β-hydroxybutyrate profile to include $AUC_{0\text{-}inf}$, $AUC_{0\text{-}last}$, C_{max}, and t_{max}
To compare the change in body weight after 28 days of treatment with MEDI0382 or placebo in subjects treated with dapagliflozin and metformin	• 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
To evaluate 24-hour urinary glucose excretion in subjects treated with dapagliflozin and metformin receiving MEDI0382 or placebo for 28 days	• Total glucose excreted in urine collected for 24 hours

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. 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 posttreatment follow-up period. There will be 2 inpatient stays.

Four-week run-in period:

Following a screening period of up to 60 days, eligible subjects on metformin monotherapy only will enter a 4-week run-in period during which time they will receive oral dapagliflozin 10 mg once a day for 28 days prior to randomization.

Four-week treatment period:

Subjects will be admitted to the clinical unit on Day -2. Study subjects will undergo initial safety assessments including but not limited to blood collection for laboratory tests, medical history, abbreviated physical examination, vital signs, and training on SC injection administration. At this time, an ambulatory blood pressure monitoring (ABPM) device will be fitted on Day -2 and worn for 24 hours. Subjects will be expected to conduct daily finger-prick testing for ketone measurements throughout the treatment period. On Day -1, after an overnight fast of approximately 10 hours and verification of eligibility criteria, subjects will undergo their first MMTT. After the MMTT, subjects will be fitted with a CGM sensor on the contralateral arm to the ABPM, which will expire and be replaced every 14 days. Subjects will be expected to wear this sensor for the duration of treatment. Other procedures on Day -1 include blood collection for laboratory tests, dapagliflozin and ketones PK sampling, and training on SC administration. On Day -1, the subject will have the option to remain in the unit or return home. Discharged subjects must ensure they undergo an overnight fast for approximately 10 hours, and they will return the clinic on Day 1. Subjects can be randomized after confirming eligibility at any time from Day -1 to Day 1 (predose) to receive either MEDI0382 or placebo. On Day 1, following an overnight fast, dosing will commence after predose safety measures including vital signs, an ECG, and blood collection for laboratory tests; blood collection for dapagliflozin PK, ketones PK, and ADA; and measurement of weight are performed. Subjects will then receive the following:

- MEDI0382 SC once daily (titrated up from 100 µg for 7 days to 200 µg for 7 days and 300 µg for 14 days) in the morning for 28 days (N = 23)
- Placebo SC once daily in the morning for 28 days (N = 23)

Subjects will be monitored for safety, glucose, and ketones and will be discharged from the unit approximately 6 hours postdose. Capillary glucose and ketones monitoring will be done at the site using a glucometer. A 24-hour urine collection for glucose excretion will be collected from Day 1 to Day 2. The subject will return to the unit on Day 2 for safety monitoring and supervision of investigational product administration.

Subjects will then return to the clinical unit at weekly intervals until a maintenance dose of 300 µg is achieved. Subjects will return to the unit for outpatient visits on Days 7, 8, 14, 15, and 22 to undergo safety assessments including but not limited to an abbreviated physical examination and ECG (Days 7, 14, and 22), vital signs (all visits, with ABPM fitted on Day 14 only), urine tests (eg, pregnancy test on Day 14 and Day 22), and blood collection for laboratory tests (Days 7, 14, and 22). MEDI0382, dapagliflozin, and ketones PK sampling will be performed on Days 7, 8, 14, and 15. Uptitration of SC investigational product will occur on Day 8 and Day 15. After uptitration of investigational product, subjects will be monitored for safety, glucose, and ketones and will be discharged 6 hours postdose. The CGM device will be replace on Day 14.

Subjects will be expected to return to the unit for final admission on Day 27 to Day 29 to undergo final safety assessments including but not limited to an abbreviated physical examination, an ECG, and urine tests (eg, pregnancy and drug and alcohol screening) on Day 27 and vital signs (including ABPM) and blood collection for laboratory tests on Day 28. On Day 28, following an overnight fast of 10 hours the day before, subjects will undergo a final MMTT. On Day 28, PK sampling of MEDI0382, dapagliflozin, and ketones will be taken relative to time zero of administration of investigational product. A 24-hour urine collection for glucose excretion will be collected from Day 28 to Day 29. On Day 29, vital signs, a measurement of weight, and additional blood collection for ADA and MEDI0383, dapagliflozin, and ketones PK will be performed, and subjects will be discharged if no safety concerns are identified.

Safety follow-up period:

Once subjects have completed the 4-week combination treatment phase, they will be followed up for safety for an additional 4 weeks. Subjects will continue to wear the CGM until approximately 28 days after the last dose and will continue to test their ketone level once daily prebreakfast until approximately 14 days after the last dose using the testing strips provided.

TARGET SUBJECT POPULATION

Male or female subjects ≥ 18 years of age with a body mass index ≥ 25 and ≤ 40 kg/m^2 and a diagnosis of T2DM treated with metformin monotherapy or metformin plus dapagliflozin dual therapy with an inadequate blood glycemic control (defined by an HbA1c of ≥ 7.0% to ≤ 10.0%). Females of childbearing potential must not be pregnant and lactating females will be excluded. Females of childbearing potential should be using appropriate contraception.

INVESTIGATIONAL PRODUCT, DOSAGE, AND MODE OF ADMINISTRATION

Run-in period:

Eligible subjects on metformin monotherapy will receive oral dapagliflozin 10 mg once a day for 28 days, which will be provided by the sponsor.

Treatment period:

Following the run-in period for subjects on metformin monotherapy or screening period for subjects on dual therapy, subjects will be randomized as follows:

- MEDI0382 SC once daily (titrated up from 100 µg for 7 days to 200 µg for 7 days and 300 µg for 14 days) in the morning for 28 days (N = 23)
- Placebo SC once daily in the morning for 28 days (N = 23)

The dose of MEDI0382 will be titrated up from a starting dose of 100 µg in 100 µg increments to the target dose of 300 µg over 2 weeks. Subjects entering the study must have been treated with daily stable oral doses of blood glucose-lowering therapy with metformin (maximum tolerated dose ≥ 1 gram) for at least 8 weeks prior to screening. The sponsor will provide dapagliflozin to all subjects during the treatment period.

STATISTICAL ANALYSIS PLAN

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 the relative change from baseline in glucose $AUC_{0\text{-}4h}$ at a two-sided alpha of 5%, assuming a common 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.

Statistical analyses:

Efficacy and pharmacodynamics (PD) data will be analyzed based on the Intent-to-Treat population. The primary endpoints, change and % change in glucose $AUC_{0\text{-}4h}$ as measured by a MMTT from baseline to the end of 28 days of treatment, will be summarized by treatment group. Statistical comparisons of these endpoints between MEDI0382/dapagliflozin/metformin and placebo/dapagliflozin/metformin treatment groups will be performed using an analysis of covariance by adjusting baseline and treatment group with last-observation-carried-forward (LOCF) approach to handle missing data. Other efficacy and PD endpoints including CGM glucose parameters ($AUC_{0\text{-}24h}$, 24-hour mean glucose, SD, CV, MAGE, % of 24-hour glucose readings in euglycemic, hyperglycemic, hypoglycemic, and clinically-significant hypoglycemic ranges), FPG, HbA1c, change from baseline in $AUC_{0\text{-}4h}$ of MMTT parameters (GLP-1, glucagon, insulin, and c-peptide), fasting FFA level, 24-hour urinary glucose excretion, and body weight will be summarized and analyzed similarly to the primary endpoints. For the proportion of subjects achieving ≥ 5% body weight loss from baseline after 28 days of treatment, statistical comparisons between MEDI0382/dapagliflozin/metformin and placebo/dapagliflozin/metformin treatment groups will be performed using a logistic regression by adjusting baseline and treatment group. Descriptive statistics at each time point will be provided by treatment group for efficacy and PD endpoints.

Safety analyses:

Safety data including TEAEs, vital signs, safety laboratory, and ECG data will be analyzed based on the As-treated population. Treatment-emergent AEs and TESAEs will be summarized according to the Medical Dictionary for Regulatory Activities by System Organ Class and Preferred Term for type, incidence, severity, and relationship to investigational product. Other safety data such as vital signs (including 24-hour ABPM) and clinical laboratory data will be summarized by treatment group at each time point. Additional analyses of these data may include the change from baseline to each postbaseline time point where appropriate. Electrocardiogram parameters will also be assessed and summarized descriptively.

Pharmacokinetic analyses:

Pharmacokinetic parameters such as, but not limited to, C_{max}, t_{max}, AUC, $t_{1/2}$, and accumulation ratio will be estimated from plasma concentration-time data for MEDI0382 and β-hydroxybutyrate at each dose level separately and for 10 mg dapagliflozin. Moreover, if data allow, additional parameters such as Cl/F may be derived for MEDI0382 at all dose levels and for 10 mg dapagliflozin. Descriptive statistics will be generated for PK parameters for MEDI0382 and dapagliflozin in each cohort. Subjects who have at least one measurable concentration time point of investigational product will be used for these analyses.

[redacted]

Interim analysis:

No interim analysis is planned.

TABLE OF CONTENTS

PROTOCOL SYNOPSIS 2
LIST OF ABBREVIATIONS 12
1 INTRODUCTION 14
1.1 Disease Background 14
1.2 MEDI0382 Background 14
1.3 Summary of Nonclinical Experience 15
1.4 Summary of Clinical Experience 15
1.5 Rationale for Conducting the Study 16
1.6 Benefit-risk and Ethical Assessment 17
1.6.1 Nausea and Vomiting 17
1.6.2 Hypoglycemia 18
1.6.3 Volume Depletion 18
1.6.4 Diabetic Ketoacidosis/Euglycemic Ketoacidosis 19
1.7 Research Hypotheses 21
1.7.1 Primary Hypothesis 21
1.7.2 Secondary Hypotheses 21
2 OBJECTIVES AND ENDPOINTS 21
2.1 Primary Objective and Associated Endpoints 21
2.2 Secondary Objectives and Associated Endpoints 22
2.3 Exploratory Objectives and Associated Endpoints 23
3 STUDY DESIGN 24
3.1 Description of the Study 24
3.1.1 Overview 24
3.1.2 Treatment Regimen 27
3.1.3 Dose Escalation 28
3.2 Study Design [redacted]
3.2.1 Dose Rationale 28
3.2.1.1 Dapagliflozin and Metformin 28
3.2.1.2 MEDI0382 28
3.2.2 Rationale for Study Population 30
3.2.2.1 Recruitment of Subjects with Type 2 Diabetes Mellitus and a Body Mass Index 25 to 40 kg/m^2 30
3.2.2.2 Recruitment of Subjects on Metformin and Dapagliflozin Therapy 30

3.2.2.3 Selection of Subjects with Type 2 Diabetes Mellitus and Stable Glycated Hemoglobin in the Range of 7.0% to 10.0% 31
3.2.3 Rationale for Endpoints 31
3.2.3.1 Primary Endpoint 31
3.2.3.2 Secondary Endpoints 31
3.2.3.3 Exploratory endpoints 33
4 MATERIALS AND METHODS 33
4.1 Subjects 33
4.1.1 Number of Subjects 33
4.1.2 Inclusion Criteria 33
4.1.3 Exclusion Criteria 34
4.1.4 Subject Enrollment and Randomization 36
4.1.5 Withdrawal from the Study 36
4.1.6 Discontinuation of Investigational Product 37
4.1.7 Replacement of Subjects 38
4.1.8 Withdrawal of Informed Consent for Data and Biological Samples 38
4.2 Schedule of Study Procedures 38
4.2.1 Enrollment/Screening Period 38
4.2.2 Run-in Period 39
4.2.3 Randomized Treatment Period 40
4.2.4 Follow-up Period 49
4.2.4.1 Early Discontinuation Visit or Unscheduled Study Visit 50
4.3 Description of Study Procedures 50
4.3.1 Efficacy 50
4.3.1.1 Mixed-meal Tolerance Test 50
4.3.1.2 Body Weight 51
4.3.2 Safety Assessments 51
4.3.2.1 Medical History and Physical Examination 51
4.3.2.2 Assessment of the Injection Site 52
4.3.2.3 Vital Signs 52
4.3.2.4 Electrocardiograms 53
4.3.3 Clinical Laboratory Tests 53
4.3.4 Pharmacokinetic Evaluation and Methods 55
[redacted]
4.3.6 Pharmacodynamic Evaluation and Methods 56
4.3.6.1 Training for Application and Wearing of Continuous Glucose Monitoring Sensor 56

4.3.6.2 Glucometer Measure Capillary Blood Glucose/Ketones Reading 57
4.3.6.3 Training for Application and Wearing of ABPM Device 57
4.3.7 Estimate of Volume of Blood to Be Collected 58
4.4 Study Suspension or Termination 58
4.5 Investigational Products 59
4.5.1 Identity of Investigational Product(s) 59
4.5.1.1 Investigational Product Handling 60
4.5.1.2 Investigational Product Inspection 61
4.5.1.3 Treatment Administration 61
4.5.1.4 Monitoring of Dose Administration 62
4.5.1.5 Reporting Product Complaints 62
4.5.2 Additional Study Medications 63
4.5.3 Labeling 63
4.5.4 Storage 63
4.5.5 Treatment Compliance 63
4.5.6 Accountability 64
4.6 Treatment Assignment and Blinding 64
4.6.1 Methods for Assigning Treatment Groups 64
4.6.2 Methods for Ensuring Blinding 64
4.6.3 Methods for Unblinding 65
4.6.3.1 Unblinding in the Event of a Medical Emergency 65
4.6.3.2 Unblinding for PK and Immunogenicity Analysis 65
4.7 Restrictions During the Study and Concomitant Treatment(s) 66
4.7.1 Permitted Concomitant Medications 66
4.7.2 Prohibited Concomitant Medications 66
4.8 Statistical Evaluation 67
4.8.1 General Considerations 67
4.8.1.1 Analysis Population 67
4.8.2 Sample Size and Power Calculations 67
4.8.3 Efficacy 68
4.8.3.1 Primary Efficacy Analysis 68
4.8.3.2 Secondary Efficacy Analyses 68
4.8.3.3 Exploratory Analyses 69
4.8.4 Safety 69
4.8.4.1 Analysis of Adverse Events 69
4.8.4.2 Analysis of Safety Data 70
4.8.4.3 Analysis of Clinical Laboratory Parameters 70

4.8.5Analysis of [redacted] Pharmacokinetics 70
4.8.5.1 Pharmacokinetic Analyses 70
[redacted]
4.8.6Interim Analysis 71
5 ASSESSMENT OF SAFETY 71
5.1 Definition of Adverse Events 71
5.2 Definition of Serious Adverse Events 72
5.3 Definition of Adverse Events of Special Interest 72
5.3.1Hepatic function Abnormalities 72
5.4 Recording of Adverse Events 73
5.4.1Time Period for Collection of Adverse Events 73
5.4.2Follow up of Unresolved Adverse Events 73
5.5 Reporting of Serious Adverse Events 73
5.6 Other Events Requiring Immediate Reporting 74
5.6.1Overdose 74
5.6.2Hepatic Function Abnormality 74
5.6.3Pregnancy 75
5.6.3.1 Maternal Exposure 75
6 STUDY AND DATA MANAGEMENT 76
6.1 Training of Study Site Personnel 76
6.2 Monitoring of the Study 76
6.2.1Source Data 76
6.2.2Study Agreements 77
6.2.3Archiving of Study Documents 77
6.3 Study Timetable and End of Study 77
6.4 Data Management 77
6.5 Medical Monitor Coverage 78
7 ETHICAL AND REGULATORY REQUIREMENTS 78
7.1 Ethical Conduct of the Study 78
7.2 Subject Data Protection 78
7.3 Ethics and Regulatory Review 78
7.4 Informed Consent 79
7.5 Changes to the Protocol and Informed Consent Form 80
7.6 Audits and Inspections 80
8 REFERENCES 81
9 CHANGES TO THE PROTOCOL 82
10 APPENDICES 83
10.1 Appendix 1 - Signatures 83

10.2 Appendix 2 - Contraception Guidance 85
10.3 Appendix 3 - Additional Safety Guidance 86
10.4 Appendix 4 - National Institute of Allergy and Infectious Diseases and Food and Allergy Anaphylaxis Network Guidance for Anaphylaxis Diagnosis 89
10.5 Appendix 5 - Actions Required in Cases of Increases in Liver Biochemistry and Evaluation of Hy's law 90
10.6 Appendix 6 - Biological Samples 94

LIST OF IN-TEXT TABLES

Table 2.1-1 Primary Objective(s) and Associated Endpoints 21
Table 2.2-1 Secondary Objectives and Associated Endpoints 22
Table 2.3-1 Exploratory Objectives and Associated Endpoints 23
Table 3.2.1-1 Proposed Study Doses and Predicted Safety Margins Based on Safety Data from the Cynomolgus Monkey 30
Table 4.2.1-1 Schedule of Screening Period Procedures 39
Table 4.2.2-1 Schedule of Run-in Period Procedures 40
Table 4.2.3-1 Schedule of Treatment Period Procedures 42
Table 4.2.4-1 Schedule of Follow-up Procedures 49
Table 4.5.1-1 Identification of Investigational Products 59

LIST OF IN-TEXT FIGURES

Figure 3.1.1-1 Study Flow Diagram 27

LIST OF ABBREVIATIONS

Abbreviation or Specialized Term	Definition
ABPM	ambulatory blood pressure monitoring
[redacted]	[redacted]
AE	adverse event
AESI	adverse event of special interest
ALT	alanine transaminase
AST	aspartate transaminase
AUC	area under the concentration-time curve
AUC_{0-4h}	area under the concentration-time curve from zero to 4 hours
AUC_{24h}	area under the concentration-time curve at 24 hours
AUC_{0-inf}	area under the concentration-time curve from zero to infinity
AUC_{0-last}	area under the concentration-time curve from zero to last observation
AUC_{tau}	area under the concentration-time curve during the dosing period
BMI	body mass index
BP	blood pressure
CGM	continuous glucose monitoring
CI	confidence interval
Cl/F	apparent clearance
C_{max}	maximum-observed serum concentration
CSP	clinical study protocol
DKA	diabetes ketoacidosis
ECG	electrocardiogram
EDC	electronic data capture
eCRF	electronic case report form
eDKA	euglycemic diabetes ketoacidosis
eGFR	estimated glomerular filtration rate
FFA	Free fatty acid
FPG	fasting plasma glucose
GCP	Good Clinical Practice
GI	Gastrointestinal
GLP-1	glucagon-like peptide-1
GMP	Good Manufacturing Practice
HbA1c	hemoglobin A1c
HR	heart rate
IB	investigator's brochure
ICF	informed consent form
ICH	International Council for Harmonization
IEC	Independent Ethics Committee

Abbreviation or Specialized Term	Definition
IFU	instructions for use
ITT	intent-to-treat
LLN	lower limit of normal
LOCF	last observation carried forward
LS	least squares
MAGE	mean amplitude of glucose excursion
MedDRA	Medical Dictionary for Regulatory Activities
MMTT	mixed meal tolerance test
MDRD	Modification of Diet in Renal Disease
MTD	maximum tolerated dose
NOAEL	no-observed-adverse-effect level
OTC	over-the-counter
PD	pharmacodynamic(s)
PK	pharmacokinetic(s)
RR	respiratory rate
SAE	serious adverse event
SC	subcutaneous(ly)
SD	standard deviation
SGLT2	sodium-glucose cotransporter-2
SID	subject identification
T2DM	type 2 diabetes mellitus
$t_{1/2}$	terminal elimination half-life
TBL	total bilirubin
TEAE	treatment-emergent adverse event
TESAE	treatment-emergent serious adverse event
t_{max}	time to maximum-observed serum drug concentration
ULN	upper limit of normal

1 INTRODUCTION

1.1 Disease Background

The rising prevalence of type 2 diabetes mellitus (T2DM) and obesity is a cause of substantial health and economic burden worldwide. In many cases of T2DM, significant weight loss (typically 5% of body weight or more) can promote improvements in glycemic control, and it may even slow or reverse disease progression (Petersen et al, 2005). Many existing therapies for T2DM focus upon lowering blood glucose; however, there is a major unmet need for treatments that improve glycemic control and achieve disease-modifying weight loss simultaneously.

Achieving optimal glycemic control early in the course of T2DM is an important goal for patients and treating physicians. Early interventions may prevent disease progression and decrease the risk of developing long-term T2DM comorbidities. Traditional step-wise pharmacotherapy begins with metformin as first-line therapy for the treatment of T2DM; however, patients often require combination therapy to achieve and maintain glycemic control because of the progressive nature of the disease. The combination of dapagliflozin and metformin is a common dual oral therapy in T2DM patients who fail treatment with monotherapy. The addition of a third noninsulin agent may be considered in patients with hemoglobin A1c (HbA1c) above the individualized target after 3 months of treatment with a combination of 2 drugs.

Dapagliflozin (Forxiga) is a potent and highly selective inhibitor of sodium-glucose cotransporter-2 (SGLT2) and is currently approved for improvement of glycemic control in adults with T2DM as monotherapy or as add-on combination therapy with metformin and other oral antiglycemic therapies. SGLT2 is localized to the renal proximal tubule where it reabsorbs most of the approximately 180 g of glucose normally filtered through the glomeruli each day. Inhibition of glucose reabsorption leads to glycosuria and consequently to glycemic-lowering effects including decreased levels of fasting plasma glucose (FPG) and HbA1c. In addition, the caloric loss associated with the excreted glucose is associated with body weight loss. Dapagliflozin has a half-life of approximately 12 hours, thus allowing for once daily oral administration. Additional information can be found in Forxiga's Summary of Product Characteristics (Forxiga Summary of Product Characteristics, 2017).

1.2 MEDI0382 Background

MEDI0382 is briefly described below. Refer to the current Investigator's Brochure (IB) for details. MEDI0382 is a synthetic peptide with both glucagon-like peptide-1 (GLP-1) and

glucagon-receptor coagonist activity, and it is under development for the treatment of T2DM and obesity. GLP-1 receptor agonists are established treatments for T2DM that improve glycemic control, delay gastric emptying, and depress appetite, thus leading to modest but unsustained weight loss (typically 3% versus baseline at 1 year). Glucagon has similar effects to GLP-1 on gastric emptying and appetite and has also been shown to promote increased energy expenditure (Lynch et al, 2014; Habegger et al, 2013). Oxyntomodulin, a naturally-occurring peptide with GLP-1 and glucagon-receptor coagonist activity, has been shown to promote weight loss through effects on appetite and energy expenditure (Wynne et al, 2006). In addition, coinfusion of GLP-1 and glucagon has synergistic effects on reducing food intake and promoting weight loss in human subjects (Bagger et al, 2015).

1.3 Summary of Nonclinical Experience

Refer to the current MEDI0382 IB for a complete summary of nonclinical information. Consistent with other GLP-1 receptor agonists, MEDI0382 exposure resulted in the anticipated pharmacologic effects on body weight (reduced gain or loss), food consumption (sporadic reductions), gastric emptying (delayed in rats), liver (changes indicative of an effect on energy homeostasis), pancreas (hypercellularity of the pancreatic islets, acinar degranulation), adrenal glands (increased prominence of the zona glomerulosa), and lungs (increased macrophage) and rodent-specific effects on the thyroid gland (C-cell hyperplasia/adenoma/carcinoma), which had partially or fully reversed (with the exception of adenoma/carcinoma) by the end of the treatment-free periods. Increases in heart rate (HR), diastolic and mean arterial blood pressure (BP), and nocturnal body temperature noted in cynomolgus monkeys were not associated with significant effects on QTc and PR interval, QRS duration, systolic BP, or qualitative electrocardiogram (ECG) abnormalities. In general, these effects were considered to be consistent with the known effects of licensed GLP-1 receptor agonists. MEDI0382 was not genotoxic and was not considered to be toxic to fertility or embryo-fetal development in the rat and rabbit, with most findings generally being associated with maternal stress.

1.4 Summary of Clinical Experience

In prior clinical experience with MEDI0382 (Cohort 4 of Study D5670C00002), 51 overweight and obese subjects with T2DM were randomized to receive MEDI0382 titrated up from a starting dose of 100 µg to a dose of 200 µg or placebo for up to 41 days. MEDI0382 was shown to have a similar tolerability to marketed GLP-1 receptor agonists, with no significant increases in systolic or diastolic BP observed. Following a mixed-meal tolerance test (MMTT), a least squares (LS) mean for percent change from baseline in glucose area under the concentration-time curve from 0 to 4 hours (AUC_{0-4h}) of -32.78%

(90% confidence interval [90% CI] -36.98, -28.57) was observed in MEDI0382-treated subjects versus -10.16% (90% CI -14.10, -6.21) in placebo-treated subjects ($p < 0.0001$). A LS mean change from baseline in body weight of -3.84% (90% CI -4.55, -3.12) was observed in MEDI0382-treated subjects versus -1.70% (90% CI -2.40, -1.01) in placebo-treated subjects ($p < 0.001$). In the same study (D5670C00002), doses of 300 µg were studied for 7 days in 2 separate cohorts, each exploring different uptitration schedules to reach this dose. The tolerability and efficacy profiles were similar to that observed in previous cohorts.

The combination of MEDI0382 with dual therapy of dapagliflozin and metformin has not been studied previously. However, given the commercial availability of dapagliflozin, this drug (and other SGLT2 inhibitors) will likely be a concomitant medication in future Phase 3 clinical studies of MEDI0382. Because the 2 agents exert their glycemic and weight-lowering effects via different mechanisms, the coadministration of the 2 compounds is expected to show improved effects on glycemic control and body weight as well as positive effects on BP (due to renal sodium loss driven by both SGLT2 inhibition and glucagon) compared to the oral, dual therapy of dapagliflozin and metformin given alone.

Given the likelihood of concomitant administration of MEDI0382 with SGLT2 inhibitors and metformin in the ongoing clinical development program, this exploratory study aims to (a) explore the efficacy and safety profile associated with the combination of MEDI0382 and dual therapy of SGLT2 inhibitor (dapagliflozin) and metformin and (b) characterize the profile of glycemic and metabolic control following administration of the triple combination therapy versus oral, dual-combination therapy.

1.5 Rationale for Conducting the Study

This is an exploratory Phase 2a efficacy study designed to investigate the effects on glycemic control and the safety profile associated with MEDI0382 titrated up to a dose level of 300 µg when coadministered with dapagliflozin and metformin in subjects with T2DM with a body mass index (BMI) of ≥ 25 kg/m^2 to ≤ 40 kg/m^2 and a HbA1c of $\geq 7.0\%$ to $\leq 10.0\%$. The results of this study will provide additional information about the efficacy, safety, tolerability, and pharmacokinetic (PK) profile of MEDI0382 in the likely intended clinical T2DM population.

Previous clinical experience with another GLP-1 monoagonist (exenetide) coadministered with dapagliflozin demonstrated that the combination resulted in significant reductions in HbA1c, FPG, weight, and systolic BP compared to either agent alone on a background of metformin (Frías et al, 2016). Therefore, the simultaneous administration of MEDI0382 with dapagliflozin is expected to show superior effects on glycemic control, body weight, and BP.

SGLT2 inhibitors have emerged as an effective therapy for glucose control and are likely to be a concomitant medication for subjects in the ongoing development program for MEDI0382. In addition, prior to including such subjects in Phase 3 studies, it is important to study the safety profile of MEDI0382 when given in combination with a SGLT2 inhibitor.

1.6 Benefit-risk and Ethical Assessment

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with International Council for Harmonization (ICH)/Good Clinical Practice (GCP) and applicable regulatory requirements.

MEDI0382 is a GLP-1 and glucagon receptor coagonist that promotes glucose lowering and weight loss and is targeted at subjects with T2DM. MEDI0382 has the potential to deliver improvements in glycemic control and lipid homeostasis, and it is predicted to be a useful therapy for T2DM.

The study design aims to minimize potential risks to subjects participating in this study based on the proposed inclusion/exclusion criteria, safety monitoring, and uptitration dosing schedule. Euglycemic diabetic ketoacidosis (eDKA) and hypovolemia are rare potential risks in subjects taking SGLT2 inhibitors. All subjects will be monitored throughout the study to ensure adequate glycemic control, ketones production, and intravascular volume status. Subjects will be given appropriate training in subcutaneous (SC) injection administration as well as use of any devices. Refer to the current MEDI0382 IB and dapagliflozin IB for further information on the potential benefits of MEDI0382 and dapagliflozin and an assessment of the potential and known risks. Identified risks for this study include nausea and vomiting. Potential risks for this study include hypoglycemia, volume depletion, and diabetes ketoacidosis (DKA).

1.6.1 Nausea and Vomiting

If a subject experiences nausea and vomiting in relation to the investigational product, in the first instance, conservative measures should be advised including reducing meal size and maintaining adequate hydration. When necessary, if there is persistent vomiting, a subject may be given an antiemetic to control his/her symptoms; a 5HT3 receptor antagonist (eg, ondansetron) or cyclizine is preferable in this situation rather than antiemetics, which may affect gastric emptying, and in particular dopamine receptor antagonists (eg, metoclopramide or domperidone).

1.6.2 Hypoglycemia

A hypoglycemic event is considered severe if associated with severe cognitive impairment requiring external assistance for recovery as defined by the American Diabetes Association. Spontaneous and clinically significant hypoglycemia defined as blood glucose < 54 mg/dL [3.0 mmol/L] with or without symptoms (Skyder et al, 2017) has not been seen in prior studies with MEDI0382 (up to a dose of 300 µg) alongside metformin. In addition, no episodes of major and minor hypoglycemia were reported in a randomized control study evaluating the efficacy and safety of exenatide (a GLP-1 monoagonist) in combination with dapagliflozin on a background of metformin (Frías et al, 2016). Furthermore, the mechanism of action of dapagliflozin (SGLT2 inhibition) does not interfere with normal endogenous glucose production in response to hypoglycemia and does not stimulates insulin release. Therefore, the risk of hypoglycemia in this study is considered low. However, all subjects will be provided with a diary and a glucometer and will be advised to check their capillary blood glucose level if they have symptoms of hypoglycemia (hunger, dizziness, shaking, sweating, or irritability) or feel unwell and will be expected to record the blood glucose level in their diary and contact the study team immediately. Management of the event should be as per standard local protocols. Hypoglycemia episodes should be documented as an adverse event (AE). Pharmacological treatments administered for hypoglycemia (eg, dextrose/glucose tablets, glucagon) should be recorded in the electronic case report form (eCRF) as concomitant medications.

1.6.3 Volume Depletion

MEDI0382 treatment with doses of up to 300 µg has been associated with a reduction in BP compared to baseline (-2.26 mmHg for diastolic BP and -8.49 mmHg for systolic BP) as estimated by ambulatory blood pressure monitoring (ABPM).

GLP-1 receptor agonist augment renal sodium excretion (Tonneijck et al, 2016). The mechanism by which a GLP-1 receptor agonist increase renal excretion is not well understood, but it includes vasodilation and possibly a direct effect on the renal tubule. (DeFronzo, 2017).

Dapagliflozin causes glucosuria and a subsequent mild osmotic diuretic effect and decreased intravascular volume. Due to its mechanism of action, dapagliflozin increases diuresis associated with a modest decrease in BP, which could be more pronounced in patients with very high blood glucose concentrations. Refer to the current dapagliflozin IB for more information on this risk.

The combined sodium loss and the potential tolerability risk (vomiting) resulting from GLP-1on a background of dapagliflozin raises a theoretical risk of higher incidence of symptomatic hypovolemia in subjects given both products in combination.

During the course of this study, the subject volume status will be closely monitored at each visit by assessing vital signs with BP (including lying and standing measurements). In addition, an ABPM device will be used during inpatient and outpatient visits.

Subjects will be advised to maintain adequate fluid intake throughout the study and to contact the study team if they experience dizziness or feel unwell. Management of volume depletion events should be as per standard local protocols.

Any episodes of symptomatic volume depletion (eg, hypotension, dehydration, or syncope) should be recorded as an AE.

1.6.4 Diabetic Ketoacidosis/Euglycemic Ketoacidosis

The glucagon component of MEDI0382 may lead to an increase in ketone production due to the potential increased oxidation of free fatty acid (FFA). It is also hypothesized that SGLT2-induced glycosuria predisposes subjects to increased ketogenesis (Qiu et al, 2017). Therefore, the combination of MEDI0382 and dapagliflozin (or any other SGLT2 inhibitor) might theoretically increase the risk to ketosis. In MEDI0382 clinical studies to date, there have been no cases of ketoacidosis (either hyper- or euglycemic cases).

Diabetes ketoacidosis, sometimes with normal glucose levels (ie, eDKA), has been reported very rarely in patients taking SGLT2 inhibitors (canagliflozin, dapagliflozin, or empagliflozin) in postmarketing surveillance (Rosenstock and Ferrannini, 2015). The clinical risk of developing DKA upon concomitant use of MEDI0382 and dapagliflozin is deemed very low. However, adequate monitoring will be implemented as described below to minimize the risk to study subjects.

During the course of the study, subjects will test their blood ketone level daily using ketone finger-prick testing strips and ketone monitor provided. In addition, subjects will be supplied with a paper diary, which will be reviewed by study staff at each visit. Subject will test their capillary ketone bodies every day before breakfast. Furthermore, subjects will be advised to check their blood for the presence of ketones and check their blood glucose using finger-prick testing with a glucometer if they experience any of the symptoms listed below and/or during acute illness.

Subjects will be instructed to contact the site immediately if the results indicate the presence of ketonemia (> 3 mmol/L), and/or elevated glucose levels (> 140 mg/dL [> 7.8 mmol/L]), and/or experience the following symptoms:

- Polyuria or polydipsia
- Malaise, generalized weakness, or fatigability
- Nausea and vomiting—may be associated with diffuse abdominal pain, decreased appetite, and anorexia
- Altered consciousness (eg, mild disorientation, confusion)

At the unit, the investigator should assess and determine whether the subject is at risk to develop ketoacidosis or is progressing towards ketoacidosis based on the subject's medical history, physical examination, and supportive laboratory results. The investigator should then determine whether the subject can be treated at the unit or should be referred to the local hospital for further evaluation and treatment of DKA.

The diagnosis of DKA will be made if the following are seen:

- Plasma glucose > 250 mg/dL (> 13.9 mmol/L)
- Increased anion gap metabolic acidosis (> 10-12 mEq/l) associated with pH < 7.30 and bicarbonate level < 18 mEq/l
- Elevated plasma ketone levels (> 3.0 mmol/L)

The diagnosis of eDKA will be made if the subject has the following:

- Increased anion gap metabolic acidosis as outlined above
- Elevated plasma ketones with plasma glucose < 250 mg/mL

However, any subject with a pH of < 7.35 associated with ketones > 3.0 mmol/L (regardless of glucose levels) may be considered to be progressing towards ketoacidosis. Therefore, such subjects should be discontinued from the study (Section 4.1.6) and monitored closely per local protocols.

Any event of DKA or eDKA should be managed according to standard local protocols.

In reporting DKA events, it is important to distinguish ketosis from DKA. Low levels of ketosis, in which blood or urine ketone values are elevated, can occur in individuals who follow a low-carbohydrate, high-fat diet or after prolonged periods of fasting. Ketosis is a

benign condition if symptoms are absent and the blood pH remains within normal limits (ie, no acidosis). In contrast, a DKA episode may be confirmed when a subject has potential symptoms of DKA as described above, elevated blood/urine ketone values, metabolic acidosis (characterized by low arterial blood pH, decreased serum bicarbonate, and an increased anion gap), and hyperglycemia (although some individuals may have normal or only mildly elevated blood glucose levels).

1.7 Research Hypotheses

1.7.1 Primary Hypothesis

The administration of MEDI0382 SC once daily will improve glycemic control in overweight/obese subjects with T2DM treated concurrently with dapagliflozin and metformin.

1.7.2 Secondary Hypotheses

- The administration of MEDI0382 SC will have an acceptable safety profile and be well tolerated when coadministrated with dapagliflozin and metformin.
- The PK profile of MEDI0382 will remain unchanged in the presence of coadministered dapagliflozin and metformin.
- The immunogenicity profile of MEDI0382 will remain unchanged in the presence of coadministered dapagliflozin and metformin.
- The administration of MEDI0382 decreases 24-hour glycemic variation when coadministrated with dapagliflozin and metformin.

2 OBJECTIVES AND ENDPOINTS

2.1 Primary Objective and Associated Endpoints

Table 2.1-1 Primary Objective(s) and Associated Endpoints

Type	Objective	Endpoints
Efficacy	To compare the change in glucose AUC as measured by a standardized MMTT in subjects treated with dapagliflozin and metformin receiving MEDI0382 or placebo for 28 days	• Change from baseline (Day-1) to the end of 28 days of treatment (Day 28) in glucose AUC_{0-4h} as measured by a MMTT • Percentage change from baseline (Day -1) to the end of 28 days of treatment (Day 28) in glucose AUC_{0-4h} as measured by a MMTT

AUC = area under the concentration-time curve; AUC_{0-4h} = area under the concentration-time curve from zero to 4 hours; MMTT = mixed meal tolerance test;

2.2 Secondary Objectives and Associated Endpoints

Table 2.2-1 Secondary Objectives and Associated Endpoints

Type	Objective [a]	Endpoints
Safety	To compare the safety and tolerability profile of MEDI0382 (titrated up to a dose level of 300 µg SC) compared to placebo after 28 days of treatment in subjects treated with dapagliflozin and metformin	Measures of safety and tolerability include: • Incidence of TEAEs and TESAEs • Clinically important changes in 12-lead ECG, vital signs (including 24-hour HR and BP), physical examination, and clinical laboratory evaluations
PK	To evaluate the PK profile of MEDI0382 and dapagliflozin (in subjects treated with dapagliflozin, metformin, and MEDI0382) and dapagliflozin (in subjects treated with dapagliflozin, metformin, and placebo)	PK profile of both MEDI0382 and dapagliflozin administered simultaneously and dapagliflozin administered with placebo include: • $AUC_{0\text{-}inf}$, $AUC_{0\text{-}last}$, and AUC_{tau} • C_{max}, t_{max}, $t_{1/2}$, and Cl/F
Immunogenicity	To evaluate the immunogenicity profile of MEDI0382 (titrated up to a dose level of 300 µg) in subjects treated with dapagliflozin and metformin receiving placebo or MEDI0382 for 28 days	• Immunogenicity as measured by the presence of ADA to MEDI0382 (and titer if positive) during dosing and follow-up periods
Efficacy/PD	To evaluate 24-hour glucose control as measured by CGM in subjects treated with dapagliflozin and metformin receiving MEDI0382 or placebo for 28 days	• Change from baseline to the end of dosing at each dose level (Days 7, 14, and 28) in glucose 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 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 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

Table 2.2-1 Secondary Objectives and Associated Endpoints

Type	Objective [a]	Endpoints
		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)

[redacted] AUC_{24h} = area under the concentration-time curve at 24 hours; $AUC_{0\text{-}inf}$ = area under the concentration-time curve from zero to infinity; $AUC_{0\text{-}last}$ = area under the concentration-time curve from zero to last observation; AUC_{tau} = area under the concentration-time curve during the dosing period; BP = blood pressure; Cl/F = apparent clearance; CGM = continuous glucose monitoring; C_{max} = maximum-observed serum drug concentration; CV = coefficient of variation; ECG = electrocardiogram; HR = heart rate; MAGE = mean amplitude of glucose excursion; PD = pharmacodynamics; PK = pharmacokinetics; SC = subcutaneous; SD = standard deviation; $t_{1/2}$ = terminal elimination half-life; TEAEs = treatment-emergent adverse events; TESAEs = treatment-emergent serious adverse events; t_{max} = time to maximum-observed serum drug concentration

[a] Secondary efficacy, safety, PK, immunogenicity, and PD endpoints will be evaluated in subjects receiving MEDI0382 or placebo coadministered with 10 mg dapagliflozin and metformin.

2.3 Exploratory Objectives and Associated Endpoints

Table 2.3-1 Exploratory Objectives and Associated Endpoints

Type	Objective [a]	Endpoint
Efficacy	To compare additional measures of glucose control (FPG, HbA1c) in subjects treated with dapagliflozin and metformin receiving MEDI0382 or placebo for 28 days	• Change from baseline (Day -1) to Day 28 in FPG • Change from baseline (Day -2) to Day 28 in HbA1c
PD	To evaluate pancreatic and incretin hormone AUC profiles (ie, active 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	• Change from baseline (Day -1) to Day 28 in GLP-1, glucagon, insulin, and c-peptide $AUC_{0\text{-}4h}$ as measured by MMTT
PD	To compare the fasting FFA levels in subjects treated with dapagliflozin and metformin receiving MEDI0382 or placebo for 28 days	• Change from baseline (Day -1) to Days 7, 14, and 28 in fasting FFA level
PD	To compare plasma ketone profile (β-hydroxybutyrate) in subjects treated with dapagliflozin and metformin receiving MEDI0382 or placebo for 28 days	• β-hydroxybutyrate profile to include $AUC_{0\text{-}inf}$, $AUC_{0\text{-}last}$, C_{max}, and t_{max}

Table 2.3-1 Exploratory Objectives and Associated Endpoints

Type	Objective [a]	Endpoint
Efficacy	To compare the change in body weight after 28 days of treatment with MEDI0382 or placebo in subjects treated with dapagliflozin and metformin	• 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
PD	To evaluate 24-hour urinary glucose excretion in subjects treated with dapagliflozin and metformin receiving MEDI0382 or placebo	• Total glucose excreted in urine collected for 24 hours

AUC = area under the concentration-time curve; AUC_{0-4h} = area under the concentration-time curve from zero to 4 hours; AUC_{0-inf} = area under the concentration-time curve from zero to infinity; AUC_{0-last} = area under the concentration-time curve from zero to last observation; C_{max} = maximum-observed serum drug concentration; FFA = free fatty acid; FPG = fasting plasma glucose; GLP-1 = glucagon-like peptide-1; HbA1c = hemoglobin A1c; MMTT = mixed meal tolerance test; PD = pharmacodynamics; t_{max} = time to maximum-observed serum drug concentration

[a] Exploratory endpoints will be evaluated after 28 days of treatment in subjects receiving MEDI0382 or placebo alongside 10 mg dapagliflozin and metformin administered simultaneously as background therapy.

3 STUDY DESIGN

3.1 Description of the Study

3.1.1 Overview

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.

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 treated with metformin monotherapy only will enter a 4-week run-in period where subjects will be administered oral dapagliflozin 10 mg a day, which will be provided by the sponsor. Enrolled subjects that 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, which will be provided by the sponsor.

Forty-six subjects are expected to 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 follow-up posttreatment period. There will be a total of 2 inpatient stays with a duration of 2 to 3 days.

Four-week run-in period

After screening, subjects on metformin monotherapy only will begin an open-label, run-in period on Day -28 and will receive oral dapagliflozin 10 mg a day for 28 days prior to randomization. On Day -14, subjects will return to the clinical unit for an abbreviated physical examination, vital signs, and blood collection for safety laboratory assessments.

Subjects on dual therapy (metformin plus dapagliflozin) can be randomized after the screening period. In addition, all subjects will be given diet and lifestyle advice to follow for the duration of the study.

Four-week treatment period

On Day -2, subjects will be admitted to the clinical unit for 1 to 2 nights (ie, subject may choose to stay a second night or leave the clinic). Subjects will undergo initial safety assessments including but not limited to an abbreviated physical examination, medical history, vital signs, blood collection for laboratory tests (eg, lactate, pH, and HbA1c), urine tests (eg, pregnancy, drug and alcohol screen), and training in SC injection administration. An ABPM device will be fitted on Day -2 and worn for 24 hours. On Day -1, after an overnight fast of approximately 10 hours, subjects will undergo a mixed-meal tolerance test (MMTT). Subjects will be asked to drink 1 entire can of Ensure Plus® (a nutritional supplement containing the components of fat, carbohydrate, and protein that make up a standard MMTT) within 5 minutes. Blood samples will be drawn after consumption of the drink for quantification of glucose, active GLP-1, insulin, c-peptide, and glucagon per the treatment schedule (Table 4.2.3-1). At this visit, eligibility criteria verification and additional training in SC injection administration will be performed. Blood will be collected for laboratory tests (eg, FFA, FPG), dapagliflozin PK, and ketone PK sampling. After the MMTT on Day -1, the subject will be fitted with a continuous glucose monitoring (CGM) device on the contralateral arm to the ABPM, which will expire and be replaced every 14 days. Subjects will be expected to wear the CGM sensor continuously for the duration of treatment (Section 4.2.3 and Table 4.2.3-1 for additional details). Subjects will also be expected to conduct daily finger-prick testing for ketone measurements throughout the treatment period.

Following completion of the MMTT test and assessments on Day -1, subjects are given the option to remain in the unit or return home, but subjects must ensure they undergo an

overnight fast for approximately 10 hours. Discharged subjects will return to the clinic on Day 1. Subjects can be randomized after confirming eligibility at any time from Day -1 to Day 1 (predose) to receive either MEDI0382 or placebo. On Day 1, following the overnight fast, dosing of MEDI0382 SC or placebo SC will commence after predose safety measures including but not limited to vital signs, an ECG, and blood collection for laboratory tests (eg, lactate, pH); [redacted] dapagliflozin and ketones PK sampling; and measurement of weight are performed. A 24-hour urinary collection for glucose excretion will be collected from Day 1 to Day 2. Subject s will be monitored for safety, glucose, and ketones, and will be discharged from the unit approximately 6 hours postdose. Capillary glucose and ketones monitoring will be done at the site using a glucometer. The subject will return to the unit on Day 2 for safety monitoring and supervision of investigational product administration. The subjects will be discharged with the same syringe pack of investigational product supplies and will continue to self-administer investigational product on an outpatient basis.

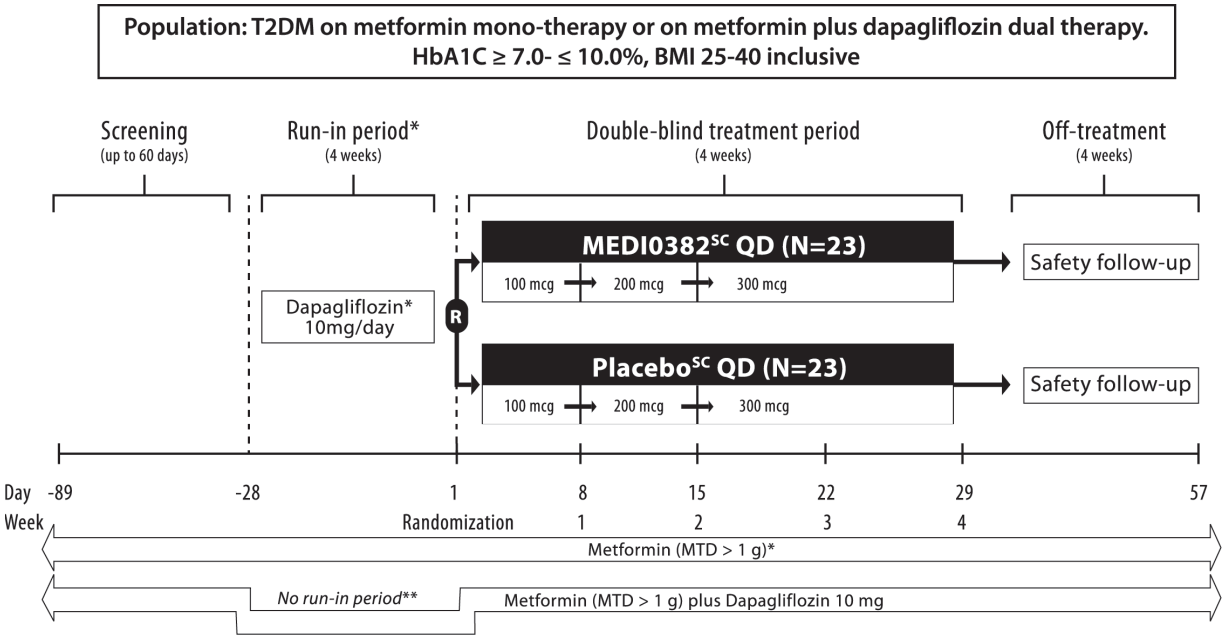
Subjects will then return to the clinical unit at weekly intervals until a maintenance dose of 300 µg is achieved. Subjects will return to the unit for outpatient visits on Days 7, 8, 14, 15, and 22 to undergo safety assessments including but not limited to an abbreviated physical examination and ECG (Days 7, 14, and 22), vital signs (all visits with ABPM fitted on Day 14 only), urine tests (eg, pregnancy test on Day 14 and Day 22), and blood collection for laboratory tests (Days 7, 14, and 22). MEDI0382, dapagliflozin, and ketones PK sampling will be performed on Days 7, 8, 14, and 15. Uptitration of SC investigational product will occur on Day 8 and Day 15. After uptitration of investigational product, subjects will be monitored for safety, capillary glucose and ketones and will be discharged 6 hours postdose. A 10-hour overnight fast is required prior to visits on Days 7 and 14, and a standardized breakfast meal will be provided 2 hours postdosing on these days. The CGM device will be replace on Day 14.

Subjects will return to the unit for admission on Days 27 to 29 (Visit 11) to undergo final safety assessments including but not limited to an abbreviated physical examination, an ECG, and urine tests (eg, pregnancy and drug and alcohol screening) on Day 27 and vital signs (including ABPM) and blood collection for laboratory tests (eg, lactate, pH, HbA1c) on Day 28. On Day 28, following an overnight fast of 10 hours, a final MMTT will be performed. On Day 28, PK sampling of MEDI0382, dapagliflozin, and ketones will be taken relative to time zero of administration of investigational product. A 24-hour urine collection for glucose secretion will also be performed from Day 28 to Day 29. On Day 29, vital signs, a measurement of weight, and [redacted] MEDI0382, dapagliflozin, and ketones PK will be performed. Subjects will be discharged if no safety

concerns are identified. Subjects will then enter the 4-week, posttreatment safety follow-up period, and they will continue to wear the CGM until approximately 28 days after the last dose of investigational product.

Throughout the entire combination treatment period and in the follow-up period, subjects will be required to continue wearing the CGM sensor (up to 28 ± 4 days after the last dose of investigational product) and to test their ketone level once daily prebreakfast (up to 14 ± 2 days after the last dose) using the testing strips provided.

Figure 3.1.1-1 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

The endpoints to be measured in this study are described in Section 2.

3.1.2 Treatment Regimen

Four-week run-in period

Following screening, subjects previously treated with metformin monotherapy only will enter an open-label, run-in period and will receive oral dapagliflozin 10 mg a day for 4 weeks, which will be provided by the sponsor.

Four-week treatment period

Following the run-in period for subjects on metformin monotherapy or the screening period for subjects on metformin and dapagliflozin dual therapy, subjects will be randomized as follows:

- MEDI0382 SC once daily (titrated up from 100 µg for 7 days to 200 µg for 7 days and to 300 µg for 14 days) in the morning for 28 days (N = 23) or
- Placebo SC once daily in the morning for 28 days (N = 23)

The sponsor will provide dapagliflozin to all subjects entering the treatment period.

3.1.3 Dose Escalation

Doses of MEDI0382 and placebo will escalate from an initial 100 to 300 µg in 7-day intervals during the 4-week combination-treatment phase (Section 3.1.2).

3.2 Study Design [redacted]

[redacted]

3.2.1.1 Dapagliflozin and Metformin

The combination of 10 mg dapagliflozin and metformin (maximum tolerated dose [MTD] of ≥ 1 g) as dual therapy has been extensively studied in T2DM subjects and has demonstrated a favorable benefit-risk profile. The 10 mg dapagliflozin dose is the most effective approved dose and was chosen for this study as it has been extensively studied in previous Phase 3 studies with a favorable benefit-risk profile (Forxiga Summary of Product Characteristics, 2017).

3.2.1.2 MEDI0382

To date, the development program for MEDI0382 has studied doses up to 300 µg as part of a multiple ascending dose study (D5670C00002). The 300 µg dose has been specifically studied for a period of 7 days in 2 separate cohorts, each exploring different uptitration schedules to reach this dose. At the 300 µg dose level, the safety and tolerability profile was comparable with previous clinical data with lower doses of MEDI0382 and other GLP-1 mimetics at this stage of development, and there was no increase in systolic or diastolic BP. In fact, a nonsignificant trend towards reduction of systolic BP was observed (~2-5 mmHg reduction across the cohorts after data correction for placebo). Across the 2 cohorts, the LS mean for percent change from baseline to the end-of-treatment period in glucose $AUC_{0\text{-}4h}$

following a MMTT was -36.73% to -41.65% in MEDI0382-treated subjects versus -8.02% to -14.54% in placebo-treated subjects. The LS mean for change from baseline in body weight was -2.07% to -3.40% in MEDI0382-treated subjects versus -0.68% to -0.86% in placebo-treated subjects. Of note, no events of DKA have been observed in the MEDI0382 development program to date.

The current study intends to minimize the likelihood of observing adverse effects by titrating MEDI0382 up to 300 µg (ie, the highest dose previously tested). In addition, this study ensures that all doses that are likely to be included in later stages of MEDI0382 development (ie, 100 µg through 300 µg) are studied in combination with dapagliflozin.

Similar studies conducted with exenatide in combination with dapagliflozin showed no significant impact on the PK of either drug in the combination arm, despite the delay in gastric emptying due to the GLP-1 component of exenatide. Furthermore, given the earlier time to maximum-observed serum drug concentration (t_{max}) of dapagliflozin (~1 hour) compared to MEDI0382 (~4 hours), the potential for additional delay in gastric emptying due to the glucagon component of MEDI0382 is not deemed to be relevant to the absorption phase of dapagliflozin. Therefore, it is expected that MEDI0382 and dapagliflozin will retain their typical PK profile in the presence or absence of the coadministered drug.

The no-observed-adverse-effect level (NOAEL) of 90 µg/kg/day was based on findings in a 9-month, daily SC, repeat-dose toxicology study in cynomolgus monkey. These findings were consistent with pharmacology-mediated induction of weight loss/lower weight gain, reversible changes in the pancreas (acinar degranulation and hypercellularity of the pancreatic islets), and changes in energy utilization and associated metabolic stress (minor changes in blood chemistry parameters, lower thymus weights). Treatment was also associated with changes in the skin (dermal irritation, acanthosis, and hyperkeratosis).

Although the NOAEL determined in a 6-month, daily SC, repeat-dose toxicology study in rat (7.5 µg/kg/day) was lower than that in the cynomolgus monkey (90 µg/kg/day), this was driven primarily by findings in the thyroid gland (c-cell hyperplasia, adenoma, and carcinoma), which were considered adverse in the rat. These findings are a well-known class effect of anti-GLP-1 agonists; however, they are considered to be rodent specific and of unknown relevance to humans (CDER, 2005). Therefore, cynomolgus monkey and the toxicity profile of MEDI0382 in that species is considered to be the most appropriate nonclinical species for clinical risk assessment and setting of safety margins.

Table 3.2.1-1 shows the proposed clinical dose levels and estimated safety margins over the predicted maximum-observed serum drug concentration (C_{max}) and area under the

concentration-time curve (AUC) for this human study and the observed C_{max} and AUC at the NOAEL in the 9-month, repeat-dose toxicity study in cynomolgus monkeys.

The steady state C_{max}- and AUC-based safety margins at the maximum proposed human dose of 300 µg (after 4 uptitration steps) based on cynomolgus monkey NOAEL (90 µg/kg/day) are 14-fold and 17-fold, respectively, which indicate that the exposure in humans is anticipated to be lower than that determined in monkeys at the NOAEL.

Table 3.2.1-1 Proposed Study Doses and Predicted Safety Margins Based on Safety Data from the Cynomolgus Monkey

	Predicted median Human Exposure at steady state		Safety Margin Over Cynomolgus Monkey Exposure at NOAEL [a] at Day 273	
Human Dose (µg)	AUC_{tau} (ng•h/mL)	C_{max} (ng/mL)	AUC	C_{max}
100 + 200 + 300	250	16.5	17	25

AUC = area under the concentration-time curve; AUC_{tau} = area under the concentration-time curve where tau is the end of a dosing interval; C_{max} = maximum observed drug concentration; h = hour; NOAEL = no-observed-adverse-effect level.

Note: The information in this table is based on 80 kg human body weight

[a] NOAEL = 90 µg/kg/day

3.2.2 Rationale for Study Population

3.2.2.1 Recruitment of Subjects with Type 2 Diabetes Mellitus and a Body Mass Index 25 to 40 kg/m^2

The mechanisms of action of both MEDI0382 (GLP-1/glucagon coagonism) and dapagliflozin (SGLT2 inhibition) result in glucose-lowering effects; therefore, the target population for both drugs in combination is subjects with T2DM. In addition, because both drugs have demonstrated effects on body weight, subjects who are already overweight or obese are most likely to benefit. Although subjects with a BMI > 40 kg/m^2 or > 35 kg/m^2 plus comorbidities may be offered bariatric surgery, those with a BMI in the range of 25 kg/m^2 through 40 kg/m^2 generally rely upon conservative or medical management for weight reduction. The entry criteria with respect to T2DM and a BMI of 25 kg/m^2 through 40 kg/m^2 will provide efficacy, safety, and tolerability data in the likely intended clinical population.

3.2.2.2 Recruitment of Subjects on Metformin and Dapagliflozin Therapy

Metformin is a first-line therapy for T2DM and forms the basis of initial and continuing oral therapy for a significant proportion of subjects. Subjects with T2DM taking metformin as monotherapy or metformin and dapagliflozin dual therapy have been chosen to provide a balance between observing the effect on both safety and efficacy of MEDI0382 when

administered alongside with dapagliflozin and metformin. Metformin cotherapy with MEDI0382 has been shown to be safe and well tolerated during short-term treatment of up to 41 days (D5670C00002). Metformin concentrations were measured during this period and there were no significant changes in the PK profile of metformin or MEDI0382.

3.2.2.3 Selection of Subjects with Type 2 Diabetes Mellitus and Stable Glycated Hemoglobin in the Range of 7.0% to 10.0%

The specified HbA1c range ensures that recruitment to the study is feasible, but also that any acute effect of MEDI0382 on glucose metabolism can be robustly assessed in the target clinical population. Further intervention to lower blood glucose levels should not be delayed by entry into a study for those with an HbA1c > 10.0%. At HbA1c levels < 7.0%, the ability to measure clinically significant changes in glucose homeostasis will be limited. In addition, the use of multiple antidiabetic medications is generally not clinically indicated at HbA1c levels < 7.0%.

3.2.3 Rationale for Endpoints

3.2.3.1 Primary Endpoint

The primary objective of this study is to assess the antihyperglycemic effect of daily MEDI0382 treatment (titrated up from 100 µg for 7 days to 200 µg for 7 days and to a final dose of 300 µg for 14 days) versus placebo in subjects with T2DM treated with 10 mg dapagliflozin and metformin. The change and % change in glucose $AUC_{0\text{-}4h}$ from baseline to the end-of-treatment period following a MMTT will be evaluated in subjects with T2DM treated with MEDI0382 or placebo plus dual therapy (ie, dapagliflozin and metformin). On the basis of prior evidence, it is known that both MEDI0382 and dapagliflozin given individually will result in improved glucose control. However, the extent to which MEDI0382 will lower blood glucose when given simultaneously to an add-on, oral dual therapy of dapagliflozin and metformin (in a late-stage diabetes population) is unknown. The MMTT is well established as a measure of glucose control, and it is used in this study to evaluate the effect of MEDI0382 on lowering glucose by measuring changes in glucose AUC after consumption of a standardized liquid meal.

3.2.3.2 Secondary Endpoints

Safety and Tolerability

The secondary objective of the study is to evaluate the safety and tolerability profile of MEDI0382 versus placebo in combination with a dual therapy of dapagliflozin and metformin

In a prior study (D5670C00002), 300 µg of MEDI0382 was administered to 23 obese and overweight subjects with T2DM for 7 days after 2 uptitration steps. This dose was shown to have an acceptable tolerability and safety profile over this period of dosing. During treatment, there was no significant increase in systolic or diastolic BP, but a significant increase in HR of 6.6 beats per minute (90% CI 4.1, 9.1) was recorded after 7 days of dosing (Cohorts 5 and 6 pooled data; n = 19). In the cohorts that received MEDI0382 uptitrated to 300 µg, nausea were observed in a maximum of 41.7% (Cohort 6) of subjects, and vomiting were observed in a maximum of 27.3% (Cohort 5) of subjects. Safety and tolerability of MEDI0382 (uptitrated up to 300 µg) in subjects treated with dual therapy of dapagliflozin and metformin will be measured with safety laboratory tests, vital signs including ABPM recording of HR and BP, and recording of AEs.

Pharmacokinetics

Plasma concentrations of MEDI0382 and dapagliflozin will be used to evaluate the PK profile: C_{max}, t_{max}, and plasma AUC from zero to infinity ($AUC_{0\text{-}inf}$), from zero to last observation ($AUC_{0\text{-}last}$), and during the dosing interval (AUC_{tau}). The expectation is that the PK profile of MEDI0382 will not be significantly altered when administered simultaneously with dapagliflozin and metformin.

[redacted]

Efficacy

Continuous glucose monitoring is a minimally invasive device applied to the skin in the upper arm that provides a measure of interstitial glucose levels every 15 minutes. Exploration of the glucose-lowering effect of MEDI0382 in combination with dapagliflozin and metformin dual therapy versus the dual therapy alone will be assessed by CGM over a 24-hour and 7-day periods. Continuous glucose monitoring will allow measurements of glucose excursions during different meals and at different times of the day and will allow determination of the percentage of time subjects have abnormally high or low blood glucose levels. Continuous glucose monitoring will also provide additional safety information such as glucose measurements any time a subject is in the hypoglycemic range. This data will help determine whether the glucose-lowering effect is exacerbated by the combination of MEDI0382 plus dual therapy compared to the dual therapy alone.

3.2.3.3 Exploratory endpoints

Further characterization of the additive effects of MEDI0382 in combination with dapagliflozin and metformin as dual therapy versus the dual therapy and placebo will be assessed by measuring plasma glucagon, insulin, and c-peptide after a MMTT.

It is hypothesized that the glucagon component of MEDI0382 may lead to increased fatty acid oxidation in the liver, thus resulting in increased ketogenesis. This effect alongside the dapagliflozin-induced glycosuria may predispose subjects to increase ketogenesis. Changes in serum ketones (β-hydroxybutyrate) and FFA profile are used as exploratory endpoints to investigate whether or not concomitant treatment of MEDI0382 and SGLT2 inhibitors increases the propensity to develop ketosis.

4 MATERIALS AND METHODS

4.1 Subjects

4.1.1 Number of Subjects

Enrollment of 46 subjects across sites is planned, with 23 subjects to receive MEDI0382 SC and 23 subjects to receive placebo SC once daily in the morning for 28 days.

4.1.2 Inclusion Criteria

Subjects must meet all of the following criteria:

1. Male and female subjects aged ≥ 18 years at screening.
2. Provision of signed and dated informed consent form (ICF) prior to any study specific procedures.
3. BMI between 25 kg/m^2 and 40 kg/m^2 (inclusive) at screening.
4. HbA1c range between 7.0% and 10.0% (inclusive) at the time of screening.
5. Diagnosed with T2DM and treated with of metformin monotherapy (MTD > 1 g) at least 8 weeks prior to screening or treated with stable, oral doses of dapagliflozin 10 mg and metformin (MTD > 1 g) for at least 3 months prior screening.
6. Subjects prescribed oral dual therapy with sulphonylurea, glitinide, or dipeptidyl peptidase-4 inhibitor (in addition to metformin) may be eligible to enter the study following a washout period of these medications totaling at least 28 days before initial screening evaluations have been completed.
7. Female subjects of childbearing potential must have a negative pregnancy test at screening and randomization and must not be lactating.
8. Females of childbearing potential who are sexually active with a nonsterilized male partner must use at least one highly effective method of contraception from screening and must agree to continue using such precautions through to the end of the study (see

Section 10.2 for accepted methods of contraception). It is strongly recommended for the male partner of a female subject to also use male condom plus spermicide throughout this period. Cessation of contraception after this point should be discussed with a responsible physician. Periodic abstinence, the rhythm method, and the withdrawal method are not acceptable methods of contraception.

4.1.3 Exclusion Criteria

Any of the following would exclude the subject from participation in the study:

1. History of, or any existing condition that in the opinion of the investigator would interfere with evaluation of the investigational product, put the subject at risk, influence the subject's ability to participate, or affect the interpretation of the results of the study and/or any subject unable or unwilling to follow study procedures
2. Any subject who has received another investigational product not included in the protocol as part of a clinical trial or a GLP-1 analogue or SGLT2-containing preparation (excluding dapagliflozin) within the last 30 days or 5 half-lives of the drug (whichever is longest) at the time of screening
3. Any subject who has received any of the following medications prior to the start of the screening period (Visit 1) or prior to the study start period (Visit 4) (see Section 4.7.2 for further details):
   - Concurrent use of any medicinal products, or herbal or over-the-counter (OTC) preparations licensed for control of body weight or appetite at the time of screening (Visit 1)
   - Concurrent or previous use of drugs approved for weight loss (eg, orlistat, bupropion-naltrexone, phentermine-topiramate, phentermine, lorcaserin) within the last 30 days or 5 half-lives of the drug (whichever is longest) at the time of screening (Visit 1)
   - Concurrent use of aspirin (acetylsalicylic acid) at a dose greater than 150 mg once daily and within the last 72 hours prior to the start of the study (Visit 4)
   - Concurrent use of paracetamol (acetaminophen) or paracetamol-containing preparations at a total daily dose of greater than 3000 mg and within the last 72 hours prior to the start of the study (Visit 4)
   - Concurrent use of ascorbic acid (vitamin C) supplements at a total daily dose greater than 1000 mg and within the last 72 hours prior to the start of the study (Visit 4)
   - Concurrent use of opiates, domperidone, metoclopramide, or other drugs known to alter gastric emptying and within the last 72 hours prior to the start of the study (Visit 4)
4. Concurrent participation in another study of any kind and repeat randomization in this study is prohibited
5. Severe allergy/hypersensitivity to any of the proposed study treatments or excipients
6. Diagnosis of type 1 diabetes mellitus, maturity-onset diabetes of the young, or latent autoimmune diabetes of adulthood or presence of anti-glutamic acid decarboxylase, anti-islet cell, or anti-insulin antibodies

7. Symptoms of acutely decompensate blood glucose control (eg, thirst, polyuria, weight loss) at screening or randomization, a history of DKA, or hyperosmolar nonketotic coma or treatment with daily SC insulin within 90 days prior to screening
8. Fasting hyperglycemia (> 250 mg/dL/ > 13.9 mmol/L) prior to randomization
9. C-peptide level < lower limit of normal (LLN)
10. History of acute or chronic pancreatitis or pancreatectomy
11. Hypertriglyceridemia (> 400 mg/dL) at screening
12. Significant inflammatory bowel disease, gastroparesis, or other severe disease or surgery affecting the upper gastrointestinal (GI) tract (including weight-reducing surgery and procedures) which may affect gastric emptying or could affect the interpretation of safety and tolerability data
13. Significant hepatic disease (except for nonalcoholic steatohepatitis or nonalcoholic fatty liver disease without portal hypertension or cirrhosis) and/or subjects with any of the following results at screening:
    - Aspartate transaminase (AST) ≥ 3 × upper limit of normal (ULN)
    - Alanine transaminase (ALT) ≥ 3 × ULN
    - Total bilirubin (TBL) ≥ 2 × ULN
14. Impaired renal function defined as estimated glomerular filtration rate (eGFR) ≤ 60 mL/minute/1.73m^2 at screening (eGFR according to Modification of Diet in Renal Disease [MDRD] using the isotope dilution mass spectrometry-traceable MDRD Study Equation (SI units).
15. Use of loop diuretics within 1 month prior to screening
16. Poorly controlled hypertension as defined below:
    - Systolic BP > 160 mm Hg
    - Diastolic BP or ≥ 100 mm Hg

    After 10 minutes of supine rest and confirmed by repeated measurement at screening (Visit 1 for all subjects)
17. Unstable angina pectoris, myocardial infarction, transient ischemic attack, or stroke within 3 months prior to screening, or subjects who have undergone percutaneous coronary intervention or a coronary artery bypass graft within the past 6 months or who are due to undergo these procedures at the time of screening
18. Severe congestive heart failure (New York Heart Association Class III and IV)
19. Basal calcitonin level > 50 ng/L at screening or history/family history of medullary thyroid carcinoma or multiple endocrine neoplasia
20. Hemoglobinopathy, hemolytic anemia, or chronic anemia (hemoglobin concentration < 11.5 g/dL [115 g/L] for males and < 10.5 g/dL [105 g/L] for females) at screening or any other condition known to interfere with interpretation of HbA1c measurement
21. History of neoplastic disease within 5 years prior to screening, except for adequately treated basal cell skin cancer, squamous cell skin cancer, or *in situ* cervical cancer.
22. Any positive results for serum hepatitis B surface antigen, hepatitis C antibody, and human immunodeficiency virus antibody

23. Recent viral infection or illness requiring the use of antibiotics in the month prior to screening (Visit 1) for subjects on dual therapy or prior to run-in period (Visit 2) for subjects on monotherapy
24. History of recurrent (at least 2) urinary tract and/or genital tract infections (including mycotic infections such as thrush) within 6 months prior to screening
25. Substance dependence likely to impact subject safety or compliance with study procedures
26. Involvement of any AstraZeneca, MedImmune, contract research organization, or study site employees and their close relatives

Note: Subjects may be rescreened once, if in the opinion of the Investigator there is a reason to believe they may be eligible. Subjects should continue to meet all inclusion and none of the exclusion criteria to qualify for rescreening. If subject is rescreened, all screening procedures including laboratory tests must be repeated.

4.1.4 Subject Enrollment and Randomization

Study participation begins, ie, a subject is "enrolled", once written informed consent is obtained. Once informed consent is obtained, a subject identification (SID) number will be assigned by a central system (eg, an interactive voice/web response system, interactive response technology such as IXRS), and the screening evaluations may begin to assess study eligibility (inclusion/exclusion) criteria. The SID number will be used to identify the subject during the screening process and throughout study participation if applicable.

A master log of all consented subjects will be maintained at the site and will document all screening failures (ie, subjects who are consented but do not meet study eligibility criteria and/or are not randomized) including the reason(s) for screening failure.

Subjects who fail to meet the inclusion/exclusion criteria (ie, screening failures) should not be randomized (if applicable) or receive investigational product. There can be no exceptions to this rule. Subjects who are enrolled, but subsequently found not to meet all the eligibility criteria must not be randomized or initiated on treatment and must be withdrawn from the study.

4.1.5 Withdrawal from the Study

Subjects are free to withdraw from the study at any time (investigational product and assessments) without prejudice to future treatment (withdrawal of consent). At the time of withdrawing consent, subjects will be asked about the reason(s) for withdrawing and the presence of any AEs. After consent is withdrawn, no further study visits or data collection should take place.

4.1.6 Discontinuation of Investigational Product

An individual subject will not receive any further investigational product if any of the following occur in the subject:

1. Withdrawal of consent from further treatment with investigational product or lost to follow up
2. An AE that in the opinion of the investigator or the sponsor warrants discontinuation from further dosing
3. Subject is determined to have met one or more of the exclusion criteria or failed to meet all of the inclusion criteria for study participation at study entry, and at the decision of the investigator, continuing of investigational product might constitute a safety risk.
4. Subject noncompliance that in the opinion of the investigator or sponsor warrants withdrawal (eg, refusal to adhere to scheduled visits)
5. Pregnancy in a female subject
6. Evidence of ketoacidosis or progression to ketoacidosis, ie, blood ketones (β-hydroxybutyrate) > 3.0 mmol/l and pH < 7.35 ± serum bicarbonate < 18 mmol/L in conjunction with clinical symptoms. The presence of elevated plasma glucose is not required as part of this diagnosis. The investigator should consider interrupting dapagliflozin temporarily if DKA is suspected. The subject should be promptly evaluated. If DKA is confirmed, dapagliflozin should be discontinued permanently.
7. Hypoglycemia events: Subjects should discontinue investigational product if they experience severe hypoglycemia as define by the American Diabetes Association
   - Requiring assistance of another person to actively administer carbohydrates, glucagon, or take other corrective actions
   - Plasma glucose concentrations may not be available during an event, but neurological recovery following the return of plasma glucose to normal is considered sufficient evidence that the event was induced by a low plasma glucose concentration
8. Kidney disorders as determine by a decrease in renal function that would preclude continued treatment with metformin according to local guidance
9. Hepatic disorders: subjects with central laboratory ALT and/or AST > 3 × ULN will be scheduled for a follow-up visit within 3 days following the receipt of the results. Subjects should be discontinued from receiving investigational product if initial and repeat laboratory tests meet any of the following:
   - ALT and/or AST are 3 × ULN and TBL > 2 × ULN
   - ALT and/or AST are 5 × ULN for 14 consecutive days, at any time after initial confirmatory results.
   - ALT and/or AST are 8 × ULN

If a subject is required to or chooses to discontinue the investigational product, every reasonable effort should be made for the subject to remain in the study for follow up and to complete all other study procedures until the scheduled end of the study. It is important that

investigators and site staff familiarize themselves with procedures for maintaining such subjects in the study to collect their data as scheduled. Subjects who are permanently discontinued from receiving investigational product will be followed for protocol-specified assessments including follow-up of any AEs unless consent is withdrawn specifically from further study participation (Section 4.1.5), the subject is lost to follow-up, the subject starts alternative treatment, or the subject is enrolled in another clinical study.

4.1.7 Replacement of Subjects

Subjects who withdraw from the study may be replaced where possible.

4.1.8 Withdrawal of Informed Consent for Data and Biological Samples

Biological Samples Obtained for the Main Study

Study data are protected by the use of a SID number, which is a number specific to the subject. The investigator is in control of the information that is needed to connect a study sample to a subject. A subject's consent to the use of data does not have a specific expiration date, but the subject may withdraw consent at any time by notifying the investigator. If consent is withdrawn, any samples collected prior to that time may still be given to and used by the sponsor but no new data or samples will be collected unless specifically required to monitor safety of the subject.

If a subject withdraws consent to the use of donated biological samples, the samples will be disposed of/destroyed and the action documented. If samples are already analyzed, MedImmune is not obliged to destroy the results of this research (Appendix 10.6).

4.2 Schedule of Study Procedures

Whenever vital signs, 12-lead ECGs, and blood draws are scheduled for the same nominal time, the assessments should occur in the following order: 12-lead ECG, vital signs, and then blood draws. The timing of the first 2 assessments should be such that it allows the blood draw (eg, PK blood sample) to occur at the exact nominal time.

4.2.1 Enrollment/Screening Period

Table 4.2.1-1 shows all procedures to be conducted at the screening visit. Assessments should be performed in the order shown in the table.

Table 4.2.1-1 Schedule of Screening Period Procedures

Study Period	Screening
Visit Number	**V1**
Procedure/Study Day	**Day -89 to Day -29**
Written informed consent/ assignment of SID number	X
Medical history (including smoking and alcohol history)	X
Concomitant medications	X
Physical examination (full)	X
Body weight, height, and BMI calculations	X
12-lead digital ECG	X
Vital signs (HR, BP, body temperature, and RR)	X
Collect blood for:	
Serum chemistry (including eGFR calculation)	X
Hematology	X
Calcitonin	X
HbA1c	X
Coagulation parameters	X
Hepatitis B and hepatitis C serology; HIV-1 and HIV-2 antibodies	X
Serum pregnancy test (β-hCG, female subjects only)	X
Collect urine for:	
Urinalysis (dipstick)	X
Drug and alcohol screen [a]	X
Check willingness and ability to self-administer IP [b]	X
Verify eligibility criteria	X

β-hCG = beta human chorionic gonadotropin; BMI = body mass index; BP = blood pressure; ECG = electrocardiogram; eGFR = estimated glomerular filtration rate; HbA1c = hemoglobin A1c; HIV = human immunodeficiency virus; HR = heart rate; IP = investigational product; RR = respiratory rate; SID = subject identification; V = visit.

[a] Breath alcohol testing is acceptable as an alternative to urine testing.

[b] Subject's ability to self-administer investigational product will be verified using normal saline SC injections.

4.2.2 Run-in Period

Table 4.2.2-1 shows all procedures to be conducted at the run-in period visits for subjects on metformin monotherapy only.

Table 4.2.2-1 Schedule of Run-in Period Procedures

Study Period	Run-in	
Visit Number	**V2**	**V3**
Procedure/Study Day	**Day -28**	**Day -14**
Verify eligibility criteria	X	
Medical history (including smoking and alcohol history)	X	
Abbreviated physical examination	X	X
Concomitant medications	X	
Body weight	X	
12-lead digital ECG	X	
Vital signs	X	X
Collect blood for:		
Serum chemistry (predose)[a]	X	X
Hematology (predose) [a]	X	X
HbA1C (predose) [a]	X	
Amylase, lipase and lactate (predose) [a]	X	X
PK for dapagliflozin	X	
Collect urine for:		
Urinalysis (dipstick)	X	
Drug and alcohol screen [b]	X	
β-hCG (pregnancy test)	X	X
Assessment of AEs/SAEs	X	X
Diet and lifestyle counselling	X	X
Discharge from unit	X	X
Subject administration of oral dapagliflozin 10 mg	X	X
Training of subject on glucose and ketone monitoring	X	
Subject finger-prick testing of ketones using test strips		X

AE = adverse event; ECG = electrocardiogram; β-hCG = beta human chorionic gonadotropin; HbA1c = hemoglobin A1c; PK = pharmacokinetics; SAE = serious adverse event; V = Visit

[a] Blood collection is predose on Day -14 only.

[b] Breath alcohol testing is acceptable as an alternative to urine testing.

4.2.3 Randomized Treatment Period

Table 4.2.3-1 shows all procedures to be conducted from inpatient Visit 4 (Day -2 to Day 1) until the end of the treatment period (inpatient Visit 11, Day 27 to Day 29). Assessments should be performed in the order shown in the table.

Whenever vital signs, 12-lead ECGs, and blood draws are scheduled for the same nominal time, the assessments should occur in the following order: 12-lead ECG, vital signs, and then

blood draws. The timing of the first 2 assessments should be such that it allows the blood draw (eg, PK blood sample) to occur at the exact nominal time.

Table 4.2.3-1 Schedule of Treatment Period Procedures

Study Period	Treatment period											
MEDI0382 Dose level	100 µg					200 µg		300 µg				
Visit Number	V4			V5	V6	V7	V8	V9	V10	V11		
Procedure/ Study Day	-2	-1	1	2	7	8	14	15	22	27	28	29
Inpatient or Outpatient	Inpatient			Outpatient	Outpatient	Outpatient	Outpatient	Outpatient	Outpatient	Inpatient		
Verify eligibility criteria [a]		X										
Admit to clinic	X									X		
Discharge home [b]		X	X									X
Medical and disease history	X											
Physical examination (abbreviated)	X				X		X		X	X		
Body weight [c]			X									X
12-lead digital ECG [d]			X		X		X		X	X		
Vital signs [e]	X		X		X	X	X	X	X		X	X
24-hour ABPM [f]	X						X				X	
Randomization [g]		X	X									
SC injection training [h]	X	X										
Administration of dapagliflozin [i]	←----------For the duration of the study----------→											
Administration of metformin [i]	←----------For the duration of the study----------→											

Table 4.2.3-1 Schedule of Treatment Period Procedures

Study Period	Treatment period											
MEDI0382 Dose level	100 µg					200 µg		300 µg				
Visit Number	V4			V5	V6	V7	V8	V9	V10	V11		
Procedure/ Study Day	-2	-1	1	2	7	8	14	15	22	27	28	29
Inpatient or Outpatient	Inpatient			Outpatient	Outpatient	Outpatient	Outpatient	Outpatient	Outpatient	Inpatient		
Administration of SC IP (MEDI0382 or placebo) [j]			X	X	X	X	X	X	X	X	X	
Uptitration of SC medication						X		X				
Capillary glucose and ketones monitoring [k]			X			X		X				
Visit requires 10-hour overnight fast the day before arrival [l]		X	X		X		X				X	
Collect Blood samples for:												
Serum chemistry (predose where applicable) [m]	X		X		X		X		X		X	
Serum amylase and lipase (predose where applicable)[m]	X				X		X				X	
Serum lactate	X		X		X		X		X		X	
Serum calcitonin	X										X	
pH	X		X		X		X		X		X	
Hematology (predose where applicable) [m]	X		X		X		X		X		X	
MEDI0382 PK [n]					X	X	X	X			X	X

Table 4.2.3-1 Schedule of Treatment Period Procedures

Study Period	Treatment period											
MEDI0382 Dose level	100 µg					200 µg		300 µg				
Visit Number	V4			V5	V6	V7	V8	V9	V10	V11		
Procedure/ Study Day	-2	-1	1	2	7	8	14	15	22	27	28	29
Inpatient or Outpatient	Inpatient			Outpatient	Outpatient	Outpatient	Outpatient	Outpatient	Outpatient	Inpatient		
Dapagliflozin PK [n]		X	X		X	X	X	X			X	X
Ketones PK [o, r]		X	X		X	X	X	X			X	X
[redacted]			[redacted]									[redacted]
MMTT sampling for glucose, c-peptide, glucagon, insulin, active GLP-1[q]		X									X	
FFA (fasting)		X			X		X				X	
HbA1c	X										X	
FPG		X			X		X				X	
Collect urine for:												
Urinalysis	X						X		X	X		
Pregnancy test	X						X		X	X		
24-hour urinary glucose [s]			X								X	

Table 4.2.3-1 Schedule of Treatment Period Procedures

Study Period	Treatment period											
MEDI0382 Dose level	100 µg					200 µg		300 µg				
Visit Number	V4			V5	V6	V7	V8	V9	V10	V11		
Procedure/ Study Day	-2	-1	1	2	7	8	14	15	22	27	28	29
Inpatient or Outpatient	Inpatient			Outpatient	Outpatient	Outpatient	Outpatient	Outpatient	Outpatient	Inpatient		
Drug and alcohol screen [t]	X									X		
Staff review of daily ketone testing data	X				X		X		X	X		
Subjects finger-prick testing of ketones using test strips [u]	←----------For the duration of the study until 14 ± 2 days after last dose----------→											
CGM [v]	←----------From Day -1 until 28 ± 4 days after last dose ----------→											
CGM sensor application/change [w]		X					X				X	
Assessment of AEs/SAEs	←----------For the duration of the study----------→											
Concomitant medications	←----------For the duration of the study----------→											

ABPM = ambulatory blood pressure monitoring; [redacted] AEs = adverse events; BP = blood pressure; CGM = continuous glucose monitoring; ECG = electrocardiogram; FFA = free fatty acid; FPG = fasting plasma glucose; GLP-1 = Glucagon-like peptide-1; HbA1c = hemoglobin A1c; HR = heart rate; IP = investigational product; MMTT = mixed meal tolerance test; PK = pharmacokinetics; RR = respiratory rate; SAEs = serious adverse events; SC = subcutaneous(ly); V = visit

[a] The eligibility check should be based on all clinical measurements and blood tests taken during the screening visit (V1) with the exception of vital signs, urinary illicit drug, and pregnancy tests, which should be rechecked on Day -2. An abbreviated physical examination and repeat medical history should also be undertaken on Day -2 to ensure the subject is well enough to commence dosing.

[b] On Day -1, following completion of the MMTT test, subjects are given the option to remain in the unit or return home. Discharged subjects must ensure they undergo an overnight fast for approximately 10 hours, and they will return to the clinic on Day 1.

[c] Body weight should be measured in the morning prior to breakfast on Day 1 (predose on Day 1) and on Day 29. The subject should take off their shoes and remove bulky clothing. Calibrated scales should be used.

[d] A single, digital ECG recording should be performed predose after the subject has rested for 10 minutes on Day 1, 7, 14, 22, and 27.

[e] **Vital Signs schedule:** Vital signs include BP, HR, RR, and body temperature. On days when ABPM device is due to be checked, a predose set of vital signs should be performed only prior to application of the ABPM cuff. BP should be measured once at heart level in the nondominant arm where possible, and opposite to the arm where the CGM device is applied. The subject should seat and rest for 10 minutes prior to the measurement. Both lying and standing measurements should be taken.

- Day -2, 14, and 28: vital signs to be taken prior to fitting ABPM
- Day 1: vital signs to be taken predose (-15 minutes); immediately after dosing (+ 3 minutes); 15, 30, and 60 minutes (± 5 minutes) postdose; and 2 hours (±10 minutes) postdose
- Day 15 and 29: vital signs to be taken once ABPM is removed
- Day 7, 8, and 22: vital signs to be taken at no specific time point

[f] Subjects will be fitted with the ABPM device shortly after they arrive at the clinical unit. Subjects may be involved in practice inflations. On Day -2, 14, and 28, ABPM should be applied predose. From Day 14 to Day 15, the subject will wear the monitor/cuff for approximately 24 hours (including overnight) and will remove the device at home at the end of the 24-hour period. Subjects will return the device to the clinic. On Day -1 and Day 29, the device will be removed at the clinic during the inpatient stay.

[g] Randomization may occur any time from Day -1 to Day 1 (predose).

[h] Normal saline will be used for SC injection administration training.

[i] Metformin and dapagliflozin to be administered before investigational product administration. For PK sample collection, dapagliflozin should be administered by staff at the clinic on Days -1, 1, 7, 8, 14, 15, and 28 shortly before investigational product.

[j] Subjects to dose at home on Day 22 and 27 prior to coming to the clinic. Investigational product will be administered in the clinic on Days 1, 2, 7, 8, 14, 15, and 28. Please refer to Investigational Medicinal Product Manual for more details.

[k] After investigational product administration (MEDI0382 or placebo) on Day 1 (first dose) and on Days 8 and 15 (uptitration days), subjects will be monitored for safety, glucose, and ketones. Capillary blood ketones and glucose monitoring will be done with a glucometer before meal, predose, 2 hours postdose, and 4 hours postdose. The subject will be discharge 6 hours postdose.

[l] Outside of fasting times meals/snacks and fluid intake should be standardized across each inpatient stay.

[m] Predose labs not applicable on Day 7, 14, 22, and 28. N-B Serum chemistry will include bicarbonate measurements.

[n] **PK sampling schedule**: Blood samples for PK (MEDI0382 and dapagliflozin) to be drawn as follow:

- Dapagliflozin:
  - Day -1, 7, 14, 28: Predose; 0.5, 1, and 2 hours (± 15 minutes) postdose; and 4, 6, 8, and 12 hours (± 30 minutes) postdose
  - Day 1, 8, and 15: Predose
  - Day 29: 24 hours after dosing time on Day 28

- MEDI0382
  - Day 7, 14, and 28: Predose; 0.5, 1, and 2 hours (± 15 minutes) postdose; and 4, 6, 8, and 12, (± 30 minutes) postdose
  - Day 8 and 15: Predose
  - Day 29: 24 hours after dosing time on Day 28

[o] **Ketone blood sampling schedule:**

- Blood samples for ketone (β-hydroxybutyrate) PK to be drawn following an overnight fast of at least 10 hours at the following times:
  - Day -1, 7, 14, and 28: Predose; 0.5, 1, and 2 hours (± 15 minutes) postdose; and 4, 6, 8, and 12, (± 30 minutes) postdose. A standardized breakfast meal will be provided 2-hour post dose on Day 7 and 14 (see footnote "r")
- Additional blood samples for ketone PK to be drawn as follow:
  - Day 1, 8, and 15: Predose
  - Day 29: 24 hours after dosing time on Day 28 (± 30 minutes)

[redacted]

[q] **MMTT schedule:** The MMTT is conducted on Day -1 and Day 28 following a minimum 10-hour fast the day before. On Day -1, the MMTT starts 2 hours after dapagliflozin administration. On Day 28, the MMTT starts 2 hours after investigational product (MEDI0382 or placebo) and dapagliflozin administration. A blood sample for glucose metabolism panel (glucose, insulin, c-peptide, glucagon, and active GLP-1) will be taken immediately prior to the subject drinking one entire can of Ensure Plus as a standardized meal (ie, "0 minutes"). In addition, blood samples for glucose metabolism panel will be drawn at 15, 30, 45, 60, 90, 120, 180, and 240 minutes (±5 minutes) after consumption of the standardized meal. Additional sampling for glucagon, insulin, c-peptide, and glucose to be taken at 6, 8, 12, and 24 hour after time 0 (± 30 minutes) of the standardized meal administration on Days -1 and Day 28.

[r] **Standardized breakfast meal:** On Day 7 and 14, a standardized breakfast meal will be provided approximately 2 hours after dapagliflozin and investigational product administration. The meal will have approximately 450 kilocalories and will consist of 1 egg, 2 slices of white bread, 1 slide of Swiss cheese and 1 cup (240 ml) of orange juice (approximately 30% fat, 15% protein and 55% carbohydrates).

[s] Twenty-four-hour urinary collection for measurements of glucose excretion to start first thing in the morning soon after waking on Day 1 and Day 28. Instruct the subject to pass urine soon after waking and flush down the toilet. Note the exact time this was done. The collection of urine will start from this time. Proceed to collect every drop of urine day and night for 24 hours and finish by passing urine the next morning at exactly the same time collection was started the day before. This urine should also be added to the bottle.

[t] Breath alcohol testing is acceptable as an alternative to urine testing.

[u] Subjects will be provided with a ketones monitor and strips for capillary blood ketone testing and will be instructed to test once a day (prebreakfast) and to do additional tests including glucose if they feel unwell. Subjects will be asked to record ketone values in a paper diary, which will be provided and checked by study staff.

[v] CGM device to be fitted and worn continuously throughout the study. The sensor should be applied to the arm, taking into account which side the subject sleeps on and also which side the ABPM device will be applied. The sensor applied to the skin is single use and may not be reattached once removed.

[w] CGM sensors last 14 days and should be changed at 14-day intervals at the same time of day (± 20 minutes) as originally applied on Day -1. For example, if the sensor is applied at 6:00 am on Day -1, it should also be applied at 6:00 am (± 20 minutes) predose on Day 14 and 28. If the sensor fails, or needs to be replaced, it should be reapplied as soon as possible.

4.2.4 Follow-up Period

Table 4.2.4-1 shows all procedures to be conducted during the follow-up period.

After the end of the follow-up period, subjects will return to the care of their own physicians according to local requirements and local standards.

Table 4.2.4-1 Schedule of Follow-up Procedures

Study Period	Follow-up Period	
Visit Number	**V12**	**End-of-Study Visit V13**
Procedure/Study Day	**14 days post last dose (±2 days)**	**28 days post last dose (±4 days)**
Physical examination (abbreviated)	X	X
Body weight		X
ECG		X
Vital signs (HR, BP, RR, temperature)	X	X
Serum chemistry		X
Calcitonin		X
Hematology		X
Urinalysis		X
[redacted]		[redacted]
Assessment of AEs/SAEs	X	X
Concomitant medications	X	X
Staff review of daily finger-prick ketone testing data	X	
CGM sensor change	X	
Remove CGM sensor		X

[redacted] AE = adverse event; BP = blood pressure CGM = continuous glucose monitoring; ECG = electrocardiogram; EOS = end of study visit; HR = heart rate; RR = respiratory rate; SAE = serious adverse event; V = visit

[redacted]

4.2.4.1 Early Discontinuation Visit or Unscheduled Study Visit

The following study procedures should be conducted for subjects who prematurely discontinue from the study or for subjects who require an unscheduled study visit. Assessments should be performed in the order shown below:

- Abbreviated physical examination
- ECG
- Vital signs
- Body weight
- MEDI0382 and dapagliflozin PK
- Blood tests: chemistry and hematology panel
- [redacted]
- Assessment of AEs/ serious adverse events (SAEs)
- Concomitant medications
- Pregnancy test (if applicable)

4.3 Description of Study Procedures

4.3.1 Efficacy

4.3.1.1 Mixed-meal Tolerance Test

Subjects will be admitted to the unit on Day -2 and on Day 27. On Day -1 and on Day 28, following a minimum 10-hour fast, a blood sample for glucose metabolism panel (glucose, insulin, c-peptide, glucagon, and active GLP-1) will be taken immediately prior to the subject drinking a standardized mixed meal (t = "0 minutes"). The subject will then consume a can of Ensure Plus, which is a nutritional supplement containing the components of fat, carbohydrate, and protein that make up a standard MMTT. After the meal, timed, serial blood samples will be obtained for measurement of glucose and parameters related to glucose metabolism (with no additional food intake during this time). The MMTT will be performed on Day -1 and Day 28 as specified in the schedule of procedures.

Blood samples for the glucose metabolism panel will be drawn at t = "0 minutes" (before meal) and at 15, 30, 45, 60, 90, 120, 180, and 240 minutes (± 5 minutes) after consumption of the standardized meal. Additional sampling for glucagon, insulin, c-peptide, and glucose will be taken at 6, 8, 12, and 24 hours (± 30 minutes) postadministration (t = "0 minutes") of the standardized meal on Day -1 and 28.

The change and % change from baseline (Day-1) to the end of the 28 days of treatment (Day 28) in glucose AUC_{0-4h} will be determined as measured by the MMTT. In addition, the change from baseline (Day -1) to Day 28 in active GLP-1, glucagon, insulin, and c-peptide AUC_{0-4h} will also be measured by MMTT.

4.3.1.2 Body Weight

Body weight will be measured during the screening period, at the start of the run-in period (Day -28), and prior to breakfast on Day 1 (predose) and Day 29. The subject should take off their shoes and remove bulky clothing. Calibrated scales should be used.

The change and % change in body weight from baseline (Day 1) to Day 29 (kg) will be determined. The proportion of subjects achieving ≥ 5% body weight loss from baseline (Day 1) to Day 29 will also be determined.

4.3.2 Safety Assessments

4.3.2.1 Medical History and Physical Examination

Complete medical history will include history and current medical conditions; past or present cardiovascular disorders; respiratory, GI, renal, hepatic, neurological, endocrine, lymphatic, hematologic, immunologic, dermatological, psychiatric, genitourinary, drug, and surgical history; and any other diseases or disorders.

Physical examinations will be performed by a physician or qualified designee and will include examination of the following body systems: immunologic/allergy; head, ears, eyes, nose, and throat; respiratory; cardiovascular; GI; musculoskeletal; neurological (structured neurological examination to encompass mental status, cranial nerves, nystagmus, motor system/muscle strength, sensory system/sensation, bowel and bladder function, deep tendon reflexes, gait, station, coordination, fundoscopy, and cerebellar function); psychiatric (to the extent of determining whether or not the subject is willing and able to cooperate with the required study procedures in the investigator's judgment); dermatological, hematologic/lymphatic; and endocrine.

Any focal deficit identified at baseline should be documented in the eCRF.

A full physical examination including structured neurological examination will be conducted during the screening period (Day -89 to Day -29, Visit 1), and abbreviated physical examinations (evaluation of selective body systems at the judgment of the physician or qualified designee based on subject presentation) will be conducted on Day -28, -14, -2, 7,

14, 22, and 27. Abbreviated physical examinations will also be performed during the follow-up period.

Clinically significant abnormal findings will be recorded. Physical examinations will be performed at the time points specified in the schedules of procedures. Height will be measured at screening.

4.3.2.2 Assessment of the Injection Site

Site staff will check the injection site for injection-site reactions during study visits as required. Injection-site reactions may include (but are not limited to) local erythema, pain, tenderness, induration, swelling, pruritus, ulceration, and pigmentation.

4.3.2.3 Vital Signs

Vital sign measurements (BP, HR, body temperature, and respiratory rate [RR]) will be obtained after the subject has rested in the supine position at the time points specified in the schedules of procedures for at least 10 minutes. For any time points where ECG recording precedes vital signs measurements, the 10-minute rest prior to the ECG suffices for the rest prior to vital sign measurement). Route of body temperature measurement will be according to local protocols.

For ambulatory BP checks, subjects will be fitted with the ABPM device shortly after they arrive at the clinical unit; subjects may practice inflations at this point. The ABPM device should be applied predose on Days -2, 14, and 28. The ABPM device should be applied on the arm opposite to where the CGM device is applied. The subject will then wear the monitor/cuff for approximately 24 hours (including overnight) and will remove the device at home at the end of the 24-hour period. Subjects will return the device to the clinic.

On days when the ABPM device is due to be checked, a predose set of vital signs (BP, HR, RR, and temperature) should be performed only prior to application of the ABPM cuff. Blood pressure should be measured once at heart level in the nondominant arm where possible and opposite to the arm where the CGM device is applied. The subject should sit and rest for 10 minutes prior to the measurement. Both lying and standing measurements should be taken. The vital sign schedule will be conducted as follows:

- Day -2, 14, and 28: vital signs to be taken prior to fitting ABPM
- Day 1: vital signs to be taken predose (-15 minutes); immediately after dosing (+ 3 minutes); 15, 30, and 60 minutes (± 5 minutes) postdose; and 2 hours (±10 minutes) postdose

- Day 15, and 29: vital signs to be taken once ABPM is removed
- Day 7, 8, and 22: vital signs to be taken at no specific time point

4.3.2.4 Electrocardiograms

A single, digital ECG recording should be performed during the screening, treatment, and follow-up periods at the visits specified in schedule of procedures (Table 4.2.1-1, Table 4.2.3-1, and Table 4.2.4-1). A single ECG recording should be conducted predose after the subject has rested for 10 minutes on Days 1, 7, 14, 22, and 27. The ECG recording can be taken at no specific time point for other days.

The same recorder will be used for each subject at each time point, if possible. Date and time settings should be checked at the start of each study day and aligned with an official timekeeper for all machines used in the study.

Skin preparation should be thorough and electrode positions should be according to standard 12-lead ECG placement.

In this study, lead V2 will be analyzed and reported as primary. For all visits, lead V5 will be analyzed as backup for any subject where analysis in lead V2 is not deemed possible predose, for significant parts of whole visits, or for whole visits.

The following variables will be reported: HR, RR, PR, QRS, and QT intervals from the primary lead of the digital 12-lead ECG. The investigator may add extra 12-lead ECG safety assessments if there are any abnormal findings or if the investigator considers it is required for any other safety reason.

4.3.3 Clinical Laboratory Tests

A Laboratory Manual will be provided to the sites that specifies the procedures for collection, processing, storage, and shipment of samples, as well as laboratory contact information, specific to this clinical research study.

Clinical laboratory safety tests including serum pregnancy tests will be performed in a licensed, central or local clinical laboratory. Any abnormal laboratory results should be repeated as soon as possible (preferably within 24 to 48 hours).

Clinical laboratory tests will be performed on the days specified on the schedule of procedures (Table 4.2.1-1, Table 4.2.3-1, and Table 4.2.4-1).

The following clinical laboratory tests will be performed as specified in the schedule:

Serum Chemistry

- Bicarbonate *
- Glucose
- Calcium
- Chloride
- Potassium
- Sodium
- Bilirubin
- AST
- ALT
- TBL
- Creatinine
- Blood urea
- Albumin
- Magnesium
- ALP

ALP = alkaline phosphatase; ALT = alanine transaminase; AST = aspartate transaminase; FFA = free fatty acids; TBL = total bilirubin
Notes:
Liver function tests = AST, ALT, ALP, TBL, and albumin
Tests for AST, ALT, ALP, and TBL must be conducted concurrently and assessed concurrently.
* May be measured via serum chemistry sample of blood gas analyzer per local procedures.

Hematology

- White blood cell count with differential
- Red blood cell count
- Hematocrit
- Hemoglobin
- Platelet count
- Mean corpuscular volume
- Mean corpuscular hemoglobin concentration
- Coagulation panel PT, PTT, INR

INR = international normalized ratio; PT = prothrombin time; PTT = partial thromboplastin time

Urinalysis

- Glucose
- Protein
- Blood
- Drug and alcohol screen
- Ketones

Note: Urinalysis for protein, glucose, ketones, and blood may be performed at the site using a licensed test (dipstick).

Pregnancy Test (females of childbearing potential only)

- urine human chorionic gonadotropin (hCG)
- serum β-hCG (at screening only)

β-hCG = beta human chorionic gonadotropin; hCG = human chorionic gonadotropin

Other Tests

- Calcitonin
- [redacted]
- Pancreatic amylase, lipase
- Glucose metabolism panel for MMTT: timed glucose, insulin, active and total GLP-1, and glucagon
- Fasting FFA
- Lactate
- pH
- fasting plasma glucose

- HbA1c
- c-peptide
- 24- hour urine collection for glucose excretion
- HIV-1 and HIV-2 antibodies (at screening)
- HBsAg, hepatitis C antibody (at screening)
- Plasma ketone profile (β-hydroxybutyrate)

[redacted] FFA = free fatty acid; GLP-1 = glucagon-like peptide-1; HbA1c = hemoglobin A1c; HBsAg = hepatitis B surface antigen; HIV = human immunodeficiency virus; MMTT = mixed-meal tolerance test

Notes:

- Tests for pancreatic and incretin hormone profiles: active GLP-1, glucagon, insulin, and c-peptide
- Test for additional measures of glucose control: fasting plasma glucose, HbA1c

4.3.4 Pharmacokinetic Evaluation and Methods

Blood will be collected to evaluate PK of MEDI0382 and dapagliflozin in plasma (see Table 4.2.3-1 for collection time points). The PK of MEDI0382 and dapagliflozin in serum will be measured utilizing a validated immunoassay method.

Sampling within the specified window around the specified time will not be considered a protocol deviation, but the exact time of sampling should be recorded. Pharmacokinetics samples should be taken at the specified times and prior to administration of investigational product where indicated, and before meals or other assessments.

Samples will be collected, labelled, stored, and shipped as detailed in the Laboratory Manual.

[redacted]

4.3.6 Pharmacodynamic Evaluation and Methods

4.3.6.1 Training for Application and Wearing of Continuous Glucose Monitoring Sensor

A Freestyle Libre® Pro CGM device will be used to measure interstitial glucose levels during the study. The Freestyle Libre® Pro CGM device measures interstitial glucose levels every 15 minutes continuously for 2 weeks and does not require any calibration or periodic near-field/bluetooth connections with the device to perform this function. The Freestyle Libre® Pro CGM device does not permit flash glucose measurements. Study-site staff and investigators should avoid periodic reviews of interstitial glucose levels during the study to avoid the risk of unblinding. However, should a subject experience an AE or SAE, and the investigator deems information acquired by CGM to be useful in the subject's ongoing management, interstitial glucose readings may be reviewed by the investigator as described in the manual, but they should avoid review of baseline readings taken on Day -1. The CGM sensor, which is a small plastic circular device of 35 mm diameter and 5 mm depth, should be applied to the arm, taking into account which side the subject sleeps on and also which side the ABPM device will be applied. The selected site should be shaved where necessary, and a sterile alcohol wipe (supplied with the kit) should be used to clean the site prior to application. Study-site staff should refer to the training materials and manual for application of the CGM sensor. Subjects will be expected to wear the CGM sensor continuously up until the time of a sensor change, which should occur within 14 days. Moreover, subjects are to be advised that they may bathe, shower, or swim (up to 3 m depth for up to 30 minutes) while wearing the CGM sensor. The CGM sensor should be removed at the specified times in the schedule of assessments (CGM sensor change). At this time, the site should be inspected and cleaned, and a new CGM sensor may be reapplied. Ideally, the new sensor should be applied close to the original site but taking into account the subject's preference on site. The CGM sensor should be changed at the same time of day (± 20 minutes) as originally applied on Day -1. CGM sensors are single use and cannot be reapplied once removed. CGM sensors may only be applied to the upper arm and not to any other site in the body. It should be noted that monitors should remain at the study site and not be provided to subjects to take home.

If a subject is unable to tolerate wearing the CGM sensor for the entire duration of the study, the sensor should be removed; but the subject should remain in the study with or without continued CGM.

4.3.6.2 Glucometer Measure Capillary Blood Glucose/Ketones Reading

At the start of the study, each subject in both cohorts will be issued with a standardized glucometer, testing strips for glucose and ketones, and a diary. For the duration of the study, subjects will be encouraged to perform finger-prick tests if they feel unwell and in particular if they feel the symptoms may be due to hypoglycemia, but they will not be required to test routinely. If the investigator or site staff feel that a subject could be experiencing hypo- or hyperglycemia, capillary blood glucose should be tested with a standardized glucometer. Capillary blood glucose levels of < 3 mmol/L (54 mg/dL) should be recorded as an AE regardless of whether the subject has symptoms or not.

During the course of the study, subjects will test their blood ketone level daily (prebreakfast) using the ketone finger-prick testing strips and ketone monitor provided. Furthermore, subjects will be advised to check their blood for the presence of ketones and check their blood glucose using finger-prick testing with a glucometer if they experience any of the symptoms described in Section 1.6.4 and/or during acute illness. Subjects will be instructed to contact the site immediately if the results indicate the presence of ketonemia (> 3 mmol/L), and/or elevated glucose levels (> 140 mg/dL [> 7.8 mmol/L]), and/or present the symptoms described in Section 1.6.4. Subjects will be asked to record ketone values in a paper diary, which will be provided and checked by study staff during the outpatient visits (ie, when subjects bring the paper diary back in house). The clinic staff will provide training on how to use the ketones monitor.

4.3.6.3 Training for Application and Wearing of ABPM Device

Subjects will be given training at their local study site on how to set up and apply the ABPM device. In brief, an appropriate size cuff encircling 80% to 100% of the arm will be selected, the device will be fitted to the nondominant arm of the subject (with the bladder placed over the artery), and an initial test reading will be performed. The subjects will be advised that the device will inflate to a pressure of 180 mm Hg for the first reading; thereafter, the device will adapt to inflate to a pressure just above the last recorded BP. The subject will be advised to undergo normal daily activities while wearing the cuff, and he/she will be advised to avoid any strenuous form of activity, bathing, or showering while wearing the cuff. The subject will be advised to remain still during a measurement with the arm relaxed at heart level. The subject will also be given advice on (a) how to wear the device during the day and at night

while sleeping, and (b) what to expect in terms of frequency of readings during the day (every 15 minutes) and overnight (every 30 minutes). During ABPM, systolic and diastolic BP, HR pressure, HR, and mean arterial pressure readings will be recorded over a period of 24 hours.

Subjects will be fitted with the ABPM device shortly after they arrive at the clinical unit on Day -2. On Days 14 and 28, ABPM should be applied predose. The ABPM device should be applied on the opposite arm to the arm where the CGM device is applied. On Days 14 to 15, the subject will wear the monitor/cuff for approximately 24 hours (including overnight) and will remove the device at home at the end of the 24-hour period. Subjects will return the device to the clinic. On Day -1 and Day 29, the device will be removed at the clinical during the inpatient stay.

4.3.7 Estimate of Volume of Blood to Be Collected

The total blood drawn during the study is 670 mL, but no more than 440 mL will be drawn in a 4-week period.

4.4 Study Suspension or Termination

The sponsor reserves the right to temporarily suspend or terminate this study at any time. The reasons for temporarily suspending or terminating the study may include but are not limited to the following:

- The incidence or severity of AEs in this or other studies indicates a potential health hazard to subjects (eg, drug-related SAEs, anaphylactic reaction, hepatic enzyme alterations meeting Hy's law, signs of renal toxicity, QT interval prolongation).
- Subject enrollment is unsatisfactory
- Noncompliance that might significantly jeopardize the validity or integrity of the study
- Sponsor decision to terminate development
- Sponsor decided to terminate the study

If MedImmune determines that temporary suspension or termination of the study is required, MedImmune will discuss the reasons for taking such action with all participating investigators (or head of the medical institution, where applicable). When feasible, MedImmune will provide advance notice to all participating investigators (or head of the medical institution, where applicable) of the impending action.

If the study is suspended or terminated for safety reasons, MedImmune will promptly inform all investigators, heads of the medical institutions (where applicable), and/or institutions conducting the study. MedImmune will also promptly inform the relevant regulatory authorities of the suspension/termination along with the reasons for such action. Where required by applicable regulations, the investigator or head of the medical institution must inform the Independent Ethics Committee (IEC) promptly and provide the reason(s) for the suspension/termination. If the study is suspended for safety reasons and it is deemed appropriate by the sponsor to resume the study, approval from the relevant regulatory authorities (and IECs when applicable) will be obtained prior to resuming the study.

4.5 Investigational Products

4.5.1 Identity of Investigational Product(s)

MedImmune will provide the investigator(s) with investigational product (Table 4.5.1-1) using designated distribution centers.

Table 4.5.1-1 Identification of Investigational Products

Investigational Product	Manufacturer	Concentration and Formulation as Supplied
MEDI0382	MedImmune	Solution for injection in 1.0 mL prefilled syringe, 100 µg per dose, 1 dose
MEDI0382	MedImmune	Solution for injection in 1.0 mL prefilled syringe, 200 µg per dose, 1 dose
MEDI0382	MedImmune	Solution for injection in 1.0 mL prefilled syringe, 300 µg per dose, 1 dose
Placebo	MedImmune	Solution for injection in 1.0 mL prefilled syringe, 1 dose
Dapagliflozin	Bristol-Myers Squibb	10 mg green, plain, diamond shaped, film-coated tablet

MEDI0382 is provided as a sterile liquid drug product (nominal concentration of 0.5 mg/mL) in 50 mM sodium phosphate buffer, propylene glycol 1.85 % w/v, (pH 7.8), and it is intended for SC administration.

Placebo is provided as a sterile solution of 50 mM sodium phosphate buffer, propylene glycol 1.85 % w/v, (pH 7.8), and it is intended for SC administration.

MEDI0382 and placebo will be supplied to the site in blinded kits each containing 8 prefilled syringes. Each kit has a unique number that is printed on all labels within the kit (ie, the outer

carton label and the label of the prefilled syringe within the carton). When supplying the investigational product for at-home dosing, each subject will receive sufficient quantity of drug to last until the next visit, and the kits containing 8 prefilled syringes will be supplied in an additional take-home carton.

Dapagliflozin tablets will be provided in open label bottles containing 70 tablets. The tablets may contain lactose.

4.5.1.1 Investigational Product Handling

In-clinic Investigational Product Handling

The investigational product manager or study personnel who receives, inspects, and stores the investigational product will be unblinded. The MEDI0382 or placebo kits must be stored at 2°C to 8°C in their original container. Subjects should be instructed to refer to the Instructions for Use (IFU) of investigational product.

The staff at the clinic should refer to the IFU of the investigational product for additional information.

At-home Investigational Product Handling

Subjects will be given training in self-administration of investigational product, disposal of used prefilled syringes, and other investigational product handling steps, and will be provided with an IFU booklet detailing instructions for at-home administration. An IFU booklet must be provided to each subject on each occasion investigational product is dispensed for at-home use. Subjects will also be asked to return used investigational product kit boxes along with sharps bins and unused prefilled syringes to the investigational site.

The entire kit of investigational product (MEDI0382 or placebo) should be stored in the refrigerator. Subjects should be asked to ensure they have a normal domestic refrigerator at home, which should be between 2°C and 8°C.

The subject is to remove from the refrigerator only the prefilled syringe required for their daily dose. All other syringes are to be kept in the refrigerator until required. The subject is to avoid the risk of freezing the investigational product (MEDI0382 or placebo) by carefully placing the investigational product (MEDI0382 or placebo) within their refrigerator, and they should not use investigational product (MEDI0382 or placebo) if it has been frozen. The prefilled syringe should always be safely discarded after use. The subject will return any unused prefilled syringes to the site for accountability at the outpatient/inpatient visit.

Investigational product should be protected from heat and light. Subjects should be instructed to refer to the IFU of investigational product.

4.5.1.2 Investigational Product Inspection

MEDI0382 is supplied as a sterile liquid solution in a prefilled syringe for single use. Each syringe selected for in-clinic treatment administration should be inspected by the unblinded investigational product manager or unblinded study personnel prior to injection. MEDI0382 is supplied at a concentration of 0.5 mg/mL. The solution should not be cloudy, discolored, or contain any visible particles.

Subjects should be instructed to refer to the IFU of investigational product.

If there are any defects noted with the investigational product, the investigator and site monitor should be notified immediately. Refer to the Product Complaint (Section 4.5.1.5) for further instructions.

4.5.1.3 Treatment Administration

In-clinic Treatment Administration

MEDI0382 or placebo should be stored at 2°C to 8°C in the original container. The dose to be administered should be allowed to warm up at room temperature for about 30 minutes before injection. The first day of dosing with MEDI0382 or placebo is considered Day 1. On the day of each dose, investigational product (MEDI0382 or placebo) will be administered according to the schedule of procedures. On study days where fasting is required for an additional assessment, the investigational product (MEDI0382 or placebo) should be taken approximately 2.5 hours prior to the applicable assessment. Investigational product (MEDI0382 or placebo) will be administered by SC injection in the lower abdomen.

Subjects should be instructed to take a whole tablet of dapagliflozin with a half glass of water.

At-home Treatment Administration

Investigational product (MEDI0382 or placebo) should be removed from the refrigerator for at about 30 minutes for temperature equilibration. The subject is not to administer investigational product (MEDI0382 or placebo) if the time outside of the refrigerator has exceeded 8 hours. If the storage time exceeds this limit, a new prefilled syringe should be used. After injection, the subject is to place the used prefilled syringe in the supplied sharps bin. A once-daily dose is to be self-administered by SC injection using the prefilled syringe

as soon as practicable upon waking each morning prior to breakfast. Each prefilled syringe contains only a single dose, and cannot be reused. The subject should be instructed not to reuse the prefilled syringe after administration of the single-dose administration. Subjects should refer to the IFU document for at-home administration details.

If a dose of MEDI0382 or placebo is missed, subjects should take the dose as soon as it is remembered unless it is almost time for the next dose, in which case subjects should skip the missed dose and take the study drug at the next regularly scheduled time.

Subjects should take dapagliflozin (10 mg oral) once daily from the run-in period (for eligible subjects on metformin monotherapy) or randomization (for eligible subjects on dual therapy) until Day 29. Subjects should be instructed to take a whole tablet of dapagliflozin with a half glass of water. If a dose of dapagliflozin is missed, subjects should take the dose as soon as it is remembered unless it is almost time for the next dose, in which case subjects should skip the missed dose and take the study drug at the next regularly scheduled time.

4.5.1.4 Monitoring of Dose Administration

As with any exogenous peptide, allergic reactions to dose administration are possible.

In prior experience with MEDI0382, there has been 1 injection-site reaction and no anaphylactic reactions. During visits to the clinical unit, the site of administration will be checked for signs of injection-site reaction as required (Section 4.3.2.2).

4.5.1.5 Reporting Product Complaints

Any defects with the investigational product must be reported *immediately* to the MedImmune Product Complaint Department by the site with further notification to the site monitor. All defects will be communicated to MedImmune and investigated further with the Product Complaint Department. During the investigation of the product complaint, all investigational product must be stored at labelled conditions unless otherwise instructed.

MedImmune contact information for reporting product complaints:

Email: productcomplaints@medimmune.com

Phone: +1-301-398-2105
+1-877-MEDI-411 (+1-877-633-4411)

Fax: +1-301-398-8800

Mail: MedImmune, LLC
Attn: Product Complaint Department
One MedImmune Way,
Gaithersburg, MD USA 20878

4.5.2 Additional Study Medications

Subjects entering the study must have been treated either with daily, stable doses of oral, blood glucose-lowering therapy with metformin (MTD > 1 gram) monotherapy for at least 8 weeks or stable doses of metformin (MTD >1gram) plus oral dapagliflozin 10 mg once daily dual therapy for at least 3 months prior to screening. Metformin is not provided by the study sponsor.

After screening, eligible subjects on metformin monotherapy will begin an open-label, run-in period on Day -28 and will receive oral dapagliflozin 10 mg per day for 28 days prior to randomization until Day 29. Eligible subjects on dual therapy will receive oral dapagliflozin 10 mg per day from randomization until Day 29.

4.5.3 Labeling

Labels for the investigational product will be prepared in accordance with Good Manufacturing Practice (GMP) and local regulatory guidelines. The label will fulfil GMP Annex 13 requirements for labeling. Label text will be translated into local languages, as required.

4.5.4 Storage

All investigational product should be kept in a secure place under appropriate storage conditions. The label on the investigational product kit specifies the appropriate storage.

4.5.5 Treatment Compliance

In-clinic administration

At the clinic, investigational product (MEDI0382 or placebo) is administered by study-site personnel, who will monitor compliance.

At-home administration

Compliance during the at-home dosing period to be monitored via daily diary entries, returned prefilled syringes, and bottles of dapagliflozin. The distribution of investigational product for self-administration should be recorded in the appropriate sections of the eCRF.

4.5.6 Accountability

The investigator's or site's designated investigational product manager is required to maintain accurate investigational product accountability records and will account for all investigational product dispensed to and returned by the subject. Study-site staff, if applicable, or the site monitor delegated to investigational product management will account for all investigational product received at the site, unused investigational product, and for appropriate disposition of investigational product in accordance to local procedures. Upon completion of the study, copies of investigational product accountability records will be returned to MedImmune. All unused investigational product will be returned to a MedImmune-authorized depot or disposed of upon authorization by MedImmune.

In the case of a malfunctioning prefilled syringe, the designated investigational product manager (pharmacist/study nurse) should contact the site monitor delegated to investigational product management to initiate a product complaint process according to Section 4.5.1.5.

4.6 Treatment Assignment and Blinding

4.6.1 Methods for Assigning Treatment Groups

An 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 IXRS 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.

4.6.2 Methods for Ensuring Blinding

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 the 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 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.

4.6.3 Methods for Unblinding

4.6.3.1 Unblinding in the Event of a Medical Emergency

In the event of a medical emergency, the investigator may unblind an individual subject's investigational product allocation. Instructions for unblinding an individual subject's investigational product allocation are contained in the IXRS manual. In general, unblinding should only occur if management of the medical emergency would be different based on the subject having received investigational product. In the majority of cases, the management of a medical emergency would be the same whether or not investigational product was received by the subject. If this was the case, the investigational product allocation should not be unblinded.

MedImmune retains the right to unblind the treatment allocation for SAEs that are unexpected and are suspected to be causally related to an investigational product and that potentially require expedited reporting to regulatory authorities.

If a subject's investigational product allocation is unblinded, the subject should be discontinued from investigational product.

4.6.3.2 Unblinding for PK [redacted] Analysis

A small number of clinical bioanalytical personnel, who will not be involved in the treatment or clinical evaluation of subjects, will be unblinded to subject treatment allocation to analyze PK and immunogenicity samples. Local SOPs will govern maintenance of the blind and information on treatment allocation will not be communicated outside of these clinical bioanalytical personnel.

4.7 Restrictions During the Study and Concomitant Treatment(s)

The investigator must be informed as soon as possible about any medication taken from the time of screening until the end of the study (end-of-study visit). Any concomitant medication(s), including herbal preparations, taken during the study will be recorded in the eCRF.

4.7.1 Permitted Concomitant Medications

Investigators may prescribe concomitant medications or treatments deemed necessary to provide adequate supportive care, except for those medications identified as "excluded" and listed in Section 4.7.2. Specifically, subjects should receive full supportive care during the study, including transfusions of blood and blood products, and treatment with antibiotics, antiemetics, antidiarrheals, analgesics, and other care as deemed appropriate and in accordance with their institutional guidelines.

4.7.2 Prohibited Concomitant Medications

Other than the medications described above, use of concomitant medications including OTC medications, herbal supplements, vitamins, etc at the times specified in the list below is not permitted. Subjects must be instructed not to take any medications including OTC products without first consulting with the investigator.

Use of the following concomitant medications is not permitted:

- Concurrent use of SGLT2 inhibitors (except for dapagliflozin), GLP-1-analogue-containing preparation or any other glucose-lowering agent other than metformin within the last 30 days or 5 half-lives of the drug (whichever is longer) at the time of screening (Visit 1)
- Concurrent use of any medicinal products, or herbal or OTC preparations licensed for control of body weight or appetite at the time of screening (Visit 1)
- Concurrent or previous use of drugs approved for weight loss (eg, orlistat, bupropion-naltrexone, phentermine-topiramate, phentermine, lorcaserin) within the last 30 days or 5 half-lives of the drug, whichever is longest, at the time of screening. (Visit 1)
- Any other investigational agent not included in the protocol within last 30 days or 5 half-lives (whichever is longer) from screening (Visit 1)
- Concurrent use of Aspirin (acetylsalicylic acid) at a dose greater than 150 mg once daily and within the last 72 hours prior to the start of the study (Visit 4)
- Concurrent use of paracetamol (acetaminophen) or paracetamol-containing preparations at a total daily dose of greater than 3000 mg once daily and within the last 72 hours prior to the start of the study (Visit 4)

- Concurrent use of ascorbic acid (vitamin C) supplements at a total daily dose of >than 1000 mg and within the last 72 hours prior to the start of the study (Visit 4)
- Concurrent use of opiates, domperidone, metoclopramide, or other drugs known to alter gastric emptying and within the last 72 hours prior to the start of the study (Visit 4)
- Loop diuretics within one month prior to screening (Visit 1) and during the study

4.8 Statistical Evaluation

4.8.1 General Considerations

Data will be provided in listings sorted by treatment group and subject number. Tabular summaries will be presented by treatment group. 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 (SD), median, minimum, and maximum. Baseline values will be defined as the last valid assessment prior to the first administration of investigational product unless otherwise specified. Details of endpoint analyses will be described in the statistical analysis plan.

4.8.1.1 Analysis Population

Efficacy Population: The Intent-to-treat (ITT) population includes all subjects who are randomized and receive any investigation product analyzed according to their randomized treatment group.

Safety Population: The As-treated population includes all subjects who receive any investigation product analyzed according to the treatment they actually receive.

PK Population: The PK population includes all subjects who received at least 1 dose of investigational product and had at least one PK sample taken that is above the lower limit of quantitation.

[redacted]

4.8.2 Sample Size and Power Calculations

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_{0-4h} at a two-sided alpha of 5%, assuming a common 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_{0-4h} 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).

4.8.3 Efficacy

4.8.3.1 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_{0-4h} as measured by a MMTT, will be summarized by treatment group. Statistical comparisons of these endpoints between MEDI0382/dapagliflozin/metformin and placebo/dapagliflozin/metformin treatment groups will be performed using an analysis of covariance by adjusting baseline and treatment group with last-observation-carried-forward (LOCF) approach to handle missing data.

Descriptive statistics at each time point will be provided by treatment group.

4.8.3.2 Secondary Efficacy Analyses

Secondary efficacy and pharmacodynamics (PD) analysis will be based on the ITT population. The following endpoints will be summarized by treatment group and analyzed similarly to the analysis of primary efficacy endpoints.

- Change from baseline to the end of dosing at each dose level (Days 7, 14, and 28) in glucose AUC at 24 hours 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 coefficient of variation (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 of 24-hour glucose readings as measured by CGM
- Change from baseline to Days 7, 14, and 28 in the % 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 % of 24-hour glucose readings obtained from CGM that fall within the hyperglycemic range of > 180 mg/dL (> 10 mmol/L)
- Change from baseline to Days 7, 14, and 28 in the % 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 % of 24-hour glucose readings obtained from CGM that fall within the clinically significant hypoglycemic range of < 54 mg/dL (< 3.0 mmol/L)

Descriptive statistics at each time point will be provided by treatment group.

4.8.3.3 Exploratory Analyses

Exploratory efficacy and PD analysis will be based on the ITT population. The following endpoints will be summarized by treatment group and analyzed similarly to the analysis of primary efficacy endpoints.

- 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 28 in active GLP-1, glucagon, insulin, c-peptide $AUC_{0\text{-}4h}$ as measured by MMTT
- Change from baseline (Day -1) to Day 7, 14, and 28 in fasting FFA level
- 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)
- Total glucose excreted in urine collected for 24 hours

For the proportion of subjects achieving ≥ 5% body weight loss from baseline after 28 days treatment, pairwise statistical comparisons between MEDI0382/dapagliflozin/metformin and placebo/dapagliflozin/metformin treatment groups will be made using a logistic regression by adjusting baseline and treatment group with an LOCF approach to handle missing data.

Descriptive statistics at each time point will be provided by treatment group.

4.8.4 Safety

4.8.4.1 Analysis of Adverse Events

Safety analysis will be based on the As-treated population. Adverse event collection begins after the subject signs the ICF and lasts until the end of the study. Treatment-emergent AEs

(TEAEs) and treatment-emergent SAEs (TESAEs) will be coded by the most updated version of the Medical Dictionary for Regulatory Activities (MedDRA), and the type, incidence, severity and relationship to investigational product will be summarized by MedDRA's System Organ Class, Preferred Term, and by treatment group. Treatment-emergent AEs leading to discontinuation, TEAEs leading to death, and deaths will also be summarized. Specific TEAEs will be counted once for each subject for the calculation of percentages. In addition, if the same TEAE occurs multiple times within a particular subject, the highest severity and level of relationship observed will be reported.

4.8.4.2 Analysis of Safety Data

Safety data such as vital signs (including 24-hour ABPM) will be summarized by treatment group at each time point. Change from baseline to each postbaseline time point in these data will also be summarized, where appropriate. Electrocardiogram parameters will also be assessed and summarized descriptively by treatment group.

4.8.4.3 Analysis of Clinical Laboratory Parameters

Clinical laboratory data will be summarized by treatment group at each time point. Change from baseline to each postbaseline time point in these data will also be summarized, where appropriate.

4.8.5 Analysis of [redacted] Pharmacokinetics

4.8.5.1 Pharmacokinetic Analyses

If data allow, PK parameters such as C_{max}, t_{max}, AUC, and terminal elimination half-life will be estimated from plasma concentration-time data for MEDI0382 and β-hydroxybutyrate at each dose level separately and for 10 mg dapagliflozin. Moreover, if data allow, additional parameters such as apparent clearance may be derived for MEDI0382 at all dose levels and for 10 mg dapagliflozin.

Descriptive statistics will be generated for PK parameters for the MEDI0382 and dapagliflozin group in each cohort. Subjects who have at least one measurable concentration time point of investigational product will be used for this analysis.

[redacted]

[redacted]

4.8.6 Interim Analysis

No interim analysis is planned.

5 ASSESSMENT OF SAFETY

5.1 Definition of Adverse Events

The ICH Guideline for GCP E6(R1) defines an AE as:

> Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

An AE includes but is not limited to any clinically significant worsening of a subject's pre-existing condition. An abnormal laboratory finding (including ECG finding) that requires medical intervention by the investigator, or a finding judged by the investigator as medically significant should be reported as an AE. If clinical sequelae are associated with a laboratory abnormality, the diagnosis or medical condition should be reported (eg, renal failure, hematuria) not the laboratory abnormality (eg, elevated creatinine, urine red blood cell count increased). Abnormal laboratory values that are not, in the investigator's opinion, medically significant and do not require intervention should not be reported as AEs.

Adverse events may be treatment emergent (ie, occurring after initial receipt of investigational product) or non-treatment emergent. A non-TEAE is any new sign or symptom, disease, or other untoward medical event that begins after written informed consent has been obtained but before the subject has received investigational product.

Elective treatment or surgery or preplanned treatment or surgery that was scheduled prior to the subject being enrolled into the study for a documented preexisting condition that did not worsen from baseline is not considered an AE (serious or nonserious). An untoward medical event occurring during the prescheduled elective procedure or routinely scheduled treatment should be recorded as an AE or SAE.

5.2 Definition of Serious Adverse Events

An SAE is any AE that:

- Results in death
- Is immediately life-threatening
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect in offspring of the subject
- Is an important medical event that may jeopardize the subject or may require medical intervention to prevent one of the outcomes listed above

Medical or scientific judgment should be exercised in deciding whether expedited reporting is appropriate in this situation. Examples of medically important events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalizations or development of drug dependency or drug abuse.

5.3 Definition of Adverse Events of Special Interest

An adverse event of special interest (AESI) is an AE of scientific and medical interest specific to understanding of the investigational product and may require close monitoring and collecting additional information by the investigator for the sponsor. An AESI may be serious or nonserious. The rapid reporting of AESIs allows ongoing surveillance of these events in order to characterize and understand them in association with the use of this investigational product.

All AESIs should be recorded in the eCRF within 24 hours. In addition, AESIs that are also SAEs should be reported to MedImmune Patient Safety within 24 hours. Instructions to the site on how to record (in the eCRF) and report AESI is provided in Section 5.4 and Appendix 10.5, respectively. The AESI for this study is defined below.

5.3.1 Hepatic function Abnormalities

Refer to Section 5.6.2 and Appendix 10.5 for the definition and follow up for liver abnormalities. There are no other AESIs in this study.

5.4 Recording of Adverse Events

Adverse events will be recorded on the eCRF using a recognized medical term or diagnosis that accurately reflects the event. Treatment-emergent AEs will be assessed by the investigator for severity, relationship to the investigational product, possible etiologies, and whether the event meets criteria of an SAE and therefore requires immediate notification to the sponsor (Section 5.5). See Section 5.2 for the definition of SAEs and Appendix 10.3 for guidelines for assessment of severity and relationship. If a TEAE evolves into a condition that meets the regulatory definition of "serious," it will be reported in the eCRF.

5.4.1 Time Period for Collection of Adverse Events

All AEs and SAEs will be collected from the time of admission to the clinical unit (Day -2) throughout the treatment period and including the follow-up period (28 ±4 days after the last dose of investigational product (inpatient Visit 13).

5.4.2 Follow up of Unresolved Adverse Events

Any AEs that are unresolved at the subject's last visit in the study are followed up by the investigator for as long as medically indicated, but without further recording in the eCRF. MedImmune retains the right to request additional information for any subject with ongoing AE(s)/SAE(s) at the end of the study, if judged necessary. Updates regarding SAEs that were ongoing at the time of the subject's completion of study participation should be submitted to the study representative using a paper SAE follow-up form.

5.5 Reporting of Serious Adverse Events

Serious adverse events have to be reported whether or not they are considered casually related to the investigational product or to the study procedure(s). All SAEs will be recorded in the CRF.

If any SAE occurs during the course of the study, the investigator or other site personnel will inform the appropriate sponsor representative(s) within 1 day, ie, immediately but no later than 24 hours of when he/she becomes aware of the event. The designated sponsor representative works with the investigator to ensure that all the necessary information is provided to the sponsor's patient safety data entry site within 1 calendar day of initial receipt for fatal and life threatening events and within 5 calendar days of initial receipt for all other SAEs.

For fatal or life-threatening AEs where important or relevant information is missing, active follow up is undertaken immediately. Investigators or other site personnel will inform

sponsor representatives of any follow-up information on a previously reported SAE within 1 calendar day, ie, immediately but no later than 24 hours of when he/she becomes aware of the event.

Once the investigator or other site personnel indicate an AE is serious in the electronic data capture (EDC) system, an automated e-mail alert is sent to the designated sponsor representative(s).

If the EDC system is not available, then the investigator or other study-site personnel reports the SAE to the appropriate sponsor representative by telephone. The sponsor representative will advise the investigator/study site personnel how to proceed.

5.6 Other Events Requiring Immediate Reporting

5.6.1 Overdose

An overdose in this study is defined as a subject receiving a dose of investigational product that is greater than the dose that was intended to be given:

- An overdose with associated AEs is recorded as the AE diagnosis/symptoms on the relevant AE modules in the eCRF and on the Overdose eCRF module.
- An overdose without associated symptoms is only reported on the Overdose eCRF module.

If an overdose with a MedImmune investigational product occurs during the course of the study, then the investigator or other site personnel inform appropriate sponsor representatives immediately but no later than 24 hours of when he/she becomes aware of it.

The designated sponsor representative works with the investigator to ensure that all relevant information is provided to the sponsor's patient safety data entry site.

For overdoses associated with an SAE, the standard reporting timelines apply; see Section 5.5. For other overdoses, reporting must occur within 30 days.

5.6.2 Hepatic Function Abnormality

Cases where a subject shows elevations in liver biochemistry may require further evaluation, and occurrences of AST or ALT $\geq 3 \times$ ULN together with TBL $\geq 2 \times$ ULN may need to be reported as SAEs. Please refer to Appendix 10.5 for further instruction on cases of increases in liver biochemistry and evaluation of Hy's law.

5.6.3 Pregnancy

All pregnancies and outcomes of pregnancy should be reported to the sponsor.

5.6.3.1 Maternal Exposure

Women of childbearing potential in this study who are sexually active with a nonsterilized male partner are required to use 2 forms of contraception (with at least 1 highly effective method) as described in the inclusion criteria (Section 4.1.2 and Appendix 10.2). Pregnancy should be avoided for at least 28 days after receiving investigational product or until the subject completes participation in the study, whichever is longer. If a subject becomes pregnant during the course of the study, investigational product should be discontinued immediately.

Pregnancy itself is not regarded as an AE unless there is a suspicion that the investigational product under study may have interfered with the effectiveness of a contraceptive medication. Congenital abnormalities/birth defects and spontaneous miscarriages should be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs. The outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth, or congenital abnormality) should be followed up and documented even if the subject was discontinued from the study.

If any pregnancy occurs in the course of the study, then the investigator or other site personnel informs the appropriate sponsor representatives within 1 day, ie, immediately but no later than 24 hours of when he or she becomes aware of it.

The designated sponsor representative works with the investigator to ensure that all relevant information is provided within 1 to 5 calendar days for SAEs (Section 5.5) and within 30 days for all other pregnancies.

The same timelines apply when outcome information is available.

Any subject who becomes pregnant during the course of the study will be followed so that pregnancy outcome can be determined and reported to the sponsor and the regulatory authorities.

6 STUDY AND DATA MANAGEMENT

6.1 Training of Study Site Personnel

Before the first subject is entered into the study, a MedImmune representative will review and discuss the requirements of the Clinical Study Protocol (CSP) and related documents with the investigational staff and also train them in any study-specific procedures and system(s) utilized.

The Principal Investigator will ensure that appropriate training relevant to the study is given to all of these staff, and that any new information relevant to the performance of this study is forwarded to the staff involved.

The Principal Investigator will maintain a record of all individuals involved in the study (medical, nursing, and other staff).

6.2 Monitoring of the Study

During the study, a MedImmune representative will have regular contacts with the study site including visits to do the following:

- Provide information and support to the investigator(s)
- Confirm that facilities remain acceptable
- Confirm that the investigational team is adhering to the protocol, that data are being accurately and timely recorded in the eCRFs, that biological samples are handled in accordance with the Laboratory Manual and that study drug accountability checks are being performed
- Perform source data verification (a comparison of the data in the eCRFs with the subject's medical records at the hospital or practice and other records relevant to the study) including verification of informed consent of participating subjects. This will require direct access to all original records for each subject (eg, clinic charts)
- Ensure withdrawal of informed consent to the use of the subject's biological samples is reported and biological samples are identified and disposed of/destroyed accordingly, and the action is documented, and reported to the subject.

The MedImmune representative will be available between visits if the investigator(s) or other staff at the center needs information and advice about the study conduct.

6.2.1 Source Data

Refer to the Clinical Study Agreement for location of source data.

6.2.2 Study Agreements

The Principal Investigator at each/the center should comply with all the terms, conditions, and obligations of the Clinical Study Agreement, or equivalent, for this study. In the event of any inconsistency between this CSP and the Clinical Study Agreement, the terms of CSP shall prevail with respect to the conduct of the study and the treatment of subjects. In all other matters not relating to study conduct or treatment of subjects, the terms of the Clinical Study Agreement shall prevail.

Agreements between MedImmune and the Principal Investigator must be in place before any study-related procedures can take place or subjects are enrolled.

6.2.3 Archiving of Study Documents

The Investigator follows the principles outlined in the Clinical Study Agreement.

6.3 Study Timetable and End of Study

An individual subject will be considered to have completed the study if the subject was followed through the last protocol-specified visit or assessment (including telephone contact) or assessed for the primary end point of the study, regardless of the number of doses of investigational product that was received.

Subjects will be considered not to have completed the study if consent was withdrawn or the subject was lost to follow up (Section 4.1.5 and Section 4.1.6).

The end of the study ("study completion") is defined as the date of the last protocol-specified visit or assessment (including telephone contact) for the last subject in the study.

6.4 Data Management

Data management will be performed by MedImmune Data Management staff or other party according to the Data Management Plan.

A web-based data capture system will be used for data collection and query handling. The investigator will ensure that data are recorded on the eCRFs as specified in the study protocol and in accordance with the instructions provided.

The investigator ensures the accuracy, completeness, and timeliness of the data recorded and the provision of answers to data queries according to the Clinical Study Agreement. The investigator will sign the completed eCRFs. A copy of the completed eCRFs will be archived at the study site.

6.5 Medical Monitor Coverage

Each subject will be provided with contact information for the Principal Investigator. In addition, each subject will receive a toll-free number intended to provide the subject's physician with access to a medical monitor 24 hours a day, 7 days a week in the event of an emergent situation where the subject's health is deemed to be at risk. In this situation, when a subject presents to a medical facility where the treating physician or health care provider requires access to a physician who has knowledge of the investigational product and the CSP and the principal investigator is not available, the treating physician or health care provider can contact a medical monitor through this system, which is managed by a third party vendor.

7 ETHICAL AND REGULATORY REQUIREMENTS

7.1 Ethical Conduct of the Study

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with ICH/GCP, and applicable regulatory requirements.

7.2 Subject Data Protection

Each subject will be assigned a SID to ensure that personally identifiable information is kept separate from the study data. Subject data that are relevant to the trial, eg, demographic information, physical or mental health condition, diagnosis, comorbidities, laboratory test results, etc will only be collected with the subject's informed consent. The ICF will incorporate or, in some cases, be accompanied by a separate document incorporating wording that describes how subject data will be collected, used, and distributed in compliance with relevant data protection and privacy legislation.

[redacted]

7.3 Ethics and Regulatory Review

The IEC responsible for each site must review and approve the final CSP including the final version of the ICF and any other written information and/or materials to be provided to the subjects. The IEC must also approve all advertising used to recruit subjects for the study. The

investigator or representative is responsible for submitting these documents to the applicable IEC and distributing them to the study-site staff.

The opinion of the IEC should be given in writing. The investigator should submit the written approval to MedImmune before enrollment of any subject into the study.

The IEC should approve all advertising used to recruit subjects for the study.

MedImmune should approve any modifications to the ICF that are needed to meet local requirements.

If required by local regulations, the protocol should be reapproved by the IEC annually.

Before enrollment of any subject into the study, the final CSP including the final version of the ICF is approved by the national regulatory authority or a notification to the national regulatory authority is done, according to local regulations. MedImmune will handle the distribution of any of these documents to the national regulatory authorities.

MedImmune will provide Regulatory Authorities, IEC and Principal Investigators with safety updates/reports according to local requirements including suspected unexpected serious adverse reactions, where relevant.

Each Principal Investigator is responsible for providing the IEC with reports of any serious and unexpected adverse drug reactions from any other study conducted with the investigational product. MedImmune will provide this information to the Principal Investigator so that he/she can meet these reporting requirements.

7.4 Informed Consent

The Principal Investigator(s) at each center will:

- Ensure each subject is given full and adequate oral and written information about the nature, purpose, possible risk, and benefit of the study
- Ensure each subject is notified that they are free to discontinue from the study at any time
- Ensure each subject is given the opportunity to ask questions and allowed time to consider the information provided
- Ensure each subject provides signed and dated ICF before conducting any procedure specifically for the study
- Ensure the original, signed ICF(s) is/are stored in the Investigator’s Study File
- Ensure a copy of the signed ICF is given to the subject

- Ensure that any incentives for subjects who participate in the study as well as any provisions for subjects harmed as a consequence of study participation are described in the ICF that is approved by an IEC

7.5 Changes to the Protocol and Informed Consent Form

Study procedures will not be changed without the mutual agreement of the Principal Investigator and MedImmune.

If there are any substantial changes to the study protocol, then these changes will be documented in a study protocol amendment and in a new version of the study protocol, where required.

The amendment is to be approved by the relevant IEC and if applicable, also the national regulatory authority approval before implementation. Local requirements are to be followed for revised protocols.

MedImmune will distribute any subsequent amendments and new versions of the protocol to each Principal Investigator(s). For distribution to IEC see Section 7.3.

If a protocol amendment requires a change to a site's ICF, MedImmune and the site's IEC are to approve the revised ICF before the revised form is used. The IEC must also approve advertising and any other written information and/or materials resulting from the change to the protocol.

If local regulations require, any administrative change will be communicated to or approved by each IEC.

7.6 Audits and Inspections

Authorized representatives of MedImmune, a regulatory authority, or an IEC may perform audits or inspections at the center including source data verification. The purpose of an audit or inspection is to systematically and independently examine all study-related activities and documents; to determine whether these activities were conducted; and to confirm that data were recorded, analyzed, and accurately reported according to the protocol, GCP, guidelines of the ICH, and any applicable regulatory requirements. The investigator will contact MedImmune immediately if contacted by a regulatory agency about an inspection at the site.

8 REFERENCES

Bagger et al, 2015

Bagger JI, Holst JJ, Hartmann B, Andersen B, Knop FK, Vilsbøll T. Effect of oxyntomodulin, glucagon, GLP-1, and combined glucagon +GLP-1 infusion on food intake, appetite, and resting energy expenditure. J Clin Endocrinol Metab. 2015;100(12):4541-52.

CDER, 2005

Center for Drug Evaluation and Research. Byetta Pharmacology Review. 2005.9.

DeFronzo, 2017

DeFronzo RA. Combination therapy with GLP-1 receptor agonist and SGLT2 inhibitor. Diabetes Obes Metab. 2017 Apr 22. [epub ahead of print].

Forxiga Summary of Product Characteristics, 2017

Forxiga [Summary of Product Characteristics on the Internet]. Södertälje (Sweden): AstraZeneca AB, 2017 [revised 2017 May 02; cited 2017 Aug 10]. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/002322/WC500136026.pdf.

Frías et al, 2016

Frías JP, Guja C, Hardy E, Ahmed A, Dong F, Öhman P, et al. Exenatide once weekly plus dapagliflozin once daily versus exenatide or dapagliflozin alone in patients with type 2 diabetes inadequately controlled with metformin monotherapy (DURATION-8): a 28 week, multicentre, double-blind, phase 3, randomised controlled trial. Lancet Diabetes Endocrinol. 2016 Dec;4(12):1004-16.

Habegger et al, 2013

Habegger KM, Stemmer K, Cheng C, Müller TD, Heppner KM, Ottaway N, et al. Fibroblast growth factor 21 mediates specific glucagon actions. Diabetes. 2013;62(5):1453-63.

Lynch et al, 2014

Lynch AM, Pathak N, Pathak V, O'Harte FP, Flatt PR, Irwin N, et al. A novel DPP IV-resistant C-terminally extended glucagon analogue exhibits weight-lowering and diabetes-protective effects in high-fat-fed mice mediated through glucagon and GLP-1 receptor activation. Diabetologia. 2014;57(9):1927-36.

Petersen et al, 2005

Petersen KF, Dufour S, Befroy D, Lehrke M, Hendler RE, Shulman GI. Reversal of non-alcoholic hepatic steatosis, hepatic insulin resistance, and hyperglycemia by moderate weight reduction in patients with type 2 diabetes. Diabetes. 2005 Mar;54(3):603-8.

Rosenstock and Ferrannini, 2015

Rosenstock J, Ferrannini E. Euglycemic Diabetic Ketoacidosis: A Predictable, Detectable, and Preventable Safety Concern with SGLT2 Inhibitors. Diabetes Care. 2015 Sep;38(9):1638-42.

Qiu et al, 2017

Qiu H, Novikov A, Vallon V. Ketosis and diabetic ketoacidosis in response to SGLT2 inhibitors: basic mechanisms and therapeutic perspectives. Diabetes Metab Res Rev. 2017 Jul;33(5).

Skyder et al, 2017

Skyder JS, Bakris GL, Bonifacio E, Darsow T, Eckel RH, Groop L, et al. Differentiation of diabetes by pathophysiology, natural history, and prognosis. Diabetes. 2017 Feb;66(2):241-55.

Tonneijck et al, 2016

Tonneijck L, Smits MM, Muskiet MH, Hoekstra T, Kramer MH, Danser AH, et al. Acute renal effects of the GLP-1 receptor agonistexenatide in overweight type 2 diabetes patients: a randomised, double-blind placebo-controlled trial. Diabetologia. 2016 Jul;59(7):1412-21.

Wynne et al, 2006

Wynne K, Park AJ, Small CJ, Meeran K, Ghatei MA, Frost GS, et al. Oxyntomodulin increases energy expenditure in addition to decreasing energy intake in overweight and obese humans: a randomised controlled trial. Int J Obes. 2006;30(12):1729-36.

9 CHANGES TO THE PROTOCOL

Not applicable; this is an original protocol.

10 APPENDICES

10.1 Appendix 1 - Signatures

Sponsor Signature(s)

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 inadequately controlled with dapagliflozin and metformin

I agree to the terms of this protocol.

Signature and date: Electronic Signature Attached

Boaz Hirshberg, MD

Clinical Therapeutic Area Head

One MedImmune Way, Gaithersburg MD, 20878, USA

Telephone number: 1-301-398-0645

Signature of Principal Investigator

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 inadequately controlled with dapagliflozin and metformin

I, the undersigned, have reviewed this protocol, and I agree to conduct this protocol in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with the International Conference on Harmonization guidelines on Good Clinical Practice, any applicable laws and requirements, and any conditions required by a regulatory authority and/or /Independent Ethics Committee (IEC).

I understand that the protocol may not be modified without written approval of the sponsor. All changes to the protocol must be submitted to the applicable regulatory authority and IEC, and must be approved by the IEC prior to implementation except when necessary to eliminate immediate hazards to the subjects or when the change(s), as deemed by the sponsor, involves only logistical or administrative changes. Documentation of IEC approval must be sent to the sponsor immediately upon receipt.

Signature and date: _____

Name and title: _____

Address including postal code: _____

_____

Telephone number: _____

Site/Center Number (if available)_____

10.2 Appendix 2 - Contraception Guidance

For females of childbearing potential:

- Females of childbearing potential are defined as those who are not surgically sterile (ie, surgical sterilisation includes bilateral tubal ligation, bilateral oophorectomy, or complete hysterectomy) or those who are not postmenopausal (defined as at least 1 year since last menses and having an elevated follicle-stimulating hormone level in the post-menopausal range in previous laboratory test results.

A highly effective method of contraception is defined as one that results in a low failure rate (ie, less than 1% per year) when used consistently and correctly. The acceptable methods of contraception are described in **Table 10.2-1**.

Female subjects must refrain from egg cell donation while in study and for 28 days after the final dose of investigational product.

Table 10.2-1 Highly Effective Methods of Contraception

- Tubal occlusion
- Copper T intrauterine device
- Levonorgestrel-releasing intrauterine system (eg, Mirena®)
- Medroxyprogesterone injections (eg, Depo-Provera®)
- Etonogestrel implants (eg, Implanon®, Norplan®)
- Combined pills
- Norelgestromin/ethinyl estradiol transdermal system
- Intravaginal device (eg, NuvaRing®)
- Cerazette® pill

10.3 Appendix 3 - Additional Safety Guidance

Further Guidance on the Definition of a Serious Adverse Event

Life threatening

"Life-threatening" means that the subject was at immediate risk of death from an AE as it occurred or it is suspected that use or continued use of the product would result in the subject's death. 'Life-threatening' does not mean that had an AE occurred in a more severe form it might have caused death (eg, hepatitis that resolved without hepatic failure).

Hospitalization

Outpatient treatment in an emergency room is not in itself a SAE, although the reasons for it may be (eg, bronchospasm, laryngeal oedema). Hospital admissions and/or surgical operations planned before or during a study are not considered AEs if the illness or disease existed before the subject was enrolled in the study, provided that it did not deteriorate in an unexpected way during the study.

Important Medical Event or Medical Intervention

Medical and scientific judgment should be exercised in deciding whether a case is serious in situations where important medical events may not be immediately life threatening or result in death, hospitalization, disability or incapacity but may jeopardize the subject or may require medical intervention to prevent one or more outcomes listed in the definition of serious. These should usually be considered as serious.

Simply stopping the suspect drug does not mean that it is an important medical event; medical judgment must be used.

Examples of such events are the following:

- Angioedema not severe enough to require intubation but requiring intravenous hydrocortisone treatment
- Hepatotoxicity caused by paracetamol (acetaminophen) overdose requiring treatment with N-acetylcysteine
- Intensive treatment in an emergency room or at home for allergic bronchospasm
- Blood dyscrasias (eg, neutropenia or anaemia requiring blood transfusion) or convulsions that do not result in hospitalization
- Development of drug dependency or drug abuse

Assessment of Severity

Assessment of severity is one of the responsibilities of the investigator in the evaluation of AEs and SAEs. The determination of severity should be made by the investigator based upon medical judgment and the severity categories of Grade 1 to 5 as defined below.

Grade 1 (mild)	An event that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.
Grade 2 (moderate)	An event that is usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the subject.
Grade 3 (severe)	An event that requires intensive therapeutic intervention. The event interrupts usual activities of daily living, or significantly affects the clinical status of the subject.
Grade 4 (life threatening)	An event, and/or its immediate sequelae, that is associated with an imminent risk of death.
Grade 5 (fatal)	Death (loss of life) as a result of an event.

It is important to distinguish between serious criteria and severity of an AE. Severity is a measure of intensity whereas seriousness is defined by the criteria in Section 5.2. A Grade 3 AE need not necessarily be considered an SAE. For example, a Grade 3 headache that persists for several hours may not meet the regulatory definition of an SAE and would be considered a nonserious event, whereas a Grade 2 seizure resulting in a hospital admission would be considered an SAE.

Assessment of Relationship

Relationship to Investigational Product

The investigator is required to provide an assessment of relationship of AEs and SAEs to the investigational product.

An event will be considered “not related” to use of the investigational product if any of the following tests are met:

- An unreasonable temporal relationship between administration of the investigational product and the onset of the event (eg, the event occurred either before, or too long after, administration of the investigational product for it to be considered product-related)
- A causal relationship between the investigational product and the event is biologically implausible (eg, death as a passenger in an automobile accident)
- A clearly more likely alternative explanation for the event is present (eg, typical adverse reaction to a concomitant drug and/or typical disease-related event)

Individual AE/SAE reports will be considered "related" to use of the investigational product if the "not related" criteria are not met.

"Related" implies that the event is considered to be "associated with the use of the drug" meaning that there is "a reasonable possibility" that the event may have been caused by the product under investigation (ie, there are facts, evidence, or arguments to suggest possible causation).

Relationship to Protocol Procedures

The investigator is also required to provide an assessment of relationship of SAEs to protocol procedures on the SAE Report Form. This includes non-TESAEs (ie, SAEs that occur prior to the administration of investigational product) as well as TESAEs. A protocol-related SAE may occur as a result of a procedure or intervention required during the study (eg, blood collection, washout of an existing medication). The following guidelines should be used by investigators to assess the relationship of SAEs to the protocol:

Protocol related: The event occurred due to a procedure/intervention that was described in the protocol for which there is no alternative etiology present in the subject's medical record.

Not protocol related: The event is related to an etiology other than the procedure/ intervention that was described in the protocol (the alternative etiology must be documented in the study subject's medical record).

10.4 Appendix 4 - National Institute of Allergy and Infectious Diseases and Food and Allergy Anaphylaxis Network Guidance for Anaphylaxis Diagnosis

The National Institute of Allergy and Infectious Diseases and the Food and Allergy Anaphylaxis Network define anaphylaxis as a serious allergic reaction that is rapid in onset and may cause death (**Error! Reference source not found.**). They recognize 3 categories of anaphylaxis, with criteria designated to capture from 80% of cases (category 1) to > 95% of all cases of anaphylaxis (for all 3 categories).

1. Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (eg, generalized hives, pruritus or flushing, swollen lips-tongue-uvula)
   AND AT LEAST ONE OF THE FOLLOWING
   a. Respiratory compromise (eg, dyspnoea, wheeze-bronchospasm, stridor, reduced peak expiratory flow (PEF), hypoxemia)
   b. Reduced BP or associated symptoms of end-organ dysfunction (eg, hypotonia [collapse], syncope, incontinence)
2. Two or more of the following that occur rapidly after exposure to a likely allergen for that patient (minutes to several hours):
   a. Involvement of the skin-mucosal tissue (eg, generalized hives, itch-flush, swollen lips-tongue-uvula)
   b. Respiratory compromise (eg, dyspnoea, wheeze-bronchospasm, stridor, reduced peak expiratory flow (PEF), hypoxemia)
   c. Reduced BP or associated symptoms (eg, hypotonia [collapse], syncope, incontinence)
   d. Persistent GI symptoms (eg, crampy abdominal pain, vomiting)
3. Reduced BP after exposure to known allergen for that patient (minutes to several hours):
   a. Infants and children: low systolic BP (age specific) or greater than 30% decrease in systolic BP
   b. Adults: systolic BP of less than 90 mm Hg or greater than 30% decrease from that person’s baseline

Reference:

Sampson HA, Muñoz-Furlong A, Campbell RL, Adkinson NF Jr, Bock SA, Branum A, Brown SG, et al. Second symposium on the definition and management of anaphylaxis: summary report—Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network Symposium. J Allergy Clin Immunol. 2006 Feb;117(2):391-7.

10.5 Appendix 5 - Actions Required in Cases of Increases in Liver Biochemistry and Evaluation of Hy's law

Introduction

This Appendix describes the process to be followed in order to identify and appropriately report cases of Hy's Law (HL). It is not intended to be a comprehensive guide to the management of elevated liver biochemistries.

During the course of the study the investigator will remain vigilant for increases in liver biochemistry. The investigator is responsible for determining whether a subject meets potential Hy's Law (PHL) criteria at any point during the study.

The investigator participates, together with MedImmune clinical project representatives, in review and assessment of cases meeting PHL criteria to agree whether HL criteria are met. HL criteria are met if there is no alternative explanation for the elevations in liver biochemistry other than Drug Induced Liver Injury (DILI) caused by the investigational product.

The investigator is responsible for recording data pertaining to PHL/HL cases and for reporting AEs and SAEs according to the outcome of the review and assessment in line with standard safety reporting processes.

Definitions

Potential Hy's Law (PHL)

Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) ≥ 3 × upper limit of normal (ULN) together with TBL ≥ 2 × ULN at any point during the study following the start of investigational product irrespective of an increase in alkaline phosphatase (ALP).

Hy's Law (HL)

AST or ALT ≥ 3 × ULN together with TBL ≥ 2 × ULN, where no other reason, other than the investigational product, can be found to explain the combination of increases; eg, elevated ALP indicating cholestasis, viral hepatitis, another drug.

For PHL and HL the elevation in transaminases must precede or be coincident with (ie, on the same day) the elevation in TBL, but there is no specified timeframe within which the elevations in transaminases and TBL must occur.

Identification of Potential Hy's Law Cases

In order to identify cases of PHL it is important to perform a comprehensive review of laboratory data for any subject who meets any of the following identification criteria in isolation or in combination:

- ALT ≥ 3 × ULN
- AST ≥ 3 × ULN
- TBL ≥ 2 × ULN

The investigator will without delay review each new laboratory report and if the identification criteria are met will:

- Notify the sponsor study representative
- Determine whether the subject meets PHL criteria by reviewing laboratory reports from all previous visits
- Promptly enter the laboratory data into the laboratory eCRF

Follow-up

Potential Hy's Law Criteria Are Not Met

If the subject does not meet PHL criteria the investigator will:

- Inform the sponsor representative that the subject has not met PHL criteria
- Perform follow-up on subsequent laboratory results according to the guidance provided in the CSP.

Potential Hy's Law Criteria Are Met

If the subject does meet PHL criteria the investigator will notify the sponsor study representative who will then inform the central study team. The study Physician contacts the investigator, to provide guidance, discuss and agree an approach for the study subjects' follow-up and the continuous review of data. Subsequent to this contact the investigator will:

- Monitor the subject until liver biochemistry parameters and appropriate clinical symptoms and signs return to normal or baseline levels, or as long as medically indicated
- Investigate the etiology of the event and perform diagnostic investigations as discussed with the study physician.

- Complete the Liver eCRF Modules as information becomes available
- If at any time (in consultation with the Medical Monitor) the PHL case meets serious criteria, report it as an SAE using standard reporting procedures

Review and Assessment of Potential Hy's Law Cases

The instructions in this section should be followed for all cases where PHL criteria are met.

No later than 3 weeks after the biochemistry abnormality was initially detected, the Medical Monitor will contact the investigator in order to review available data and agree on whether there is an alternative explanation for meeting PHL criteria other than DILI caused by the investigational product. The Clinical Medical Monitor and Global Safety Physician will also be involved in this review together with other subject matter experts as appropriate.

According to the outcome of the review and assessment, the investigator will follow the instructions below.

If there is an agreed alternative explanation for the ALT or AST and TBL elevations, a determination of whether the alternative explanation is an AE will be made and subsequently whether the AE meets the criteria for a SAE:

- If the alternative explanation is not an AE, record the alternative explanation on the appropriate eCRF
- If the alternative explanation is an AE/SAE, record the AE /SAE in the eCRF accordingly and follow the sponsor standard processes

If it is agreed that there is no explanation that would explain the ALT or AST and TBL elevations other than the investigational product:

- Report an SAE (report term 'Hy's Law') according to sponsor standard processes.
    - The 'Medically Important' serious criterion should be used if no other serious criteria apply
    - As there is no alternative explanation for the HL case, a causality assessment of 'related' should be assigned.

If, there is an unavoidable delay, of over 3 weeks, in obtaining the information necessary to assess whether or not the case meets the criteria for HL, then it is assumed that there is no alternative explanation until such time as an informed decision can be made:

- Report an SAE (report term ‘Potential Hy’s Law’) applying serious criteria and causality assessment as per above
- Continue follow-up and review according to agreed plan. Once the necessary supplementary information is obtained, repeat the review and assessment to determine whether HL criteria are met. Update the SAE report according to the outcome of the review

References:

FDA Guidance for Industry (issued July 2009) ‘Drug-induced liver injury: Premarketing clinical evaluation’:http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM174090.pdf

10.6 Appendix 6 - Biological Samples

Storage, Reuse and Destruction of Biological Samples

Biological samples will be stored for a maximum of 15 years from the date of the Last Subject's Last Visit, after which they will be destroyed.

The results of biomarker research will be reported either in the Clinical Study Report itself or as an addendum, or separately in a scientific report or publication. The results of this biomarker research may be pooled with biomarker data from other studies with the study drug to generate hypotheses to be tested in future research. Antidrug antibody samples will be stored for up to 2 years after marketing approval.

Labelling and Shipment of Biological Samples

The principal investigator ensures that samples are labelled and shipped in accordance with the Laboratory Manual and the Biological Substance, Category B Regulations (materials containing or suspected to contain infectious substances that do not meet Category A criteria).

Any samples identified as Infectious Category A materials are not shipped and no further samples will be taken from the subject unless agreed with MedImmune and appropriate labelling, shipment and containment provisions are approved.

Chain of Custody of Biological Samples

A full chain of custody is maintained for all samples throughout their lifecycle.

The principal investigator at each study site keeps full traceability of collected biological samples from the subjects while in storage at the study site until shipment or disposal (where appropriate) and keeps documentation of receipt of arrival. The sample receiver keeps full traceability of the samples while in storage and during use until used or disposed of or until further shipment and keeps documentation of receipt of arrival.

MedImmune keeps oversight of the entire life cycle through internal procedures, monitoring of study sites and auditing of external laboratory providers.

Samples retained for further use are registered in the Translational Sciences Biorepository during the entire life cycle.

Document Name:	d5670c00007-clinical-protocol
Document Title:	d5670c00007-clinical-protocol
Document ID:	Doc ID-003552913
Version Label:	1.0 Approved CURRENT LATEST

Server Date (dd-MMM-yyyy HH:mm 'GMT'Z)	**Signed By**	**Meaning of Signature**
19-Sep-2017 13:59 GMT+0100	Frickleton Celeste	Clinical Approval
19-Sep-2017 14:25 GMT+0100	Flor Armando	Clinical Approval
19-Sep-2017 14:43 GMT+0100	Lan-Feng Tsai	Biostatistics Approval
19-Sep-2017 17:17 GMT+0100	Paolo Vicini	Research Approval
19-Sep-2017 22:10 GMT+0100	Boaz hirshberg	Clinical Development Approval

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