

**A Phase 1/2, Randomized, Double-blind,
Placebo-controlled, Multiple-ascending-dose Study
to Evaluate the Efficacy, Safety, and Pharmacokinetics
of MEDI0382 in Overweight and Obese Subjects
with a History of Type 2 Diabetes Mellitus**

Sponsor Protocol Number: D5670C00002

Application Number: EudraCT Number 2014-003716-36

Investigational Product: MEDI0382

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Contract Research Organization: Covance, Inc.

Protocol History, Date: Original Protocol, 25Nov2014,
Amendment 1, 26Feb2015
Amendment 2, 14Aug2015
Amendment 3, 10Oct2015
Administrative Change 1, 05Nov2015
Amendment 4, 18Mar2016
Amendment 5, 27Apr2016
Amendment 6, 21Jul2016
Amendment 7, 25Aug2016
Amendment 8, 23Sep2016

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PROTOCOL SYNOPSIS

TITLE

A Phase 1/2, Randomized, Double-blind, Placebo-controlled, Multiple-ascending-dose Study to Evaluate the Efficacy, Safety, and Pharmacokinetics of MEDI0382 in Overweight and Obese Subjects with a History of Type 2 Diabetes Mellitus

HYPOTHESES

Primary Hypothesis:

MEDI0382 will achieve an improvement in glucose control equivalent to at least that achieved by oral therapies in addition to metformin ($\geq 20\%$ reduction in glucose area under the concentration-time curve [AUC] after a mixed-meal test [MMT]), and at least comparable weight loss to that expected of liraglutide at the 1.8 mg dose (ie, between 1.3 and 2.0 kg) versus placebo following 4 weeks of repeat once-daily dosing in subjects with type 2 diabetes mellitus (T2DM) managed on metformin.

Secondary Hypotheses:

- MEDI0382 will achieve an improvement in glucose control as measured by hemoglobin A1c (HbA1c) and fructosamine following 4 weeks of repeat once-daily dosing.
- Gastrointestinal symptoms will be manageable during up-titration of MEDI0382, no adverse changes in cardiac and hemodynamic parameters will be observed, and the overall safety profile of MEDI0382 will be acceptable over up to 4 weeks of repeat once-daily dosing.

OBJECTIVES

Primary Objective:

The primary objective of this study is to assess the effect of MEDI0382 on glucose control (as measured by the standardized MMT glucose data) and body weight from baseline to the end of a 4-week treatment period at a stable dose.

Secondary Objectives:

1. To assess the effect of MEDI0382 on glucose control as measured by the standardized MMT, HbA1c, and fructosamine data from baseline through end of treatment
2. To characterize the safety profile of MEDI0382 following subcutaneous (SC) administration of multiple-ascending doses
3. To characterize the pharmacokinetics (PK) and immunogenicity of MEDI0382
4. To characterize the pharmacodynamics (PD) effect of MEDI0382 on glucose metabolism following a MMT

Exploratory Objectives:

[REDACTED]

5. To explore the effect of MEDI0382 on the volume and fat/water content of the liver
6. To explore the effect of MEDI0382 on visceral and subcutaneous fat

STUDY ENDPOINTS

Primary Endpoints (Cohort 4 only):

- Percent change from baseline in MMT glucose AUC (up to 240 minutes post-MMT) to end of treatment
- Change from baseline in body weight in kg to end of treatment

Secondary Endpoints (all cohorts unless stated otherwise):

- Change from baseline in HbA1c and fructosamine, and percent change from baseline in 24-hour glucose AUC post-MMT, through end of treatment (Cohort 4)
- Percent change from baseline in MMT glucose AUC (up to 240 minutes post-MMT) to end of treatment
- Change from baseline in body weight in kg to end of treatment

- Adverse events
 - Blood pressure
 - Pulse
 - Safety laboratory test results
 - Electrocardiograms (ECGs)
 - Columbia-Suicide Severity Rating Scale score (Cohorts 4, 5, and 6 only)
 - PK endpoints for MEDI0382: AUC over a dosing duration, maximum observed concentration, minimum observed concentration, time to maximum observed concentration (all cohorts); terminal half-life and accumulation ratio (Cohorts 1 to 3 only)
 - Concentration of metformin
 - Development of antidrug antibody (ADA) and titer (if positive)
 - PD endpoints (glucose metabolism panel):
 - Glucose
 - Beta cell health: insulin, pro-insulin, and c-peptide
 - Incretins: glucagon-like peptide-1, glucagon, gastric inhibitory peptide
 - Cohorts 5 and 6: insulin and glucose only
- Exploratory Endpoints (Cohort 4 only unless stated otherwise):
- [REDACTED]
 - [REDACTED]
 - [REDACTED]
 - [REDACTED]
 - [REDACTED]
 - Lipid endpoints: fasting high-density lipoprotein, low-density lipoprotein, triglycerides, non-esterified fatty acids, and beta-hydroxybutyrate (Cohorts 4, 5, and 6)
 - [REDACTED]
 - [REDACTED]
 - [REDACTED]
 - [REDACTED]
 - Change from baseline to Week 4 in:
 - Liver fat (%)
 - Liver volume (L)
 - Visceral adipose tissue (L)
 - Subcutaneous adipose tissue (L)
 - Liver diffusion
 - Sagittal diameter (image based)
 - Transversal diameter (image based)

as determined by magnetic resonance imaging (MRI) to be conducted if MRI is available to the site and the subject is suitable for and consents to scan

STUDY DESIGN

This is a randomized, double-blind (subjects and investigators/site staff blinded; MedImmune unblinded), placebo-controlled study in 3 parts (A, B, and C) with approximately 107 overweight or obese subjects with relatively well controlled T2DM (without significant late diabetic complications) planned for enrollment across approximately 12 study sites.

Part A is designed to establish a dose titration regimen for MEDI0382 and a maximal effective dose after titration, in T2DM subjects maintained on metformin therapy, over a period of approximately 12 days that can then be utilized over an extended dosing period (Part B) to establish the efficacy of MEDI0382 on weight and glycemic control. Part C is designed to establish the safety and tolerability of a 300 µg dose of MEDI0382, and to explore 2 possible up-titration schedules from 100 to 300 µg from a tolerability, safety, and PK/PD perspective.

- Part A consists of 3 cohorts: Cohort 1 consists of a stable dose of investigational product administered daily for 7 days (9 subjects), Cohort 2 consists of an initial dose of investigational product for at least 4 days and an up-titration step (titration dose 1) for 7 days (9 subjects), and Cohort 3 consists of an initial dose of investigational product for at least 4 days, an up-titration step (titration dose 1) for 4 days, and a second up-titration step (titration dose 2) for 7 days (9 subjects).
- Part B consists of 1 cohort. Subjects in Cohort 4 will be dosed at an initial dose of investigational product for at least 4 days, an up-titration step (titration dose 1) for 4 days, a second up-titration step (titration dose 2) for 4 days, then titration dose 2 for 28 days thereafter at home (approximately 48 subjects). Progression to Cohort 4 will occur following review of relevant data from Cohorts 1 through 3 (safety/tolerability, PK, and PD).
- Part C consists of 2 cohorts: Cohort 5 consists of 16 subjects (12 active, 4 placebo) who will begin dosing at 100 µg for 5 days followed by 5 days at 150 µg, 5 days at 200 µg, and 7 days at 300 µg. Cohort 6 consists of a further 16 subjects (12 active, 4 placebo) who will begin dosing at 100 µg for 5 days followed by 5 days at 200 µg, and 7 days at 300 µg. Cohorts 5 and 6 may run concurrently.

Screening procedures must be performed within the Day -60 to Day -3 window prior to randomization. The screening evaluations may be carried out over more than 1 day. Written informed consent and any locally required privacy act document authorization must be obtained prior to performing any protocol-specified procedures, including screening evaluations. Following screening, the study duration for each subject varies by cohort and consists of an inpatient multiple-ascending dose (MAD) or up-titration evaluation period (beginning on Day -2 and ending after Day 8 for Cohort 1, Day 12 for Cohort 2, Day 16 for Cohort 3, and Day 13 for Cohort 4, and Day 3 for Cohorts 5 and 6) and an outpatient follow-up period.

Cohort 4 will have a 28-day period of at-home self-administration of investigational product (with weekly site visits) after the second inpatient up-titration step and before the end of study visit.

Cohorts 5 and 6 will have an initial inpatient period ending on Day 3 followed by at-home self-administration of investigational product with a clinic visit at each dose up-titration step until initiation of the 300 µg dose.

Subjects will have a second inpatient period for the initiation of the 300 µg dose, ending the fourth day at that dose, followed by at-home self-administration of investigational product. Subjects will be re-admitted to the clinic on the evening prior to the final dose and ending approximately 24 hours after the final dose.

In the event that subjects are not assessed as competent with respect to self-administration of investigational product, alternative arrangements will be made for it to be administered by a qualified study site professional.

Subjects will be admitted to and remain in the unit for all doses and all dose levels during the up-titration period for Cohorts 1 to 4.

Subjects will be admitted to the unit two evenings prior to receiving investigational product to allow for repeat assessment of eligibility criteria, measurement of baseline MMT, and to standardize the level of physical activity before dosing the following morning. Cohort 4 subjects only will undergo a predose MRI scan of the liver/abdomen (if MRI is available to the site and the subject is suitable for and consents to the scan) between Day -7 and Day -1. On Day 1, following an overnight fast for a minimum of 8 hours, baseline blood samples will be drawn for safety, efficacy, PK, PD, and ADA laboratory tests; 12-lead ECGs will be recorded, and the subject will be administered a single subcutaneous (SC) dose of either MEDI0382 or placebo.

The subject will undergo safety tests including ECGs, telemetry, monitoring of vital signs, and assessments of

the injection site for potential reactions throughout the day and during the treatment period. Additionally, for Cohorts 4, 5, and 6, 24-hour ambulatory blood pressure monitoring will be performed according to the schedule of events. Adverse events will be collected throughout the duration of the study.

MMT procedures will be performed on Day -1 and on the last day of the highest dose level achieved for all cohorts. Additional time points will include the first day at titration dose 1 (Cohort 2), the first day at titration dose 2 (Cohort 3), the day of discharge from the up-titration inpatient period (the fifth day of titration dose 2; Cohort 4), the weekly clinic visits during the 28-day period of at-home self-administration (Cohort 4), and at baseline (Day -1) and at the start (Day 16 for Cohort 5 and Day 11 for Cohort 6) and end (Day 22 for Cohort 5 and Day 17 for Cohort 6) of the 300 µg dosing schedule. For the MMT, the subject will consume a standardized meal (Ensure Plus[®]) within 5 minutes, and timed serial blood samples will be obtained for measurement of glucose and parameters related to glucose metabolism just before and through 240 minutes after consumption of the standardized meal. During the inpatient period, finger prick glucose samples will be collected 15 minutes (± 10 minutes) prior to and 2 hours (± 10 minutes) after breakfast, mid-day, and evening meals, and prior to going to bed.

Cohort 4 subjects will be re-admitted for an overnight inpatient stay at the end of the at-home self-administration period to collect the final endpoints including repeat MRI scan. This postdose MRI scan may be done on Day 39, 40, 41, or 42.

Body weight will be measured at multiple time points including (but not limited to) prior to the first dose, during the inpatient dosing period (and during the outpatient period for Cohort 4), at discharge from the unit, and at the 7- to 14-day follow-up visit.

Pharmacokinetics samples for MEDI0382 will be obtained pre- and postdose and at various time points by cohort up until 48 hours after the last dose of MEDI0382 (for Cohorts 4 to 6 the last sample will be collected approximately 24 hours after the last dose). Samples for metformin concentration will be obtained prior to MEDI0382 dosing. Antidrug antibodies samples will be obtained predose and at various time points up through 28 days post final dose.

Subjects will be discharged from the unit the day after their final dose is administered in the study.

A follow-up visit will be performed for final safety assessments approximately 28 days after the last dose of investigational product.

TARGET SUBJECT POPULATION

The study population will consist of male or female adults, 18 through 65 years of age with T2DM and body mass index 27 to 40 kg/m² (inclusive), without significant late diabetic complications. Subjects should have been treated with a stable dose of oral blood glucose lowering therapy for 3 months prior to screening (metformin monotherapy or metformin plus dipeptidyl peptidase-4 [DPP-4], sulphonylurea [50% of the licensed dose], or a sodium-glucose co-transporter 2 [SGLT2]; and DPP-4 inhibitor, sulphonylurea, or SGLT2 inhibitor is washed out prior to randomization). Females of childbearing potential and lactating females will be excluded.

INVESTIGATIONAL PRODUCT, DOSAGE, AND MODE OF ADMINISTRATION

MEDI0382 or matched placebo will be administered once daily via SC injection.

PART A:

- Cohort 1, 9 subjects (6 active, 3 placebo) dosed for 7 days at stable dose
- Cohort 2, 9 subjects (6 active, 3 placebo) dosed for at least 4 days at initial dose, 7 days at titration dose 1
- Cohort 3, 9 subjects (6 active, 3 placebo) dosed for at least 4 days at initial dose, 4 days at titration dose 1, 7 days at titration dose 2

PART B:

- Cohort 4, approximately 48 subjects (24 active, 24 placebo are planned to be dosed) dosed for at least 4 days at initial dose, 4 days at titration dose 1, 4 days at titration dose 2, then a further 28 days at titration dose 2 for at-home dosing followed by 1 day at titration dose 2 as inpatient

The proposed initial dose is 100 µg. Titration doses 1 and 2 have been determined according to emergent data on safety, tolerability, PK, and glycemic efficacy. The maximum dose is set at 200 µg/day for Cohort 4 (Part B of the study).

PART C:

- Cohort 5, 16 subjects (12 active, 4 placebo) dosed for 5 days at 100 µg, 5 days at 150 µg, 5 days at 200 µg followed by 7 days at 300 µg
- Cohort 6, 16 subjects (12 active, 4 placebo) dosed for 5 days at 100 µg, 5 days at 200 µg followed by 7 days at 300 µg

The maximum dose of MEDI0382 in Part C is set at 300 µg/day.

The first 3 dosing days will occur as an inpatient, as will the first 4 days and the final day of 300 µg dosing. The first dose of each up-titration step will be administered in the clinic, otherwise dosing on the remaining days will occur at home if the investigator is satisfied the subject can accurately self-administer the dose as instructed.

STATISTICAL ANALYSIS PLAN

The sample size of 6 subjects in the MEDI0382 group and 3 subjects in the placebo group for Cohorts 1, 2, and 3 was empirically determined to obtain adequate safety and tolerability evaluation. Under a two-sided 10% significance level, a sample size of 44 evaluable subjects (22 per arm) for Cohort 4 will provide 80% power to detect weight loss of 1.5 kg versus placebo (assuming a standard deviation of 1.9 kg), and 98% power to detect a 20% relative reduction in MMT glucose AUC (up to 240 minutes post-MMT) versus placebo at the end of treatment (assuming a coefficient of variation [CV] of 17%). (Internal data from another investigational agent for T2DM showed a CV of 17% for 24-hour glucose AUC, and the CV for glucose AUC [up to 240 minutes post-MMT] is expected to be similar.) The sample size for Cohort 4 is adjusted to 48 subjects (24 per arm) to account for a 10% drop-out rate. For Cohorts 5 and 6, under a one-sided 2.5% significance level the combination of 24 subjects on MEDI0382 and 8 subjects on placebo from both cohorts will provide 80% power to rule out more than 20% of MEDI0382 subjects having > 5 mm Hg increase from baseline in diastolic blood pressure (BP) on the seventh day of the 300 µg dose level (Day 22 for Cohort 5 and Day 17 for Cohort 6) relative to that of placebo subjects, under the assumption that both placebo and MEDI0382 subjects have a true rate of 1% with > 5 mm Hg increase from baseline in diastolic BP. Moreover, under a one-sided 2.5% significance level, this sample size will provide 88% power to rule out > 20 beats per minute (bpm) pulse rate increase from baseline on the seventh day of the 300 µg dose level in MEDI0382 subjects relative to that of placebo subjects with assumed standard deviation of 15 bpm.

Efficacy endpoints including the percent change in MMT glucose AUC and the change in HbA1c, fructosamine, and weight, from baseline to the end of treatment will be compared between the MEDI0382 and placebo groups using analysis of covariance by adjusting for measurement at baseline and treatment group. Descriptive analyses will be provided for safety endpoints in each cohort.

Pharmacokinetic parameters such as maximum concentration (C_{max}), time to maximum observed concentration (T_{max}), AUC, elimination half-life, and accumulation ratio will be estimated from plasma concentration-time data for MEDI0382 if data permit. Descriptive statistics will be generated for PK parameters for the MEDI0382 group in each cohort. Subjects who have at least one measurable concentration time point of investigational product will be used for this analysis.

With respect to metformin PK, changes in metformin levels over time will be evaluated, as will any association between baseline metformin dose and change in metformin levels over time in the clinical study. In the event that a reduction in metformin levels is seen in Cohorts 1-3, an exploratory analysis will be performed to examine the relationship between changes in metformin level and glucose control over time.

The incidence and impact of ADA to MEDI0382 will be evaluated. The number and percentage of subjects with confirmed positive serum antibodies to MEDI0382 will be reported by cohort. If warranted by the data, the association of ADA positivity with observed PK data and safety may be explored.

LIST OF ABBREVIATIONS

| Abbreviation or Specialized Term | Definition |
|----------------------------------|--|
| ABPM | ambulatory blood pressure monitoring |
| ADA | antidrug antibody |
| AE | adverse event |
| AESI | adverse event of special interest |
| ALT | alanine transaminase |
| AST | aspartate transaminase |
| AUC | area under the concentration-time curve |
| AV | atrioventricular |
| BMI | body mass index |
| BP | blood pressure |
| bpm | beats per minute |
| CDER | Center for Drug Evaluation and Research |
| ████ | ████████████████████ |
| C _{max} | maximum observed concentration |
| CRO | contract research organization |
| C-SSRS | Columbia-Suicide Severity Rating Scale |
| ████ | ██ |
| CV | coefficient of variation |
| DEC | Dose Escalation Committee |
| dECG | digital electrocardiogram |
| DIO | diet-induced obese |
| DPPIV | dipeptidyl peptidase-4 |
| ECG | electrocardiogram |
| eCRF | electronic case report form |
| EDC | electronic data capture |
| ████ | ████████████████████ |
| ████ | ████████████████████ |
| FTIH | first-time-in-human |
| GFR | glomerular filtration rate |
| GI | gastrointestinal |
| GIP | gastric inhibitory peptide |
| GLP-1 | glucagon-like peptide-1 |
| GMP | Good Manufacturing Practice |
| HbA1c | hemoglobin A1c (glycated hemoglobin) |
| HDL | high-density lipoprotein |
| Hg | mercury |
| HIV | human immunodeficiency virus |
| HL | Hy's Law |

| Abbreviation or Specialized Term | Definition |
|----------------------------------|---|
| HOMA | Homeostasis Model Assessment |
| HR | heart rate |
| ICF | informed consent form |
| ICH | International Council for Harmonisation |
| IEC | Independent Ethics Committee |
| ■ | ■ |
| IR | insulin resistance |
| IRB | Institutional Review Board |
| ITT | intent-to-treat |
| IV | intravenous(ly) |
| IXRS | interactive voice or web response system |
| LDL | low-density lipoprotein |
| MAD | multiple-ascending dose |
| MedDRA | Medical Dictionary for Regulatory Activities |
| MDRD | Modification of Diet in Renal Disease |
| MMT | mixed-meal test |
| MRI | magnetic resonance imaging |
| NASH | non-alcoholic steatohepatitis |
| NOAEL | no-observed-adverse-effect level |
| ■ | ■ |
| PD | pharmacodynamic(s) |
| PK | pharmacokinetic(s) |
| ■ | ■ |
| PR (PQ) | electrocardiogram interval measured from the onset of the P wave to the onset of the QRS complex |
| ■ | ■ |
| QRS | electrocardiogram interval measured from the onset of the QRS complex to the J point |
| QT | electrocardiogram interval measured from the onset of the QRS complex to the offset of the T wave |
| QTc | cardiac QT interval corrected for heart rate |
| QTcF | cardiac QTc interval corrected for heart rate by the formula of Fridericia |
| RR | the time between corresponding points on 2 consecutive R waves on the electrocardiogram |
| SAD | single-ascending dose |
| SAE | serious adverse event |
| SGLT2 | sodium-glucose co-transporter 2 |
| SID | subject identification |
| SC | subcutaneous(ly) |
| SPC | Summary of Product Characteristics |
| T2DM | type 2 diabetes mellitus |

| Abbreviation or Specialized Term | Definition |
|---|--|
| TBL | total bilirubin |
| TEAE | treatment-emergent adverse event |
| TESAE | treatment-emergent serious adverse event |
| TG | triglycerides |
| TSH | thyroid-stimulating hormone |
| T _{max} | time to maximum observed concentration |
| ULN | upper limit of normal |
| USA | United States of America |
| VT | ventricular tachycardia |
| w/v | weight per volume |

1 INTRODUCTION

1.1 Disease Background

Type 2 diabetes mellitus (T2DM) is a disease characterized by insulin resistance (IR) related to central obesity and weight gain, coupled with later progressive beta-cell failure, resulting in a steady worsening of glycemic control. Whilst a range of therapies is available for the control of blood glucose, none currently achieve substantial weight loss, which remains a significant unmet need for patients. Fifty percent of patients progress from oral monotherapy for glucose control (usually with metformin) to initiation of insulin within 10 years ([Taylor, 2013](#)), often taking multiple oral combination therapies before initiating insulin. The use of insulin exacerbates weight gain, which can be as great as 6 kg in the first year after starting insulin therapy ([Douek et al, 2005](#)). This weight gain can lead to increased insulin resistance, which is associated with hypertension, dyslipidemia, and an increased risk of major adverse cardiovascular events. With respect to reducing insulin resistance, significant weight reduction (> 5%) is the optimal intervention, although this can only be achieved reliably at present through intensive dietary and lifestyle interventions and/or bariatric surgery.

1.2 MEDI0382 Background

MEDI0382 is briefly described below. Refer to the current Investigator's Brochure for additional details.

MEDI0382 is a synthetic peptide with both glucagon-like peptide-1 (GLP-1) and glucagon receptor co-agonist activity. MEDI0382 is being developed to address the unmet need for patients with T2DM to achieve both blood glucose control and weight reduction. The combination of GLP-1 and glucagon activity is expected to improve glycemic control and lipid profiles, and cause significant weight loss. These effects are hypothesized to be mediated through stimulation of glucose-mediated insulin release (the incretin effect), delayed gastric emptying, and increased fatty acid oxidation. Glucagon-like peptide-1 and glucagon agonists may also exert central effects on appetite, and glucagon agonism has been shown to drive increased energy expenditure in animal models and humans ([Lynch et al, 2014](#); [Habegger et al, 2013](#)). Furthermore, appetite suppression and increased energy expenditure in humans has been demonstrated with the use of oxyntomodulin, a peptide with weak GLP-1 and glucagon co-agonist activity ([Wynne et al, 2006](#)).

1.3 Summary of Nonclinical Experience

MEDI0382 injected subcutaneously (SC) in diet-induced obese (DIO) mice robustly and dose-dependently reduced body weight gain compared with vehicle-treated mice. A sustained lowering of body weight was observed over a 4-week treatment period with a reduction of approximately 25% at the highest dose tested (41 µg/kg, twice daily). MEDI0382 significantly improved glucose control in DIO mice following dosing of up to 4 weeks. MEDI0382-treated DIO mice showed reduced blood glucose excursion following an oral glucose challenge as compared with vehicle-treated mice. In diabetic *db/db* mice, acute and subchronic treatment with MEDI0382 reduced blood glucose excursion following an intraperitoneal glucose challenge.

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]



1.5 Rationale for Conducting the Study

Studies that have examined changes in small bowel peptide hormones following bariatric surgery revealed that increases in GLP-1 and oxyntomodulin are associated with improvements in both glycemic control and weight loss ([Falkén et al, 2011](#); [Ionut et al, 2013](#)). Nonclinical studies that have examined the effect of glucagon and GLP-1 co-agonism on blood glucose and body weight suggest that a co-agonist such as MEDI0382, delivering potent GLP-1 and some glucagon agonism, can cause more significant weight loss through combined action on delayed gastric emptying, appetite suppression, and increased energy expenditure than GLP-1 agonist therapy alone ([Tan et al, 2013](#)). Glucagon agonism is thought to improve the lipid profile via increased fatty acid oxidation. Although glucagon agonism would normally be expected to cause an increase in glucose, the effect is counterbalanced by the GLP-1 effect on reducing blood glucose and significant weight loss driven by GLP-1 and glucagon agonism.

Available nonclinical data suggest that the affinity profile of MEDI0382 is optimized to achieve enhanced weight reduction via glucagon receptor agonism without adversely impacting the expected glycemic control associated with the GLP-1 agonist component (up to 20% weight loss, with effects on blood glucose control comparable to that of liraglutide, a GLP-1 agonist). MEDI0382 is therefore a potential breakthrough therapy for T2DM, achieving both significant weight loss and glycemic control.

This study is designed to assess the efficacy, safety/tolerability, and PK of MEDI0382 and the pharmacodynamic (PD) effect on blood glucose, following SC administration of multiple-ascending doses. Cohorts 1 through 3 (Part A of the study) are designed to establish an up-titration schedule for MEDI0382 and a maximal effective repeat dose. Subjects in Cohort 4 will be dosed for an extended period (33 days) with this maximal effective dose (Part B of the study) to assess the effect of MEDI0382 on glucose control and body weight.



[illegible]

Template 16.2

in nonclinical studies of MEDI0382, such that benefit-risk balance for the subjects with T2DM in this study is considered favorable.

1.6 Research Hypotheses

1.6.1 Primary Hypothesis

MEDI0382 will achieve an improvement in glucose control equivalent to at least that achieved by oral therapies in addition to metformin ($\geq 20\%$ reduction in glucose area under the concentration-time curve [AUC] after a mixed-meal test [MMT]), and at least comparable weight loss to that expected of liraglutide at the 1.8 mg dose (ie, between 1.3 and 2.0 kg) versus placebo following 4 weeks of repeat once-daily dosing in subjects with T2DM managed on metformin.

1.6.2 Secondary Hypotheses

- MEDI0382 will achieve an improvement in glucose control as measured by hemoglobin A1c (HbA1c) and fructosamine following 4 weeks of repeat once-daily dosing.
- Gastrointestinal (GI) symptoms will be manageable during up-titration of MEDI0382, no adverse changes in cardiac and hemodynamic parameters will be observed, and the overall safety profile of MEDI0382 will be acceptable over up to 4 weeks of repeat once-daily dosing.

2 OBJECTIVES

2.1 Objectives

2.1.1 Primary Objective

The primary objective of this study is to assess the effect of MEDI0382 on glucose control (as measured by the standardized MMT glucose data) and body weight from baseline to the end of a 4-week period at a stable dose.

2.1.2 Secondary Objectives

1. To assess the effect of MEDI0382 on glucose control as measured by the standardized MMT, HbA1c, and fructosamine data from baseline through end of treatment
2. To characterize the safety profile of MEDI0382 following SC administration of multiple-ascending doses
3. To characterize the PK and immunogenicity of MEDI0382
4. To characterize the PD effect of MEDI0382 on glucose metabolism following a MMT

2.1.3 Exploratory Objectives

[REDACTED]

5. To explore the effect of MEDI0382 on the volume and fat/water content of the liver
6. To explore the effect of MEDI0382 on visceral and subcutaneous fat

2.2 Study Endpoints

2.2.1 Primary Endpoints

The primary endpoints apply to Cohort 4 only:

1. Percent change from baseline in MMT glucose AUC (up to 240 minutes post-MMT) to end of treatment
2. Change from baseline in body weight in kg to end of treatment

2.2.2 Secondary Endpoint(s)

Secondary endpoints apply to all cohorts unless stated otherwise.

1. Change from baseline in HbA1c and fructosamine, and percent change from baseline in 24-hour glucose AUC post-MMT, through end of treatment
2. Percent change from baseline in MMT glucose AUC (up to 240 minutes post-MMT) to end of treatment
3. Change from baseline in body weight in kg to end of treatment
4. AEs
5. BP
6. Pulse
7. Safety laboratory test results
8. Electrocardiograms (ECGs)
9. Columbia-Suicide Severity Rating Scale (C-SSRS) score (Cohorts 4, 5, and 6 only)
10. PK endpoints for MEDI0382: AUC over a dosing duration, maximum observed concentration (C_{max}), minimum observed concentration, time to maximum observed concentration (T_{max})(all cohorts); terminal half-life, and accumulation ratio (Cohorts 1 to 3 only)
11. Concentration of metformin
12. Development of antidrug antibody (ADA) and titer (if positive)

- Glucose
- Beta cell health: insulin, pro-insulin, and c-peptide
- Incretins: GLP-1, glucagon, gastric inhibitory peptide (GIP)
- Cohorts 5 and 6 insulin and glucose only

Unless otherwise stated, the exploratory endpoints apply to Cohort 4 only.

- [illegible]

8. Change from baseline to Week 4 in:
- Liver fat (%)
 - Liver volume (L)
 - Visceral adipose tissue (L)
 - Subcutaneous adipose tissue (L)
 - Liver diffusion
 - Sagittal diameter (image based)
 - Transversal diameter (image based)
- as determined by magnetic resonance imaging (MRI) to be conducted if MRI is available to the site and the subject is suitable for and consents to scan

3 STUDY DESIGN

3.1 Description of the Study

3.1.1 Overview

This is a randomized, double-blind (subjects and investigators/site staff blinded; MedImmune unblinded), placebo-controlled study in 3 parts (A, B, and C) with approximately 107 overweight or obese subjects with relatively well controlled T2DM (without significant late diabetic complications) planned for enrollment across approximately 12 study sites.

Part A is designed to establish a dose titration regimen for MEDI0382 and a maximal effective dose after titration, in T2DM subjects maintained on metformin therapy, over a period of approximately 12 days that can then be utilized over an extended dosing period (Part B) to establish the efficacy of MEDI0382 on weight and glycemic control.

- Part A consists of 3 cohorts: Cohort 1 consists of a stable dose of investigational product administered daily for 7 days (9 subjects), Cohort 2 consists of an initial dose of investigational product for at least 4 days and an up-titration step (titration dose 1) for 7 days (9 subjects), and Cohort 3 consists of an initial dose of investigational product for at least 4 days, an up-titration step (titration dose 1) for 4 days, and a second up-titration step (titration dose 2) for 7 days (9 subjects).
- Part B consists of 1 cohort. Subjects in Cohort 4 will be dosed at an initial dose of investigational product for at least 4 days, an up-titration step (titration dose 1) for 4 days, a second up-titration step (titration dose 2) for 4 days, then titration dose 2 for 28 days thereafter at home (approximately 48 subjects).
- Progression to Cohort 4 will occur following review of relevant data from Cohorts 1 through 3 (safety/tolerability, PK, and PD). Part C consists of 2 cohorts: Cohort 5 consists of 16 subjects (12 active, 4 placebo) who will begin dosing investigational product at 100 µg for 5 days followed by 150 µg for 5 days, 200 µg for 5 days, and 300 µg for 7 days. Cohort 6 consists of a further 16 subjects (12 active, 4 placebo) who will begin dosing investigational product at 100 µg for 5 days followed by 200 µg for 5 days, and 300 µg for 7 days (approximately 32 subjects in total). Cohorts 5 and 6 will be run in parallel.

The endpoints to be measured in this study are described in Section 2.2.

Screening procedures (Table 4.2.1-1) must be performed within the Day -60 to Day -3 window prior to randomization. The screening evaluations may be carried out over more than 1 day. Written informed consent and any locally required privacy act document authorization must be obtained prior to performing any protocol-specified procedures, including screening evaluations. Following screening, the study duration for each subject varies by cohort (refer

to Table 4.2.2-1, Table 4.2.2-2, Table 4.2.2-3, Table 4.2.2-4, Table 4.2.2-5, Table 4.2.2-6, and Table 4.2.2-7), and consists of an inpatient MAD or up-titration evaluation period (beginning on Day -2 and ending after Day 8 for Cohort 1, Day 12 for Cohort 2, Day 16 for Cohort 3, Day 13 for Cohort 4, and Day 3 for Cohorts 5 and 6) and an outpatient follow-up period. For Cohorts 5 and 6, the first 4 days and the final day of dosing at 300 µg are also inpatient periods. Additionally, only for Cohort 4, a 28-day period of at-home self-administration of investigational product (with weekly site visits) is included after the second inpatient up-titration step and before the end of study visit. For Cohorts 5 and 6, in the event that subjects are not assessed as competent with respect to self-administration of investigational product, alternative arrangements will be made for it to be administered by a qualified study site professional.

For Cohorts 1 to 4, subjects will be admitted to and remain in the unit for all doses and dose levels during the up-titration period. Subjects will be admitted to the unit two evenings prior to receiving investigational product to allow for repeat assessment of eligibility criteria and baseline MMT, and to standardize the level of physical activity before dosing the following morning. Cohort 4 subjects only will undergo a predose MRI scan of the liver/abdomen (if MRI is available to the site and the subject is suitable for and consents to scan) between Day -7 and Day -1. This may require a separate visit at the subject's discretion if not carried out on Day -2 or Day -1. On Day 1, following an overnight fast for a minimum of 8 hours, baseline blood samples will be drawn for safety, efficacy, PK, PD, and ADA laboratory tests, 12-lead ECGs will be recorded, and the subject will be administered a single SC dose of either MEDI0382 or placebo.

For Cohorts 5 and 6, subjects will be admitted to the clinic per the other cohorts; however, they will have an initial inpatient period ending on Day 3 followed by at-home self-administration of MEDI0382 with a clinic visit at each dose up-titration step until initiation of the 300 µg dose. Subjects will have a second inpatient period for the initiation of the 300 µg dose ending on the fourth day at that dose followed by at-home self-administration. The subject will undergo safety tests including ECGs, telemetry, monitoring of vital signs, and assessments of the injection site for potential reactions throughout the day and during the treatment period. Additionally, for Cohorts 4, 5, and 6, 24-hour ambulatory blood pressure monitoring (ABPM) will be performed. Adverse events will be collected throughout the duration of the study.

MMT procedures will be performed on Day -1 and on the last day of the highest dose level achieved for all cohorts. Additional time points will include the first day at titration dose 1 (Cohort 2), the first day at titration dose 2 (Cohort 3), the day of discharge from the

up-titration inpatient period (the fifth day of titration dose 2; Cohort 4), the weekly clinic visits during the 28-day period of at-home self-administration (Cohort 4), before commencing the 300 µg dose (Day 16 for Cohort 5 and Day 11 for Cohort 6), and at the end of dosing (Day 22 for Cohort 5 and Day 17 for Cohort 6). For the MMT, the subject will consume a standardized meal (Ensure Plus[®]) within 5 minutes, and timed serial blood samples will be obtained for measurement of glucose and parameters related to glucose metabolism just before and through 240 minutes after consumption of the standardized meal. During the inpatient period, finger prick glucose samples will be collected 15 minutes (prior to and 2 hours (after breakfast, mid-day, and evening meals, and prior to going to bed.

Cohort 4 subjects will be re-admitted for an overnight inpatient stay at the end of the at-home self-administration period to collect the final endpoints including repeat MRI scan. This postdose MRI scan may be done on Day 39, 40, 41, or 42. Cohort 5 and 6 subjects will also be re-admitted to the clinic for an overnight inpatient stay at the end of their final at-home self-administration period to collect the final endpoints.

Body weight will be measured at multiple time points including (but not limited to) prior to the first dose, during the inpatient dosing period (and during the outpatient period for Cohorts 4, 5, and 6), at discharge from the unit, at the 7- to 14-day follow-up visit, and at the 28-day End of Study Visit.

Pharmacokinetics samples for MEDI0382 will be obtained pre- and postdose and at various time points by cohort up until 48 hours after the last dose of MEDI0382 (for Cohorts 4 to 6 the last sample will be collected approximately 24 hours after the last dose). Samples for metformin concentration will be obtained prior to MEDI0382 dosing. Antidrug antibodies samples will be obtained predose and at various time points up through 28 days post final dose.

Subjects will be discharged from the unit the day after their final dose is administered in the study.

A follow-up visit (End of Study Visit) will be performed for final safety assessments (Table 4.2.3-1) approximately 28 days after the last dose of investigational product.

The study schematic presented below (Figure 3.1.1-1) describes the sizing and treatment duration for Cohorts 1 through 6. Refer to Section 3.1.3.1 for restrictions on dose escalation, cohort expansion, and when enrollment in Cohort 4 (Part B) of this MAD study may begin.

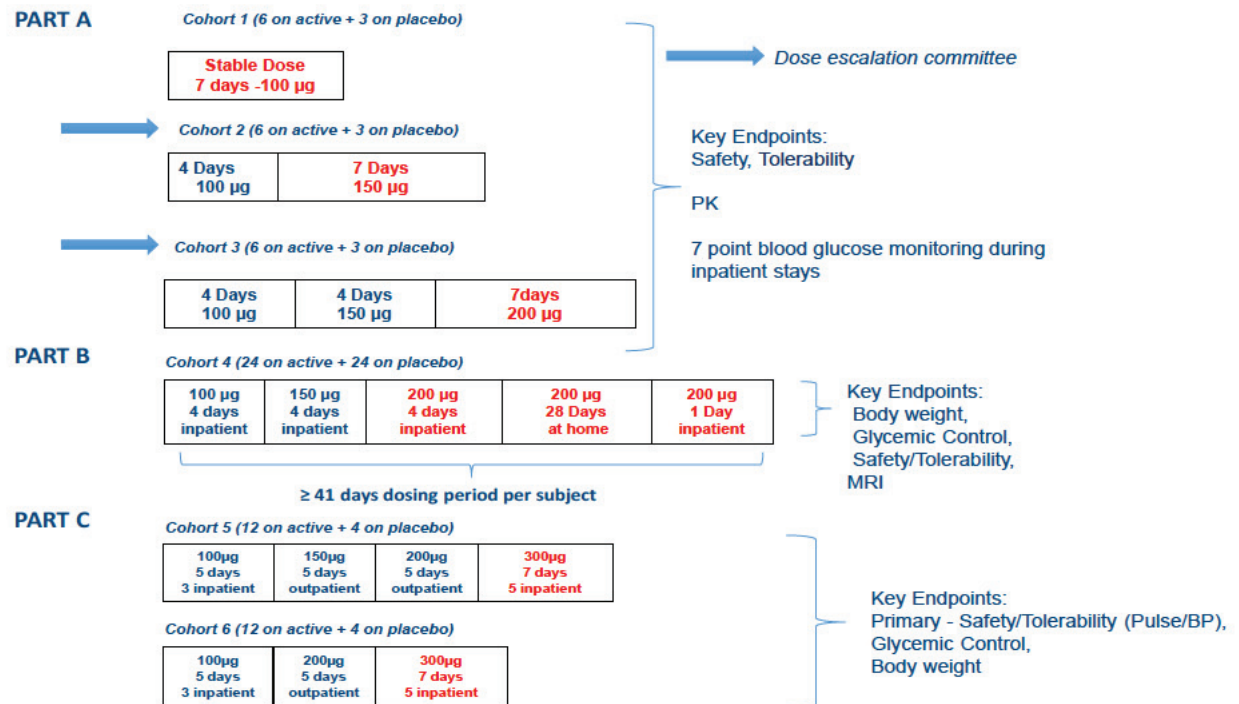


Figure 3.1.1-1 Study Flow Diagram

BP = blood pressure; MRI = magnetic resonance imaging; PK = pharmacokinetic(s).

Note: Time is not drawn to scale.

3.1.2 Treatment Regimen

MEDI0382 or matched placebo will be administered once daily via SC injection.

PART A:

- Cohort 1, 9 subjects (6 active, 3 placebo) dosed for 7 days at stable dose
- Cohort 2, 9 subjects (6 active, 3 placebo) dosed for at least 4 days at initial dose, 7 days at titration dose 1
- Cohort 3, 9 subjects (6 active, 3 placebo) dosed for at least 4 days at initial dose, 4 days at titration dose 1, 7 days at titration dose 2

PART B:

- Cohort 4, approximately 48 subjects (24 active, 24 placebo are planned to be dosed) dosed for at least 4 days at initial dose, 4 days at titration dose 1, 4 days at titration dose 2, then a further 28 days at titration dose 2 for at-home dosing followed by 1 day at titration dose 2 as inpatient

The proposed initial dose is 100 µg. Titration doses 1 and 2 have been determined according to emergent data on safety, tolerability, PK, and glycemic efficacy. The maximum dose is set at 200 µg/day for Cohort 4, (Part B of the study).

PART C:

- Cohort 5, 16 subjects (12 active, 4 placebo) dosed for 5 days at 100 µg, 5 days at 150 µg, 5 days at 200 µg followed by 7 days at 300 µg
- Cohort 6, 16 subjects (12 active, 4 placebo) dosed for 5 days at 100 µg, 5 days at 200 µg followed by 7 days at 300 µg

The maximum dose is set at 300 µg/day for Cohorts 5 and 6 (Part C of the study).

3.1.3 Cohort Progression

3.1.3.1 Progression of Cohorts within this MAD Study

The proposed initial dose level for Cohort 1 is 100 µg. Titration doses 1 and 2 will be determined according to emergent data on safety, tolerability, PK and glycemic efficacy. This study is designed to establish the titration schedule for MEDI0382 and a maximal effective repeat dose for MEDI0382 over an extended dosing period.

A sentinel dosing approach is planned for Cohorts 1, 2, and 3. Only 2 subjects in a given cohort will be dosed on Day 1, and the randomization schedule will ensure that these consist of 1 active and 1 placebo subject. A minimum of 3 days of dosing at the target dose level (ie, initial dose for Cohort 1, titration dose 1 for Cohort 2, and titration dose 2 for Cohort 3) will occur before additional subjects in the cohort are dosed. Dosing is proposed to continue based on a lack of significant safety findings in the first 2 subjects dosed. The overall randomization schedule will ensure a 2:1 randomization (active:placebo) for Cohorts 1 to 3.

A sentinel dosing approach is also planned for Cohort 5 and 6. Three subjects from Cohort 5 and 3 subjects from Cohort 6 will be dosed initially, and the randomization schedule will ensure that these consist of 2 active subjects and 1 placebo subject. The rest of the cohort will continue dosing once dosing is complete for the last sentinel subject in each cohort. This will ensure that a minimum of 7 days of dosing at the 300 µg dose will occur before additional subjects are dosed at this level. Dosing will continue based on a review of the data, and the lack of significant findings in these 6 subjects dosed.

For progression from Cohort 1 to Cohort 2, and from Cohort 2 to Cohort 3, the decision whether or not to progress will be made by DEC composed of members from the clinical

study team and the coordinating investigator. The decision to dose escalate will be based on safety/tolerability (safety laboratory test results including lactate, vital signs, ECGs, and AEs through 24 hours post final dose), PK data (for MEDI0382, through 24 hours after the Day 3 dose at the target dose level), and PD data (MMT glucose data post final dose) for each subject in the cohort. If the PK profile from Cohort 1 is as predicted, PK data from Cohort 2 may not be reviewed for the dose escalation decision.

Cohort 4 of this MAD study may begin only after relevant data from Cohorts 1 through 3 have been analyzed (safety/tolerability, PK for MEDI0382 and for metformin, and PD) and reviewed by the DEC: data for Cohorts 1 and 2 through the end of study visit, and data for Cohort 3 through Day 16 (24 hours post final dose). These data will also be summarized and provided to the appropriate regulatory body and central ethics committee. The target dose level for Cohort 4 (dosed according to the up-titration scheme described above for Cohort 3) will be decided by the DEC and will not exceed 200 µg/day (Section 3.2.1). Approval to proceed with Cohort 4 will be obtained from the appropriate regulatory body prior to initiating dosing.

Dose escalation will be stopped if, within the given cohort, DEC review determines that any of the following criteria are met. If any of these criteria are met, then data will be reviewed by a MedImmune safety review board to determine whether to continue the study and/or escalate the dose.

- Grade 2 or higher AEs assessed as possibly, probably, or definitely related to MEDI0382 occur in more than 50 % of MEDI0382 subjects in a dosing cohort, or
- One serious adverse event (SAE) occurs in a MEDI0382 subject that is assessed as possibly, probably, or definitely related to MEDI0382

Based on a review of the safety and PD data from Cohorts 1, 2, and 3, the 300 µg dose level will be explored to fully characterize the dose-response with respect to safety and tolerability. The up-titration scheme described for Cohorts 5 and 6 differs from previous cohorts to determine the optimal up-titration schedule of the 300 µg dose from a perspective of tolerability, safety and PK/PD data.

Cohorts 5 and 6 may run concurrently and the sponsor will conduct an ongoing review of safety data and AEs throughout Part C. In addition, given that telemetry will be in place for prolonged periods, arrhythmia findings will be expected to occur as part of the study population's normal background incidence ([Min et al, 2010](#)). Subjects will be randomized 2:1 (Cohorts 1 to 3), 1:1 (Cohort 4), or 3:1 (Cohorts 5 and 6) to receive MEDI0382 or placebo, and the sparse occurrence makes any such finding a priori more likely to be seen on

active treatment. If 1 or more subjects have a documented arrhythmia of concern, this may be reviewed by an external expert (or group) for opinion prior to the dose escalation decision. Study stopping criteria (including specific cardiac stopping criteria) are detailed in Section 3.1.3.2.

Based on prior clinical data from this class of agents, ADA formation is not considered to pose a high safety risk (eg, liraglutide is reported to have ADA rates of 8.6% with no clinical safety/efficacy consequence); therefore, ADA data will not be considered in dose-escalation decisions, but will be presented in the clinical study report.

After reviewing the data from a given cohort, the DEC will make one of the following recommendations:

- Escalate to the next cohort as per the protocol.
- Escalate to the next cohort with an intermediate (lower than planned) initial dose and/or titration dose increment, or expand the number of subjects dosed at a particular dose level.
- Escalate to the next cohort but extend the number of dosing days at a particular dose level before dose up-titration occurs.
- Request for review and decision by the sponsor's safety review board on how to proceed, or whether to suspend or stop the study.

Study suspension and termination are discussed in Section 0. Further details on the DEC are provided in Section 4.8.9.

3.1.3.2 Cardiac Stopping Criteria

The following criteria apply to stopping an individual from continuation in the study:

- In any subject: an average absolute (regardless of baseline value) cardiac QTc interval corrected for HR by the formula of Fridericia (QTcF) > 500 milliseconds (msec), or an increase of QTcF > 60 msec above the baseline value, confirmed (persistent for ≥ 5 minutes) on a repeat 12-lead ECG
- In a subject receiving MEDI0382: tachycardia, defined as resting supine pulse rate > 125 beats per minute persisting for at least 10 minutes (measured at 5 timepoints in the 10 minute period)
- In a subject receiving MEDI0382: symptomatic bradycardia, defined as resting supine pulse rate < 40 beats per minute while awake, persisting for at least 10 minutes; or asymptomatic bradycardia defined as resting supine pulse rate < 30 beats per minute

while awake persisting for at least 10 minutes (measured at 5 timepoints in the 10 minute period)

- In a subject receiving MEDI0382: hypertension, defined as an increase in resting supine systolic BP > 40 mm Hg or above 180 mm Hg and persisting for at least 10 minutes, or an increase in resting supine diastolic BP > 20 mm Hg or above 100 mm Hg and persisting for at least 10 minutes

The following criteria apply to stopping the study when observed in 2 or more subjects receiving MEDI0382:

- A QTc prolongation defined as QTcF > 500 msec, or an increase of QTcF > 60 msec above baseline, confirmed (persistent for ≥ 5 minutes) and determined postdose on a repeat 12-lead ECG
- Tachycardia, as defined above
- Symptomatic or asymptomatic bradycardia, as defined above
- Hypertension, as defined above

If 1 or more subjects have a documented arrhythmia of concern, this may be reviewed by an external expert (or group) for opinion prior to the DEC decision (see Section 5.3).

[REDACTED]

Prior clinical experience with both GLP-1 and glucagon agonist mechanisms (eg, liraglutide, oxyntomodulin, and human glucagon) indicates that AEs are primarily gastrointestinal, easily

observable, treatable, and reversible upon cessation of dosing ([Victoza Summary of Product Characteristics \[SPC\], 2014](#); [Wynne et al, 2005](#); [GlucaGen[®] SPC, 2013](#)).

In human studies, symptoms of nausea and vomiting are likely to precede significant weight loss. Timing of dose up-titration and the magnitude of dose level increase between Cohorts 1 and 2 and Cohorts 2 and 3, 4, 5, and 6 are expected to be limited by GI tolerability, specifically with respect to nausea and vomiting. Subjects will be instructed to manage nausea by reducing food intake or by eating smaller portions of food spaced more regularly throughout the day. Significant vomiting for the purposes of this study is defined as 3 or more episodes of vomiting on a single day or across 2 consecutive days, despite adjustment to diet having been made. Subjects who fulfil the criteria for significant vomiting will have their electrolytes monitored and the medical monitor will be contacted regarding further follow-up and to discuss any need for supplementation of electrolytes by the oral or IV route. If investigational product is withdrawn, then follow up for safety and efficacy evaluations would be maintained.

In Cohort 1, subjects will be treated at an initial dose level for a period of 7 days. Based on data from other GLP-1 agonist studies, it is likely that the effect of the first dose of MEDI0382 with respect to GI stasis will wane with repeat dosing, and thus initial symptoms of nausea and/or vomiting will decline after Day 1. An objective for all cohorts is to determine how rapidly initial symptoms of nausea and vomiting decline with repeated once-daily administration, and thus define the optimal timing for dose up-titration in future studies.

In addition to the formal dose escalation decision, SAEs and significant laboratory abnormalities will be reviewed by the DEC on a case-by-case basis to determine if discontinuation of dosing is required. In addition, criteria will be included to limit dose escalation progression, if needed, following data review by the DEC as described in Section 3.1.3. Expansion of a cohort and exploration of the effect of a lower intermediate dose level may be considered.

Up-titration for Cohort 2 is proposed after at least 4 days of dosing with the initial dose used in Cohort 1. Up-titration for Cohort 3 is proposed after at least 4 days of dosing with the initial dose used in Cohort 1 with a further up-titration after 4 days of dosing with the dose used in Cohort 2 (8 days total for up-titration). This 4-day up-titration schedule may be increased according to observed safety/tolerability, ie, if the GI tolerability profile with up-titration after 4 days is unacceptable, the time to up-titration may be extended for future cohorts. A similar up-titration schedule is proposed for Cohort 4 before continuing stable dosing for 33 days in total at the highest dose level achieved. Up-titration in Cohorts 5 and 6

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

The preliminary human PK parameters after single dose administration in the dose range 5 to 300 µg have been evaluated. Data indicate a linear PK in terms of C_{\max} and AUC, T_{\max} between 4.5 and 9 hours, and a half-life of approximately 9 to 12 hours. A half-life of 11.5 hours was also confirmed following repeat doses with little accumulation of MEDI0382 (approximately 1.2-fold) and achievement of PK steady state approximately after the second daily dose. Moreover, preliminary covariate analysis on population PK suggests that clearance may increase as body weight or body mass index (BMI) increases, and therefore the exposure measured during the single dose study, may be an overestimation of the exposure that will be measured in this repeat administration study. Doses for Cohort 4 have been chosen based on observed safety/tolerability and PK/PD data from Cohorts 1 through 3, and the maximum dose is 200 µg/day. Cohorts 5 and 6 will establish safety and tolerability of the 300 µg dose of MEDI0382 and explore the safety/tolerability and PK/PD of 2 different up-titration schedules.

Starting Dose and Criteria for Dose Escalation

At the proposed starting dose of 100 µg MEDI0382 showed a median (range) C_{\max} of 6.2 (4.1-9.0) ng/mL and a median (range) T_{\max} of 7.5 (4.5-10.0) hours with no apparent lag time (T_{lag}). Preliminary estimation of terminal phase showed a median (range) $\text{AUC}_{(0-\text{inf})}$ of

150.03 (118.44-190.04) ng•hr/mL and median (range) half-life of 12.0 (9.58-15.20) hours in the SAD study.

The safety margin between the predicted C_{\max} after multiple doses at the 100 µg dose in human and the observed C_{\max} at the cynomolgus monkey NOAEL is approximately 25. This dose will allow confirmation of the PK predictions for MEDI0382 after multiple doses, while being at the lower end of the potentially relevant pharmacological range.

Four dose levels are proposed for repeat once-daily dosing in this study (100, 150, 200, and 300 µg).

3.2.2 Rationale for Study Population

Recruitment of Subjects with Body Mass Index 27 to 40 kg/m²

A significant level of unmet clinical need exists with respect to both weight loss and glucose control in patients with T2DM who are overweight or obese. While patients with a BMI > 40 kg/m² are usually offered bariatric surgery, those with BMI in the range of 27-40 kg/m² are offered medical management of their weight. Current licensed therapies for glucose control in this population (GLP-1 agonists) achieve a mean weight loss of 3% over 1 year, and high-dose GLP-1 agonist therapy (3 mg liraglutide) achieves weight loss of up to 8% versus baseline. It is anticipated that MEDI0382 will achieve weight loss > 10% versus baseline over 1 year, and a greater reduction in HbA1c control than 1.8 mg liraglutide. The entry criteria with respect to BMI of 27-40 kg/m² both maximizes recruitment potential and provides efficacy, safety, and tolerability data in the likely population of clinical use.

Recruitment of Subjects with T2DM on Metformin

MEDI0382 is a GLP-1 and glucagon receptor co-agonist. Early evaluation of the relative effects on blood glucose control of the GLP-1 versus glucagon component is crucial in modeling the overall effect on HbA1c in patients with T2DM, and data on the effects of incretin hormones on glucose homeostasis are much more robust when collected in the target T2DM population.

Metformin forms the basis of initial and continuing oral therapy for a significant proportion of patients with T2DM. Metformin is associated with GI tolerability issues, including nausea, abdominal bloating, and diarrhea. Treatment with MEDI0382 concomitant with metformin will allow assessment of GI tolerability in the likely clinical-use setting early in the development pathway. Metformin concentration will be measured during this study to determine whether there is an interaction with MEDI0382 dosing.

Recruitment of Subjects in the 18 through 65 Years Age Range

This MAD study will be conducted in subjects with T2DM managed by metformin. Recruitment of adults up through age 65 years both ensures that recruitment to the MAD study is feasible and subject safety is appropriately safeguarded. The age range chosen is a balance between the significant fall off in prevalence of T2DM (below age 18 years), and the increase in comorbidities seen in patients with T2DM above age 65 years. Female subjects will not be lactating and not of childbearing potential. There is no requirement for a given number of subjects in each gender to be enrolled.

Selection of Subjects with Stable HbA1c in the Range of 6.5 to 8.5 Percent

The specified HbA1c ranges permit feasible recruitment while ensuring that any acute effect 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 the MAD study for those with an HbA1c > 8.5%.

3.2.3 Rationale for Endpoints

Rationale for Endpoints Supporting the Primary Objectives of Glucose Control and Body Weight Loss

The goal for this MAD study is to ensure that MEDI0382 provides a reliable measure of glucose control and leads to at least comparable body weight loss relative to that achieved by liraglutide at the 1.8 mg dose ([Victoza SPC, 2014](#)) to support investment in further development.

Rationale for the Endpoints Supporting the Secondary Objective of Change from Baseline in HbA1c and Fructosamine Levels

Both fructosamine and HbA1c tests are used primarily as monitoring tools to help patients with diabetes control their blood sugar. For the HbA1c test there are firm data that a *chronically* elevated HbA1c level predicts an increased risk for certain diabetic complications. Fructosamine is the product of a reaction between glucose and albumin. This test is used to evaluate the average amount of glucose in blood over a period of 2 to 3 weeks. The American Diabetes Association recognizes both tests and states that fructosamine may be more useful in situations where HbA1c cannot be reliably measured. These secondary endpoints for glucose control, namely change from baseline through end of treatment in HbA1c and fructosamine (Cohort 4), should enable modeling for longer-term Phase 2b study design.

Rationale for Endpoints Supporting the Secondary Objectives of Safety/Tolerability and PK/Immunogenicity

The goal is to ensure that repeated dosing with MEDI0382 has a suitable safety profile for further clinical development, particularly with respect to GI AE profile and effect on HR and BP. Given the mechanism of action of MEDI0382, GI events including nausea, vomiting, abdominal bloating and diarrhea may be seen with increased frequency. Elevations in HR and BP may also be seen and effects on the QTcF interval will be evaluated.

Food and Drug Administration Guidance suggests assessment of suicidality for agents recognised to cause weight loss where central nervous system penetration is predicted ([Food and Drug Administration, CDER, 2012](#)). Therefore the C-SSRS instrument is included in the study procedures.

The incidence and impact of ADA formation to MEDI0382 will be assessed. Antidrug antibodies formation to other GLP-1 receptor agonist peptides has generally been of low titer and non-neutralizing. There were no confirmed ADA responses following single administration of up to and including 300 µg MEDI0382 in the SAD study. The goal for PK endpoints is to ensure that MEDI0382 has a suitable PK profile for further development and to evaluate any interactions with metformin to determine the relevance of observations seen in rodents with respect to co-administration of metformin with MEDI0382, and evaluate combination therapy in the likely clinical use population.

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

Rationale for Endpoints Supporting the Exploratory Objective for Hepatic, Visceral, and Subcutaneous Fat Volume in T2DM Patients on a 33-day Stable Dose of MEDI0382 (Cohort 4)

Abdominal obesity and T2DM are associated with chronic liver disorders resulting from the accumulation of fat in the liver (steatosis). As weight loss is expected over the 4-week dosing period, relative changes in liver and abdominal visceral/subcutaneous fat compared to baseline will be investigated at sites which have the technical capability to perform the MRI assessment. Reductions in liver fat [REDACTED] will allow initial exploration of the utility of MEDI0382 as a treatment for NASH.

4 MATERIALS AND METHODS

4.1 Subjects

The study population will consist of male or female adults, 18 through 65 years of age with T2DM and BMI 27 to 40 kg/m² (inclusive), without significant late diabetic complications.

Subjects should have been treated with a stable dose of oral blood glucose lowering therapy for 3 months prior to screening, (metformin monotherapy or metformin plus dipeptidyl peptidase-4 [DPPIV], sulphonylurea [50% of the licensed dose], or a sodium-glucose co-transporter 2 [SGLT2]; and DPPIV inhibitor, sulphonylurea, or SGLT2 inhibitor is washed out prior to randomization). Females of childbearing potential and lactating females will be excluded.

4.1.1 Number of Subjects

A total of approximately 107 subjects are planned as described in Section 3.1.2.

4.1.2 Inclusion Criteria

Subjects must meet all of the following criteria:

1. Male or female age 18 through ≤ 65 years at the time of screening.
 2. Written informed consent and any locally required authorization (eg, European Union Data Privacy Directive) obtained from the subject/legal representative prior to performing any protocol-related procedures, including screening evaluations.
 3. Ability to complete and meet all eligibility requirements for randomization within 60 days after signing the informed consent form (ICF).
 4. Body mass index 27 to 40 kg/m² (inclusive).
 5. Diagnosis of T2DM and glucose control managed with metformin monotherapy where no significant dose change (increase or decrease ≥ 500 mg/day) has occurred in the 3 months prior to screening.
 - a. The screening HbA1c value should be within the target range of 6.5% to 8.5%.
 - b. Subjects prescribed a DPPIV inhibitor in addition to metformin monotherapy may be eligible to enter the study following a 4-week DPPIV inhibitor washout period.
 - c. Subjects who are prescribed less than 50% of the licensed dose of sulphonylurea in addition to metformin monotherapy may be eligible to enter the study following a 4-week sulphonylurea washout period.
 - d. Subjects prescribed a sodium-glucose co-transporter 2 (SGLT2) inhibitor in addition to metformin monotherapy may be eligible to enter the study following a 4-week SGLT2 inhibitor washout period.
- Note:** Subjects may be re-tested for the HbA1c entry criterion only once.
6. Venous access suitable for multiple cannulations.
 7. For subjects in Cohorts 4, 5, and 6: Willing and able to self-administer daily SC injections following an initial self-injection of placebo (or normal saline in Cohorts 5 and 6 only) during the screening period.
 8. Females must be not lactating and not of childbearing potential, defined as those who are surgically sterile (ie, bilateral tubal ligation, bilateral oophorectomy, or complete hysterectomy) or are postmenopausal (defined as at least 1 year since last menses and

having an elevated [> 40 mIU/mL] follicle stimulating hormone laboratory value at screening).

If sexually active with a female partner of childbearing potential, nonsterilized males and their partner must practice 2 effective contraceptive measures (see [Table 4.1.2-1](#)) from screening through at least 28 days after the last dose of investigational product has been administered. NOTE: Male condom plus spermicide is only considered an effective contraceptive measure when used together with another method in [Table 4.1.2-1](#). None of the methods in [Table 4.1.2-1](#) are intended to be used alone.

Table 4.1.2-1 Highly Effective Methods of Contraception

| Barrier Methods | Hormonal Methods |
|--|---|
| <ul style="list-style-type: none"> Male condom plus spermicide Copper T intrauterine device Levonorgestrel-releasing intrauterine system (eg, Mirena[®])^a | <ul style="list-style-type: none"> Implants Hormone shot or injection Combined pill Minipill Patch |

^a This is also considered a hormonal method.

4.1.3 Exclusion Criteria

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

- Any condition that, in the opinion of the investigator, would interfere with evaluations of the investigational product or interpretation of subject safety or study results. Specific examples are:
 - Past history of acute or chronic pancreatitis, or pancreatic amylase or lipase greater than twice the upper limit of normal (ULN) of the laboratory reference range at screening.
 - Past history of gastroparesis requiring treatment.
 - Past history of surgery affecting the upper GI tract likely to affect the interpretation of safety and tolerability data.
 - History of cholelithiasis leading to episodes of acute cholecystitis not treated by cholecystectomy, or known biliary disease.
 - Serum calcitonin suggestive of thyroid C-cell hyperplasia (calcitonin level > 50 ng/L), medullary thyroid carcinoma, or history or family history of multiple endocrine neoplasia at screening.
- History or presence of GI, renal, or hepatic disease (with the exception of Gilbert's syndrome), or any other condition known to interfere with absorption, distribution, metabolism, or excretion of drugs.
- History of cancer within the last 10 years, with the exception of non-melanoma skin cancer.
- History or presence of diabetic foot ulcers.
- Any clinically important illness (apart from T2DM for subjects with known diabetes), medical/surgical procedure, or trauma within 4 weeks prior to Day 1 dosing.

6. Symptoms of insulinopenia or poor blood glucose control (eg, significant thirst, nocturia, polyuria, polydipsia, or weight loss).
7. Fasting blood glucose ≥ 200 mg/dL (11.11 mmol/L).
8. Positive hepatitis B surface antigen or hepatitis C virus antibody serology at screening.
9. Positive human immunodeficiency virus (HIV) test at screening or subject taking antiretroviral medications as determined by medical history or subject's verbal report.
10. At screening blood tests, any of the following:
 - a. Aspartate transaminase (AST) $\geq 2.5 \times \text{ULN}$
 - b. Alanine transaminase (ALT) $\geq 2.5 \times \text{ULN}$
 - c. Total bilirubin $\geq 2 \times \text{ULN}$
 - d. Hemoglobin below the lower limit of the normal range
 - e. Neutrophils $< 1.5 \times 10^9/\text{L}$
 - f. Thyroid-stimulating hormone (TSH) level above the normal range
- Note:** Subjects may be re-tested for the AST and ALT criteria only once.
11. Impaired renal function defined as glomerular filtration rate (GFR) ≤ 60 mL/minute/1.73m² (GFR estimated according to Modification of Diet in Renal Disease (MDRD) using MDRD Study Equation IDMS-traceable [SI units]).
12. Persistent (defined as documented on ≥ 2 prior occasions by the subject's usual physician) macroalbuminuria (> 300 mg/L).
13. Significant late diabetic complications (macroangiopathy with symptoms of congestive heart disease or peripheral arterial disease, microangiopathy with symptoms of neuropathy, gastroparesis, retinopathy, nephropathy).
14. Cardiac conduction defect (eg, Wolff-Parkinson-White syndrome, sick sinus syndrome) during the screening period.
15. Abnormal vital signs, after 10 minutes of supine rest, defined as any of the following:
 - a. Cohorts 1 to 4:
 - If < 60 years old, systolic BP < 90 mm Hg or ≥ 140 mm Hg; if ≥ 60 years old, systolic BP < 90 mm Hg or ≥ 150 mm Hg
 - Diastolic BP < 50 mm Hg or ≥ 90 mm Hg
 - HR < 45 or > 85 bpm

Note: At the investigator's discretion, subjects who fail BP screening criteria may be considered for 24-hour ABPM. Subjects who maintain 24-hour BP at a mean of less than 140/90 mm Hg with a preserved nocturnal dip of $> 15\%$ will be considered eligible to enter Cohorts 1 to 4.

- b. Cohorts 5 and 6:
 - If systolic BP < 90 mm Hg or ≥ 140 mm Hg
 - Diastolic BP < 50 mm Hg or ≥ 90 mm Hg
 - HR < 45 or > 85 bpm

Note: At the investigator's discretion, subjects who fail BP screening criteria may be considered for 24-hour ABPM. Subjects who maintain 24-hour BP at a mean of less than

140/90 mm Hg with a preserved nocturnal dip of > 15% will be considered eligible to enter Cohorts 5 and 6.

Subjects may be re-tested for the vital signs criteria only once if, in the investigator's judgment, they are not representative of the subject.

16. Any clinically important abnormalities in rhythm, conduction or morphology of the resting ECG and any abnormalities in the 12-lead ECG that, as considered by the investigator, may interfere with the interpretation of QTc interval changes, including abnormal ST-T-wave morphology or left ventricular hypertrophy.
17. Prolonged QTcF > 450 msec (for both genders) or shortened QTcF < 340 msec, or family history of long QT syndrome.
18. PR (PQ) interval shortening < 120 msec (PR < 120 msec but > 110 msec is acceptable if there is no evidence of ventricular pre-excitation).
19. PR (PQ) interval prolongation (> 240 msec), intermittent second or third degree AV block, or AV dissociation.
20. QRS duration > 120 msec including persistent or intermittent bundle branch block.
Note: Subjects with QRS duration > 120 msec in the presence of right bundle branch block, which is not in the opinion of the investigator associated with significant respiratory or cardiovascular disease, may be enrolled in the study.
21. Subjects with implantable cardiac defibrillator or a permanent pacemaker, and subjects with symptomatic ventricular and/or atrial tachyarrhythmias
22. Subjects with unstable angina pectoris or stable angina pectoris classified higher than Canadian Cardiovascular Society class II:
 - a. or a myocardial infarction or stroke (Cohorts 1 to 4).
 - b. or any previous medical history of myocardial infarction or stroke, or a history of a transient ischemic attack within the prior 12 months (Cohorts 5 and 6).
23. History of hospitalization caused by heart failure or a diagnosis of heart failure.
24. Known or suspected history of drug abuse within the past 3 years as judged by the investigator.
25. History of alcohol abuse or excessive intake of alcohol within the past 3 years as judged by the investigator.
26. Positive screen for drugs of abuse at screening or admission to the study unit, or positive screen for alcohol on admission to the unit prior to the administration of investigational product. Patients who utilize benzodiazepines for chronic anxiety or sleep disorders may be permitted to enter the study.
27. History of severe allergy/hypersensitivity or ongoing clinically important allergy/hypersensitivity as judged by the investigator.
28. Whole blood or red blood cell donation, or any blood loss > 500 mL during the 2 months prior to screening.
29. Received another new chemical entity (defined as a compound that has not been approved for marketing), or has participated in any other clinical study that included drug treatment within at least 30 days or 5 half-lives prior to the first administration of investigational product in this study (whichever is longer). The period of exclusion to begin 30 days or 5 half-lives of investigational product after the final dose, or after the

last visit, whichever is longest. Subjects consented and screened, but not randomized into this study or a previous Phase 1 study, are not excluded.

30. Concurrent participation in another study of any kind is prohibited.
31. Use of any of the following medicinal products:
 - a. Concurrent or previous use of a GLP-1 agonist.
 - b. Use of systemic corticosteroids within 28 days prior to screening.
 - c. Use of compounds known to prolong the QTc interval.
 - d. Use of any herbal preparations or medicinal products licensed for control of body weight or appetite within 1 week prior to Day 1.
32. Psychiatric illness such that subjects have been committed to an institution by way of official or judicial order.
33. History of lactic acidosis or ketoacidosis
34. The subject is an employee, or close relative of an employee, of AstraZeneca, MedImmune, the contract research organization (CRO), or the study site, regardless of the employee's role.
35. Ongoing weight-loss diet (hypocaloric diet) or use of weight loss agents, unless the diet or treatment has been stopped at least 3 months prior to screening and the subject has had a stable body weight (± 3 kg) during the 3 months prior to screening.

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 or web response system [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.

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 meet study eligibility criteria and are randomized will be assigned to a treatment arm by the IXRS.

If a subject who does not meet all the inclusion/exclusion criteria is randomized and treated in error, the investigator should inform the medical monitor immediately; a determination whether or not to replace the subject will be made jointly between the investigator and medical monitor.

Subjects may be rescreened only once

4.1.5 Withdrawal from the Study

Subjects are at any time free to withdraw from the study (investigational product and assessments), without prejudice to further treatment (withdrawal of consent). Such subjects will always be asked about the reason(s) and the presence of any AEs. If possible, they will be seen and assessed by an investigator. Adverse events will be followed up. If a subject withdraws from further participation in the study, then 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 in question:

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. More than 2 symptomatic hypoglycemic events (symptoms of hypoglycemia with documented finger prick glucose < 50.4 mg/dL [2.8 mmol/L]); or persistent hyperglycemia (> 260 mg/dL [14.4 mmol/L] measured with 2 laboratory fasting blood glucose samples more than 3 days apart).
4. Dose-limiting symptoms with respect to GI tolerability, even after measures are taken to reduce the risk of vomiting, after discussion with the medical monitor
5. 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 continuing investigational product, in the decision of the investigator dosing might constitute a safety risk
6. Subject noncompliance that, in the opinion of the investigator or sponsor, warrants withdrawal (eg, refusal to adhere to scheduled visits)
7. Subject develops a resting supine systolic BP of ≥ 180 mm Hg or a resting supine diastolic BP of ≥ 100 mm Hg sustained for more than 10 minutes, or a sustained resting tachycardia which is symptomatic and requires urgent medical intervention (Cohorts 5 and 6)

Subjects who are permanently discontinued from receiving investigational product will be followed for safety and PK/PD unless consent is withdrawn specifically from further study participation (Section 4.1.5) or the subject is lost to follow-up.

Subjects who have not received investigational product, regardless of the reason, will not be followed.

4.1.7 Replacement of Subjects

Additional subjects may be screened and available to ensure that a sufficient number of subjects are randomized into each cohort. Subjects who withdraw from the study may be replaced, if deemed necessary by the medical monitor, to ensure that safety, PK and PD data are collected on a sufficient number of subjects.

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 an 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.

[REDACTED]

[REDACTED]

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4.2 Schedule of Study Procedures

Separate schedules of procedures are provided for the screening period, treatment period, and follow-up period.

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.

Whenever vital signs, 12-lead ECGs, and blood draws are scheduled for the same nominal time, the blood draws should occur last.

Table 4.2.1-1 Schedule of Screening Procedures

| Study Period | Screening |
|--|-------------------|
| Visit Number | V1 |
| Procedure/Study Day | Day -60 to Day -3 |
| Written general informed consent/assignment of SID number | X |
| Optional informed consent for sample for future genetic research | X |
| Optional informed consent for sample for future non-genetic research | X |
| Verify eligibility criteria | X |
| Demographics | X |
| Medical and disease history (including smoking and alcohol history) | X |
| Full physical examination (including structured neurological examination) ^a | X |
| Vital signs | X |
| 12-lead digital ECG (also printed on paper) | X |

Table 4.2.1-1 Schedule of Screening Procedures

| Study Period | Screening |
|--|-------------------|
| Visit Number | V1 |
| Procedure/Study Day | Day -60 to Day -3 |
| Body height | X |
| Body weight | X |
| Calculate GFR to confirm eligibility | X |
| Collect blood for: | |
| Pancreatic amylase, lipase, calcitonin, and TSH | X |
| HIV-1 and -2 antibodies; hepatitis B and C serology | X |
| HbA1c | X |
| Serum chemistry panel | X |
| Hematology and coagulation panels | X |
| FSH levels (females only) | X |
| Total Ig and subsets (Ig A/E/G/M) | X |
| Collect urine for: | |
| Urinalysis (dipstick) | X |
| Drug and alcohol screen ^b | X |
| Assessment of AEs/SAEs | X |
| Concomitant medications | X |
|  ^c | X |
| Cohort 4, 5, and 6 only: Check ability to self-administer investigational product ^d | X |

AE = adverse event; ECG = electrocardiogram; FSH = follicle-stimulating hormone; GFR = glomerular filtration rate; HbA1c = glycated hemoglobin; HIV = human immunodeficiency virus; Ig = immunoglobulin; SAE = serious adverse event; SID = subject identification; TSH = thyroid-stimulating hormone; V = visit.

^a Only the screening physical examination will be a full examination including a structured neurological examination. For all time points thereafter, only a targeted physical examination is required (see Section 4.3.2.1).

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

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^d Subject's ability to self-administer investigational product will be verified using placebo or normal saline subcutaneous injections.

4.2.2 Randomized Treatment Period

Procedures to be conducted during the treatment period are shown as itemized by cohort(s) below:

- Cohort1 ([Table 4.2.2-1](#))
- Cohort 2 ([Table 4.2.2-2](#))
- Cohort 3 ([Table 4.2.2-3](#))
- Cohort 4 Overview ([Table 4.2.2-4](#))
- Cohort 4 Self-administration Dosing Period Detail ([Table 4.2.2-5](#))
- Cohort 5 ([Table 4.2.2-6](#))
- Cohort 6 ([Table 4.2.2-7](#))

Table 4.2.2-1 Schedule of Treatment Period Procedures: Cohort 1

| Study Period | | Residential Inpatient | | | | | | | | | | Outpatient | |
|--|--|-----------------------|----------------|----------------|---|---|---|---|---|---|----|------------|-----------------------------|
| Visit Number | | V2 | V3 | Dose Level 1 | | | | | | | V5 | V6 | V7 |
| Study Day | | -2 | -1 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 7 to 14 Days Post Last Dose |
| Procedure | | | | | | | | | | | | | |
| Verify eligibility criteria | | | X | | | | | | | | | | |
| Admit to clinic | | X | | | | | | | | | | | |
| Medical and disease history | | X | | | | | | | | | | | |
| Targeted physical examination | | X | | | | | | | | | X | | X |
| Body weight ^a | | X | | X | | | | | | | X | | X |
| Randomization | | | X ^b | X ^b | | | | | | | | | |
| Collect blood for: | | | | | | | | | | | | | |
| Hematology panel (predose as applicable) | | X | | X | X | X | X | X | X | X | X | | X |
| Serum chemistry panel (predose as applicable) | | X | | X | X | X | X | X | X | X | X | | X |
| Amylase and lipase (predose) | | | | X | | | X | | | X | | | |
| Lactate (predose as applicable) | | | | X | X | | X | | | X | X | | |
| HbA1c | | X | | | | | | | | | | | |
| Optional future genetic research ^c | | X | | | | | | | | | | | |
| Optional future non-genetic research ^c | | X | | | | | | | | | X | | |
| Collect urine sample for: | | | | | | | | | | | | | |
| Urinalysis (dipstick; predose as applicable) | | | | X | X | | | | | | | | X |
| Pregnancy test | | X | | | | | | | | | | | |
| Drug and alcohol screen ^d | | X | | | | | | | | | | | |
| ECG ^e | | | X | X | X | X | X | X | X | X | X | | X |
| Telemetry ^f | | | X | X | X | X | X | X | X | X | X | | |
| Vital signs (BP, pulse, body temperature, RR) ^g | | X | X | X | X | X | X | X | X | X | X | | X |

Table 4.2.2-1 Schedule of Treatment Period Procedures: Cohort 1

| Study Period | Residential Inpatient | | | | | | | | | | | Outpatient | |
|---|-----------------------|----|--------------|------|------|------|------|------|------|----|----|-----------------------------|--|
| Visit Number | V2 | V3 | Dose Level 1 | | | | | | | V5 | V6 | V7 | |
| | | | V4.1 | V4.2 | V4.3 | V4.4 | V4.5 | V4.6 | V4.7 | | | | |
| Study Day | -2 | -1 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 7 to 14 Days Post Last Dose | |
| IP administration | | | X | X | X | X | X | X | X | | | | |
| PK for MEDI0382 ^h | | | X | X | | X | | | X | X | X | | |
| PK for metformin (prior to MEDI0382 dose as applicable) | | | X | X | | X | | | X | X | X | | |
| MMT and blood samples for glucose metabolism panel ⁱ | | X | | | | | | | X | | | | |
| Record start time of breakfast, mid-day, and evening meals | | | X | X | X | X | X | X | X | | | | |
| PD samples for glucose ^j | | X | X | X | X | X | X | X | X | | | | |
| ADA ^k | | | X | | | | | | | X | | X | |
| | | | | | | | | | | | | | |
| AEs/SAEs | X | X | X | X | X | X | X | X | X | X | | X | |
| Injection site assessment ^l | | | X | X | X | X | X | X | X | X | | | |
| | | | | | | | | | | | | | |
| Concomitant medications | X | X | X | X | X | X | X | X | X | X | | X | |
| Discharge from clinic | | | | | | | | | | X | | | |

ADA = antidrug antibody; AE = adverse event; BP = blood pressure; ECG = electrocardiogram; eCRF = electronic case report form; [REDACTED]; GIP = gastric inhibitory peptide; GLP-1 = glucagon-like peptide-1; HbA1c = glycated hemoglobin; IP = investigational product; min = minutes; MMT = mixed-meal test; PD = pharmacodynamic(s); PK = pharmacokinetic(s); [REDACTED] RR = respiration rate; SAE = serious adverse event; V = Visit.

Note: Whenever vital signs, ECGs, and blood draws are scheduled for the same nominal time, the ECG should occur first, then vital signs, and blood draws should occur last. The timing of the ECGs and/or vital signs should be such that it allows the blood draw (eg, for PK and PD) to occur as close as possible to the scheduled time. Ten minutes of supine rest should precede these assessments.

^a Except Day -2, body weight measurement should be taken in the morning before breakfast.

- ^b Randomization may occur on either Day -1 or Day 1.
- ^c There are separate consent forms for the genetic future research sample and the non-genetic future research sample. Only sample(s) for which the subject has consented will be taken.
- ^d Breath alcohol testing is acceptable as an alternative to urine testing.
- ^e Digital ECGs will be captured on Day -1; predose on Day 1; at 1, 2 (± 15 min); 4, 6, 8, and 12 (± 30 min); and 24 hours (± 60 min) postdose on each day of dosing (Days 1 through 8); additionally at 0.5 hours (± 15 min) postdose on Day 1 and Day 7; and at the 7 to 14 days post last dose visit (V7). All ECGs should be printed. Whenever possible, meals should be scheduled such that at least 2 hours elapse between the meal and the next scheduled ECG time point.
- ^f On Day -1, a minimum of 4 hours of cardiac telemetry will be performed, and any rhythm disturbance is to be recorded in the eCRF. Throughout the inpatient period, cardiac telemetry will be monitored continuously as tolerated, ie, balanced in consideration of potential skin abrasion AEs.
- ^g Vital Signs Schedule: On Day 1, vital signs are to be recorded predose and at 15, 30, 60 and 90 minutes postdose; 2, 4, 6, 8, and 12 hours postdose, as well as before the mid-day meal and before the evening meal (approximately 5 minutes before each meal), and at 24 hours postdose (prior to next dose). Thereafter, vital signs will be recorded on each inpatient day at 4, 12, and 24 hours postdose (prior to next dose or the morning of discharge).
- ^h PK Sampling Schedule for MED10382:
 - Day 1**: Predose and at 0.5, 1, and 2 hours (± 15 min); 4, 6, 8, and 12 hours (± 30 min) postdose.
 - Day 2**: 24 hours (± 60 min) post Day 1 dose (prior to Day 2 dose).
 - Day 4**: 24 hours (± 60 min) post Day 3 dose (prior to Day 4 dose); then 2 hours (± 15 min) and 8 hours (± 30 min) postdose.
 - Day 7**: 24 hours (± 60 min) post Day 6 dose (prior to Day 7 dose); then 0.5, 1, 2 hours (± 15 min); 4, 6, 8, and 12 hours (± 30 min) postdose.
 - Day 8**: 24 hours (± 60 min) post Day 7 dose.
 - Day 9**: 48 hours (± 2 hours) post Day 7 dose.
- ⁱ MMT Schedule: Following a minimum 8-hour fast and after collection of the 2-hour postdose PK sample (except on Day -1), a blood sample for glucose metabolism panel (glucose, insulin, pro-insulin, c-peptide, GLP-1, glucagon, and GIP) will be taken immediately prior to the subject drinking 1 entire can of Ensure Plus as a standardized meal (ie, "0 minutes"). Blood samples for glucose metabolism panel will additionally be drawn at 15, 30, 45, 60, 90, 120, 180, and 240 minutes (± 5 min) after consumption of the standardized meal.
- ^j Using the glucometer (ie, by finger-prick), except for Day -1, the PD glucose will be taken 15 minutes prior to and 2 hours after breakfast, mid-day, and evening meals, and prior to going to bed. The time of the meal start will be recorded in the eCRF every day the subject is an inpatient. For Day -1, PD glucose will be taken only at 15 minutes before the evening meal.
- ^k ADA Sampling Schedule: Day 1 predose; Day 8, and 7 to 14 days after administration of the last dose in the study.
- ^l Injection Site Assessment Schedule: On Day 1, the injection site will be assessed postdose at 4, 12, and 24 hours (prior to next dose). Thereafter, the injection site will be assessed predose on the morning of every inpatient day and on the morning of discharge.
- ^m

Table 4.2.2-2 Schedule of Treatment Period Procedures: Cohort 2

| Study Period | | Residential Inpatient | | | | | | | | | | Outpatient | |
|---|----|-----------------------|----------------|------|---------------|--------------|------|---------------|------|----|----|-----------------------------------|----|
| Visit Number | V2 | V3 | Dose Level 1 | | | Dose Level 2 | | | | | V6 | V7 | V8 |
| | | | V4.1 | V4.2 | V4.3, V4.4 | V5.1 | V5.2 | V5.3- V5.6 | V5.7 | | | | |
| Study Day | -2 | -1 | 1 | 2 | 3, 4 | 5 | 6 | 7-10 | 11 | 12 | 13 | 7 to 14 Days Post Last Dose | |
| Procedure | | | | | | | | | | | | | |
| Verify eligibility criteria | | X | | | | | | | | | | | |
| Admit to clinic | X | | | | | | | | | | | | |
| Medical and disease history | X | | | | | | | | | | | | |
| Targeted physical examination | X | | | | | | | | | X | | X | |
| Body weight ^a | X | | X | | | X | | | | X | | X | |
| Randomization | | X ^b | X ^b | | | | | | | | | | |
| Collect blood for: | | | | | | | | | | | | | |
| Hematology panel (predose as applicable) | X | | X | X | X | X | X | X | X | X | | X | |
| Serum chemistry panel (predose as applicable) | X | | X | X | X | X | X | X | X | X | | X | |
| Amylase and lipase (predose) | | | X | | D4 | | | D8 | X | | | | |
| Lactate (predose as applicable) | | | X | | | X | X | D8 | X | X | | | |
| HbA1c | X | | | | | | | | | | | | |
| Optional future genetic research ^c | X | | | | | | | | | | | | |
| Optional future non-genetic research ^c | X | | | | | | | | | X | | | |
| Collect urine sample for: | | | | | | | | | | | | | |
| Urinalysis (dipstick; predose as applicable) | | | X | X | | X | X | | | | | X | |
| Pregnancy test | X | | | | | | | | | | | | |
| Drug and alcohol screen ^d | X | | | | | | | | | | | | |
| ECG ^e | | X | X | X | X | X | X | X | X | X | | X | |
| Telemetry ^f | | X | X | X | X | X | X | X | X | X | | | |

Table 4.2.2.2 Schedule of Treatment Period Procedures: Cohort 2

| Study Period | | Residential Inpatient | | | | | | | | | | Outpatient | |
|---|-----------|-----------------------|----|--------------|------|---------------|--------------|------|---------------|------|----|------------|-----------------------------------|
| Visit Number | Study Day | V2 | V3 | Dose Level 1 | | | Dose Level 2 | | | | V6 | V7 | V8 |
| | | | | V4.1 | V4.2 | V4.3, V4.4 | V5.1 | V5.2 | V5.3- V5.6 | V5.7 | | | |
| | | -2 | -1 | 1 | 2 | 3, 4 | 5 | 6 | 7-10 | 11 | 12 | 13 | 7 to 14 Days Post Last Dose |
| Vital signs (BP, pulse, body temperature, RR) ^g | | X | X | X | X | X | X | X | X | X | X | | X |
| IP administration | | | | X | X | X | X | X | X | X | | | |
| PK for MED10382 ^h | | | | | | | | | D8 | X | X | X | |
| PK for metformin (prior to MED10382 dose as applicable) | | | | X | | | X | X | D8 | X | X | X | |
| MMT and blood samples for glucose metabolism panel ⁱ | | | X | | | | X | | | X | | | |
| Record start time of breakfast, mid-day, and evening meals | | | | X | X | X | X | X | X | X | | | |
| PD samples for glucose ^j | | | X | X | X | X | X | X | X | X | | | |
| ADA ^k | | | | X | | | | | | | X | | X |
| | | | | | | | | | | | | | |
| AEs/SAEs | | X | X | X | X | X | X | X | X | X | X | | X |
| Injection site assessment ^l | | | | X | X | X | X | X | X | X | X | | |
| | | | | | | | | | | | | | |
| Concomitant medications | | X | X | X | X | X | X | X | X | X | X | | X |
| Discharge from clinic | | | | | | | | | | | X | | |

ADA = antidrug antibody; AE = adverse event; BP = blood pressure; D = day; ECG = electrocardiogram; eCRF = electronic case report form; [REDACTED]; GIP = gastric inhibitory peptide; GLP-1 = glucagon-like peptide-1; HbA1c = glycated hemoglobin; IP = investigational product; min = minutes; MMT = mixed-meal test; PD = pharmacodynamic(s); PK = pharmacokinetic(s); [REDACTED]; RR = respiration rate; SAE = serious adverse event; V = Visit.

Note: Whenever vital signs, ECGs, and blood draws are scheduled for the same nominal time, the ECG should occur first, then vital signs, and blood draws should occur last. The timing of the ECGs and/or vital signs should be such that it allows the blood draw (eg, for PK and PD) to occur as close as possible to the scheduled time. Ten minutes of supine rest should precede these assessments.

- ^a Except Day -2, body weight measurement should be taken in the morning before breakfast.
- ^b Randomization may occur on either Day -1 or Day 1.
- ^c There are separate consent forms for the genetic future research sample and the non-genetic future research sample. Only sample(s) for which the subject has consented will be taken.
- ^d Breath alcohol testing is acceptable as an alternative to urine testing.
- ^e Digital ECGs will be captured on Day -1; predose on Day 1; at 1, 2 (\pm 15 min); 4, 6, 8, and 12 (\pm 30 min); and 24 hours (\pm 60 min) postdose on each day of dosing (Days 1 through 12); additionally at 0.5 hours (\pm 15 min) post dose on Day 5 and Day 11; and at the 7 to 14 days post last dose visit (V8). All ECGs should be printed. Whenever possible, meals should be scheduled such that at least 2 hours elapse between the meal and the next scheduled ECG time point.
- ^f On Day -1, a minimum of 4 hours of cardiac telemetry will be performed, and any rhythm disturbance is to be recorded in the eCRF. Throughout the inpatient period, cardiac telemetry will be monitored continuously as tolerated, ie, balanced in consideration of potential skin abrasion AEs.
- ^g Vital Signs Schedule: On Day 1 and the first day of each new dose level, vital signs are to be recorded predose, and at 15, 30, 60 and 90 minutes postdose; 2, 4, 6, 8, and 12 hours postdose, as well as before the mid-day meal and before the evening meal (approximately 5 minutes before each meal), and at 24 hours postdose (prior to next dose). Thereafter (but not on up-titration days), vital signs will be recorded on each inpatient day at 4, 12, and 24 hours postdose (prior to next dose or the morning of discharge).
- ^h PK Sampling Schedule for MED10382:
Day 1: Predose and at 2 hours (\pm 15 min) postdose.
Day 5: Predose and at 0.5, 1, and 2 hours (\pm 15 min); 4, 6, 8, and 12 hours (\pm 30 min) postdose.
Day 6: 24 hours (\pm 60 min) post Day 5 dose (prior to Day 6 dose).
Day 8: 24 hours (\pm 60 min) post Day 7 dose (prior to Day 8 dose); then 2 hours (\pm 15 min) and 8 hours (\pm 30 min) postdose.
Day 11: 24 hours (\pm 60 min) post Day 10 dose (prior to Day 11 dose); then 0.5, 1, 2 hours (\pm 15 min); 4, 6, 8, and 12 hours (\pm 30 min) postdose.
Day 12: 24 hours (\pm 60 min) post Day 11 dose.
Day 13: 48 hours (\pm 2 hours) post Day 11 dose.
- ⁱ MMT Schedule: Following a minimum 8-hour fast and after collection of the 2-hour postdose PK sample (except on Day -1), a blood sample for glucose metabolism panel (glucose, insulin, pro-insulin, c-peptide, GLP-1, glucagon, and GIP) will be taken immediately prior to the subject drinking 1 entire can of Ensure Plus as a standardized meal (ie, “0 minutes”). Blood samples for glucose metabolism panel will additionally be drawn at 15, 30, 45, 60, 90, 120, 180, and 240 minutes (\pm 5 min) after consumption of the standardized meal.
- ^j Using the glucometer (ie, by finger-prick), except for Day -1, the PD glucose will be taken 15 minutes prior to and 2 hours after breakfast, mid-day, and evening meals, and prior to going to bed. The time of the meal start will be recorded in the eCRF every day the subject is an inpatient. For Day -1, PD glucose will be taken only at 15 minutes before the evening meal.
- ^k ADA Sampling Schedule: Day 1 predose; Day 12; and 7 to 14 days after administration of the last dose in the study.

1 Injection Site Assessment Schedule: On Day 1 and the first day of each new dose level, the injection site will be assessed postdose at 4, 12, and 24 hours
(prior to next dose). Thereafter (but not on up-titration days), the injection site will be assessed predose on the morning of every inpatient day and on the
morning of discharge.

m [REDACTED]

Table 4.2.2-3 Schedule of Treatment Period Procedures: Cohort 3

| Study Period | | Residential Inpatient | | | | | | | | | | | | Outpatient | | |
|---|----|-----------------------|----------------|------|------------|--------------|------|------------|--------------|------|------------|------|----|------------|-----------------------------|--|
| Visit Number | V2 | V3 | Dose Level 1 | | | Dose Level 2 | | | Dose Level 3 | | | | V7 | V8 | V9 | |
| | | | V4.1 | V4.2 | V4.3, V4.4 | V5.1 | V5.2 | V5.3, V5.4 | V6.1 | V6.2 | V6.3- V6.6 | V6.7 | | | | |
| Study Day | -2 | -1 | 1 | 2 | 3, 4 | 5 | 6 | 7, 8 | 9 | 10 | 11-14 | 15 | 16 | 17 | 7 to 14 Days Post Last Dose | |
| Procedure | | | | | | | | | | | | | | | | |
| Verify eligibility criteria | | X | | | | | | | | | | | | | | |
| Admit to clinic | X | | | | | | | | | | | | | | | |
| Medical and disease history | X | | | | | | | | | | | | | | | |
| Targeted physical examination | X | | | | | | | | | | | | X | | X | |
| Body weight ^a | X | | X | | | X | | | X | | | | X | | X | |
| Randomization | | X ^b | X ^b | | | | | | | | | | | | | |
| Collect blood for: | | | | | | | | | | | | | | | | |
| Hematology panel (predose as applicable) | X | | X | X | | | X | | X | X | D11, D12 | | X | | X | |
| Serum chemistry panel (predose as applicable) | X | | X | X | | | X | | X | X | D11, D12 | | X | | X | |
| Amylase and lipase (predose) | | | X | | | | | | | | | X | | | | |
| Lactate (predose as applicable) | | | X | | | X | | | X | X | D12 | X | X | | | |
| HbA1c | X | | | | | | | | | | | | | | | |
| Optional future genetic research ^c | X | | | | | | | | | | | | | | | |
| Optional future non-genetic research ^c | X | | | | | | | | | | | | X | | | |
| Collect urine sample for: | | | | | | | | | | | | | | | | |
| Urinalysis (dipstick; predose as applicable) | | | X | X | | | X | | X | X | | | | | X | |
| Pregnancy test | X | | | | | | | | | | | | | | | |

Table 4.2.2-3 Schedule of Treatment Period Procedures: Cohort 3

| Study Period | Residential Inpatient | | | | | | | | | | | | | Outpatient | |
|---|-----------------------|----|--------------|------|------------|--------------|------|------------|--------------|-------------|-------------|-------------|-------------|-------------|-----------------------------|
| Visit Number | V2 | V3 | Dose Level 1 | | | Dose Level 2 | | | Dose Level 3 | | | | V7 | V8 | V9 |
| | | | V4.1 | V4.2 | V4.3, V4.4 | V5.1 | V5.2 | V5.3, V5.4 | V6.1 | V6.2 | V6.3-V6.6 | V6.7 | | | |
| Study Day | -2 | -1 | 1 | 2 | 3, 4 | 5 | 6 | 7, 8 | 9 | 10 | 11-14 | 15 | 16 | 17 | 7 to 14 Days Post Last Dose |
| Drug and alcohol screen ^d | X | | | | | | | | | | | | | | |
| ECG ^e | | X | X | X | X | X | X | X | X | X | X | X | X | | X |
| Telemetry ^f | | X | X | X | X | X | X | X | X | X | X | X | X | | |
| Vital signs (BP, pulse, body temperature, RR) ^g | X | X | X | X | X | X | X | X | X | X | X | X | X | | X |
| IP administration | | | X | X | X | X | X | X | X | X | X | X | | | |
| PK for MEDI0382 ^h | | | X | | | X | | | X | X | D12 | X | X | X | |
| PK for metformin (prior to MEDI0382 dose as applicable) | | | X | | | X | | | X | X | D12 | X | X | X | |
| MMT ⁱ | | X | | | | | | | X | | | X | | | |
| Blood samples for glucose, insulin, pro-insulin, c-peptide ⁱ | | X | | | | | | | X | | | X | | | |
| Blood samples for GLP-1, glucagon, GIP ⁱ | | X | | | | | | | | | | X | | | |
| Record start time of breakfast, mid-day and evening meals | | | X | X | X | X | X | X | X | X | X | X | | | |
| PD samples for glucose ^j | | X | X | X | X | X | X | X | X | X | X | X | | | |
| ADA ^k | | | X | | | | | | | | | | X | | X |
| <div></div> | | | <div></div> | | | <div></div> | | | <div></div> | <div></div> | <div></div> | <div></div> | <div></div> | <div></div> | |
| AEs/SAEs | X | X | X | X | X | X | X | X | X | X | X | X | X | | X |
| Injection site assessment ^l | | | X | X | X | X | X | X | X | X | X | X | X | | |

Table 4.2.2-3 Schedule of Treatment Period Procedures: Cohort 3

| Study Period | | Residential Inpatient | | | | | | | | | | | | Outpatient | | |
|-------------------------|-----------|-----------------------|----|--------------|------|------------|--------------|------|------------|--------------|------|------------|------|------------|----|-----------------------------|
| Visit Number | Study Day | V2 | V3 | Dose Level 1 | | | Dose Level 2 | | | Dose Level 3 | | | | V7 | V8 | V9 |
| | | | | V4.1 | V4.2 | V4.3, V4.4 | V5.1 | V5.2 | V5.3, V5.4 | V6.1 | V6.2 | V6.3- V6.6 | V6.7 | | | |
| █ ██████ | | -2 | -1 | 1 | 2 | 3, 4 | 5 | 6 | 7, 8 | 9 | 10 | 11-14 | 15 | 16 | 17 | 7 to 14 Days Post Last Dose |
| | | █ | | | | | | | | █ | | | █ | | | |
| | X | X | X | X | X | X | X | X | X | X | X | X | X | X | | X |
| Concomitant medications | | | | | | | | | | | | | | | | |
| Discharge from clinic | | | | | | | | | | | | | | X | | |

ADA = antidrug antibody; AE = adverse event; BP = blood pressure; D = day; ECG = electrocardiogram; eCRF = electronic case report form; [REDACTED]
[REDACTED] GIP = gastric inhibitory peptide; GLP-1 = glucagon-like peptide-1; HbA1c = glycated hemoglobin; IP = investigational product; min = minutes; MMIT = mixed-meal test; PD = pharmacodynamic(s); PK = pharmacokinetic(s); [REDACTED] RR = respiration rate; SAE = serious adverse event; V = Visit.

Note: Whenever vital signs, ECGs, and blood draws are scheduled for the same nominal time, the ECG should occur first, then vital signs, and blood draws should occur last. The timing of the ECGs and/or vital signs should be such that it allows the blood draw (eg, for PK and PD) to occur as close as possible to the scheduled time. Ten minutes of supine rest should precede these assessments.

- ^a Except Day -2, body weight measurement should be taken in the morning before breakfast.
- ^b Randomization may occur on either Day -1 or Day 1.
- ^c There are separate consent forms for the genetic future research sample and the non-genetic future research sample. Only sample(s) for which the subject has consented will be taken.
- ^d Breath alcohol testing is acceptable as an alternative to urine testing.
- ^e Digital ECGs will be captured on Day -1; predose on Day 1; at 1, 2 (± 15 min); 4, 6, 8, and 12 (± 30 min); and 24 hours (± 60 min) postdose on each day of dosing (Days 1 through 16); additionally at 0.5 hours (± 15 min) postdose on Day 9 and Day 15; and at the 7 to 14 days post last dose visit (V9). All ECGs should be printed. Whenever possible, meals should be scheduled such that at least 2 hours elapse between the meal and the next scheduled ECG time point.
- ^f On Day -1, a minimum of 4 hours of cardiac telemetry will be performed, and any rhythm disturbance is to be recorded in the eCRF. Throughout the inpatient period, cardiac telemetry will be monitored continuously, as tolerated, ie, balanced in consideration of potential skin abrasion AEs.
- ^g Vital Signs Schedule: On Day 1 and the first day of each new dose level, vital signs are to be recorded predose, and at 15, 30, 60 and 90 minutes postdose; 2, 4, 6, 8, and 12 hours postdose, as well as before the mid-day meal and before the evening meal (approximately 5 minutes before each meal), and at 24 hours postdose (prior to next dose). Thereafter (but not on up-titration days), vital signs will be recorded on each inpatient day at 4, 12, and 24 hours postdose (prior to next dose or the morning of discharge).

^h PK Sampling Schedule for MEDI0382:

Day 1: Predose and 2 hours (± 15 min) postdose.

Day 5: Predose and 2 hours (± 15 min) postdose.

Day 9: Predose and 0.5, 1, and 2 hours (± 15 min); 4, 6, 8, and 12 hours (± 30 min) postdose.

Day 10: 24 hours (± 60 min) post Day 9 dose (prior to Day 10 dose).

Day 12: 24 hours (± 60 min) post Day 11 dose (prior to Day 12 dose); then 2 hours (± 15 min) and 8 hours (± 30 min) postdose.

Day 15: 24 hours (± 60 min) post Day 14 dose (prior to Day 15 dose); then 0.5, 1, 2 hours (± 15 min); 4, 6, 8, and 12 hours (± 30 min) postdose.

Day 16: 24 hours (± 60 min) post Day 15 dose.

Day 17: 48 hours (± 2 hours) post Day 15 dose.

ⁱ MMT Schedule: Following a minimum 8-hour fast and after collection of the 2-hour postdose PK sample (except on Day -1), blood samples for the tests indicated will be taken immediately prior to the subject drinking 1 entire can of Ensure Plus as a standardized meal (ie, “0 minutes”). Blood samples for the tests indicated will additionally be drawn at 15, 30, 45, 60, 90, 120, 180, and 240 minutes (± 5 min) after consumption of the standardized meal.

^j Using the glucometer (ie, by finger-prick), except for Day -1, the PD glucose will be taken 15 minutes prior to and 2 hours after breakfast, mid-day, and evening meals, and prior to going to bed. The time of the meal start will be recorded in the eCRF every day the subject is an inpatient. For Day -1, PD glucose will be taken only at 15 minutes before the evening meal.

^k ADA Sampling Schedule: Day 1 predose; Day 16; and 7 to 14 days after administration of the last dose in the study.

^l Injection Site Assessment Schedule: On Day 1 and the first day of each new dose level, the injection site will be assessed postdose at 4, 12, and 24 hours (prior to next dose). Thereafter (but not on up-titration days), the injection site will be assessed predose on the morning of every inpatient day and on the morning of discharge.

^m

Table 4.2.2.4 Schedule of Treatment Period Procedures: Cohort 4 Overview

| Study Period | Residential Inpatient | | | | | | | | | | | | | | | Outpatient with Weekly Visits ^a | Residential Inpatient | | Outpatient | |
|--|-----------------------|----------------|----------------|--------------|------|------|----------------|------|--------------|------|------|-----------------|---------------------------|--------------------|-----------------|--|-----------------------|--|--------------------------|--|
| | Dose Level 1 | | | Dose Level 2 | | | | | Dose Level 3 | | | | | Dose Level 3 | | | | | | |
| | | V4.1 | V4.2 | V4.3 V4.4 | V5.1 | V5.2 | V5.3 V5.4 | V6.1 | V6.2 | V6.3 | V6.4 | V7 ^a | (V8- V10) ^a | V11 ^a | V12 | | V13 | | | |
| Visit Number | V2 | V3 | | | | | | | | | | | | | | | | | V14 | |
| Study Day | -2 | -1 | 1 | 2 | 3, 4 | 5 | 6 | 7, 8 | 9 | 10 | 11 | 12 | 13 ^a | 14-39 ^a | 40 ^a | 41 | 42 | | 7-14 Days Post Last Dose | |
| Procedure | | | | | | | | | | | | | | | | | | | | |
| Verify eligibility criteria | | X | | | | | | | | | | | | | | | | | | |
| Admit to clinic | X | | | | | | | | | | | | | X | | | | | | |
| Return to site for once weekly visits ^b | | | | | | | | | | | | | X | | | | | | | |
| Medical and disease history | X | | | | | | | | | | | | | | | | | | | |
| Targeted physical examination | X | | | | | | | | | | | | X | | | | X | | X | |
| Body weight ^c | X | | X | | | X | | | X | | | | X | X | | X | X | | X | |
| Randomization | | X ^d | X ^d | | | | | | | | | | | | | | | | | |
| Collect blood for: | | | | | | | | | | | | | | | | | | | | |
| Hematology panel (predose as applicable) | X | | X | | | X | X | | X | X | | | X | X | | | X | | X | |
| Serum chemistry panel (predose as applicable) | X | | X ^u | X | | X | X ^u | | X | X | | | X ^u | X ^u | | | X ^u | | X | |
| Amylase and lipase (predose) | | | X | | | X | | | X | X | | | X | X | | X | | | | |
| Lactate (predose as applicable) | | | X | | | X | | | X | X | | | X | X | | X | X | | | |
| HbA1c (predose as applicable) | X | | | | | | | | | | | | X | X | | | X | | | |
| Fructosamine (predose as applicable) | X | | | | | | | | | | | | X | X | | X | | | | |

Table 4.2.2.4 Schedule of Treatment Period Procedures: Cohort 4 Overview

| Study Period | Residential Inpatient | | | | | | | | | | | | | | | Outpatient with Weekly Visits ^a | Residential Inpatient | | Outpatient | |
|--|-----------------------|------|--------------|--------------|------|--------------|--------------|------|--------------|------|-----------------|---------------------------|-----------------|--------------------|---------------------------|--|-----------------------|--------------------------|------------|--|
| | Dose Level 1 | | | Dose Level 2 | | | Dose Level 3 | | | | | | Dose Level 3 | Dose Level 3 | | | | | | |
| | V4.1 | V4.2 | V4.3 V4.4 | V5.1 | V5.2 | V5.3 V5.4 | V6.1 | V6.2 | V6.3 | V6.4 | V7 ^a | (V8- V10) ^a | | | V11 ^a | | V12 | V13 | | |
| Visit Number | V2 | V3 | | V4.1 | V4.2 | V4.3 V4.4 | V5.1 | V5.2 | V5.3 V5.4 | V6.1 | V6.2 | V6.3 | V6.4 | V7 ^a | (V8- V10) ^a | V11 ^a | V12 | V13 | V14 | |
| Study Day | -2 | -1 | 1 | 2 | 3, 4 | 5 | 6 | 7, 8 | 9 | 10 | 11 | 12 | 13 ^a | 14-39 ^a | 40 ^a | 41 | 42 | 7-14 Days Post Last Dose | | |
| Fasting lipid profile (before breakfast and predose as applicable) | | X | | | | | | | | | | | | X | | | X | | | |
| | | | | | | | | | | | | | | | | | | | | |
| Optional future genetic research ^e | X | | | | | | | | | | | | | | | | | | | |
| Optional future non-genetic research ^e | X | | | | | | | | | | | | | | | | X | | | |
| Collect urine sample for: | | | | | | | | | | | | | | | | | | | | |
| Urinalysis (dipstick) | | | X | X | | | X | X | | X | X | | | X | X | | X | | X | |
| Urinary Ketostix ^f | | | | | | | | | | | | | | | X | X | | | | |
| Pregnancy test | X | | | | | | | | | | | | | | X | X | | | | |
| Drug and alcohol screen ^g | X | | | | | | | | | | | | | | | | | | | |
| | | | | | | | | | | | | | | | | | | | | |
| | | | | | | | | | | | | | | | | | | | | |
| ECG ^h | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | |
| Telemetry ⁱ | | X | X | X | X | X | X | X | X | X | X | X | X | X | | | X | | | |
| Vital signs (BP, pulse, body temperature, RR) ^j | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | |
| 24-hour ABPM | X | | | | | | | | | | | | | X | X | X | | | | |
| Subject completes Daily Diary | | | | | | | | | | | | | | | X | X | | | | |

Table 4.2.2.4 **Schedule of Treatment Period Procedures: Cohort 4 Overview**

| Study Period | Residential Inpatient | | | | | | | | | | | | | | | Outpatient with Weekly Visits ^a | Residential Inpatient | | Outpatient |
|---|-----------------------|----|--------------|------|--------------|--------------|------|--------------|--------------|------|------|------|-----------------|---------------------------|------------------|--|-----------------------|---------------------------|------------|
| | | V3 | Dose Level 1 | | | Dose Level 2 | | | Dose Level 3 | | | | | Dose Level 3 | Dose Level 3 | | Dose Level 3 | | |
| | | | V4.1 | V4.2 | V4.3 V4.4 | V5.1 | V5.2 | V5.3 V5.4 | V6.1 | V6.2 | V6.3 | V6.4 | V7 ^a | | | | | (V8- V10) ^a | |
| Visit Number | V2 | V3 | V4.1 | V4.2 | V4.3 V4.4 | V5.1 | V5.2 | V5.3 V5.4 | V6.1 | V6.2 | V6.3 | V6.4 | V7 ^a | (V8- V10) ^a | V11 ^a | V12 | V13 | V14 | |
| Study Day | -2 | -1 | 1 | 2 | 3, 4 | 5 | 6 | 7, 8 | 9 | 10 | 11 | 12 | 13 ^a | 14-39 ^a | 40 ^a | 41 | 42 | 7-14 Days Post Last Dose | |
| Staff review Daily Diary with subject | | | | | | | | | | | | | | X | | X | | | |
| Accelerometer receipt/ exchange/ collection | X ^k | | | | | | | | | | | | X | X | X | | | | |
| Train subject on self-administration | | | X | X | X | X | X | X | | | | | | | | | | | |
| Train subject on at-home dose preparation and glucometer use | | | | | | | | | X | X | X | X | | | | | | | |
| Staff train subject in Daily Diary completion (refer to Section 4.3.12.3) | | | | | | | | | | | | X | X | | | | | | |
| IP administration by staff | | | X | X | X | X | X | X | | | | | | | | X | | | |
| IP administration by subject | | | | | | | | | X | X | X | X | X | X | X | | | | |
| PK for MED10382 ^l | | | X | | | X | | | X | X | | | X | X | | X | X | | |
| PK for metformin (prior to MED10382 dosing as applicable) | | | X | | | | | | | | | | X | X | | X | X | | |

Table 4.2.2.4 Schedule of Treatment Period Procedures: Cohort 4 Overview

| Study Period | Residential Inpatient | | | | | | | | | | | | | | | Outpatient with Weekly Visits ^a | Residential Inpatient | | Outpatient |
|--|-----------------------|----------------|--------------|------|--------------|--------------|------|--------------|--------------|------|------|------|-----------------|---------------------------|------------------|--|-----------------------|--------------------------|------------|
| | | | Dose Level 1 | | | Dose Level 2 | | | Dose Level 3 | | | | | Dose Level 3 | | | | | |
| | | | V4.1 | V4.2 | V4.3 V4.4 | V5.1 | V5.2 | V5.3 V5.4 | V6.1 | V6.2 | V6.3 | V6.4 | V7 ^a | (V8- V10) ^a | V11 ^a | | V12 | V13 | |
| Visit Number | V2 | V3 | V4.1 | V4.2 | V4.3 V4.4 | V5.1 | V5.2 | V5.3 V5.4 | V6.1 | V6.2 | V6.3 | V6.4 | V7 ^a | (V8- V10) ^a | V11 ^a | V12 | V13 | V14 | |
| Study Day | -2 | -1 | 1 | 2 | 3, 4 | 5 | 6 | 7, 8 | 9 | 10 | 11 | 12 | 13 ^a | 14-39 ^a | 40 ^a | 41 | 42 | 7-14 Days Post Last Dose | |
| MMT ^m | | X | | | | | | | | | | | X | X | | X | | | |
| Blood samples for glucose and insulin ^m | | X | | | | | | | | | | | X | X | | X | | | |
| Blood samples for pro-insulin and c-peptide ^m | | X | | | | | | | | | | | | | | X | | | |
| Blood samples for GLP-1, glucagon, and GIP ^m | | X | | | | | | | | | | | | | | X | | | |
| Record start time of breakfast, mid-day, and evening meals | | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | | | |
| PD samples for glucose ⁿ | | X | X | X | X | X | X | X | X | X | X | X | | X | | X | | | |
| ADA ^o | | | X | | | | | | | | | | X | V9 | | X | | X | |
| <div></div> | | | <div></div> | | | | | | | | | | <div></div> | <div></div> | | | <div></div> | | |
| AEs/SAEs | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | |
| Injection site assessment ^p | | | X | X | X | X | X | X | X | X | X | X | X | X | | X | | | |
| MRI ^q | X ^r | X ^r | | | | | | | | | | | | X ^s | X ^s | X ^s | X ^s | | |
| <div></div> | | <div></div> | | | | | | | | | | | <div></div> | <div></div> | | <div></div> | | | |
| C-SSRS | | X | | | | | | | | | | | X | X | X | | | | |
| Concomitant medications | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | |

Table 4.2.2.4 Schedule of Treatment Period Procedures: Cohort 4 Overview

| Study Period | Residential Inpatient | | | | | | | | | | Outpatient with Weekly Visits ^a | Residential Inpatient | Outpatient | | | | | |
|-----------------------|-----------------------|----|------|--------------|--------------|------|--------------|--------------|------|------|--|-----------------------|-----------------|---------------------------|------------------|-----|-----|--------------------------|
| | Dose Level 1 | | | Dose Level 2 | | | Dose Level 3 | | | | | | | | | | | |
| | V2 | V3 | V4.1 | V4.2 | V4.3 V4.4 | V5.1 | V5.2 | V5.3 V5.4 | V6.1 | V6.2 | V6.3 | V6.4 | V7 ^a | (V8- V10) ^a | V11 ^a | V12 | V13 | V14 |
| Visit Number | | | | | | | | | | | | | | | | | | |
| Study Day | -2 | -1 | 1 | 2 | 3, 4 | 5 | 6 | 7, 8 | 9 | 10 | 11 | 12 | 13 ^a | 14-39 ^a | 40 ^a | 41 | 42 | 7-14 Days Post Last Dose |
| Discharge from clinic | | | | | | | | | | | | | X | | | X | | |

ABPM = ambulatory blood pressure monitoring; ADA = antidrug antibody; AE = adverse event; BP = blood pressure; C-SSRS = Columbia-Suicide Severity Rating Scale; [REDACTED] ECG = electrocardiogram; eCRF = electronic case report form; [REDACTED] GIP = gastric inhibitory peptide; GLP-1 = glucagon-like peptide-1; HbA1c = glycated hemoglobin; IP = investigational product; min = minutes; MMT = mixed-meal test; MRI = magnetic resonance imaging; [REDACTED] PD = pharmacodynamic(s); PK = pharmacokinetic(s); [REDACTED] RR = respiration rate; SAE = serious adverse event; V = Visit.

Note: Whenever vital signs, ECGs, and blood draws are scheduled for the same nominal time, the ECG should occur first, then vital signs, and blood draws should occur last. The timing of the ECGs and/or vital signs should be such that it allows the blood draw (eg, for PK and PD) to occur as close as possible to the scheduled time. Ten minutes of supine rest should precede these assessments.

- ^a The time period shown between the thickened black gridlines in this table is expanded with details in Table 4.2.2-5. Note: an “X” in the Study Day 14-39 column indicates that the procedure in the given row occurs at some time between Days 14 and 39, inclusive (ie, not necessarily on each of these days).
- ^b The subject will return to the site on Days 20, 27, and 34 for weekly visits. Refer to Table 4.2.2-5 for details of assessments/procedures.
- ^c Except Day -2, body weight measurement should be taken in the morning before breakfast.
- ^d Randomization may occur on either Day -1 or Day 1.
- ^e There are separate consent forms for the genetic future research sample and the non-genetic future research sample. Only sample(s) for which the subject has consented will be taken.
- ^f The subject should do a Ketostix test daily on non-clinic-visit days during the at-home self-administration period; the subject will indicate whether the result was negative or positive in the Daily Diary, and be instructed to call the clinic if the result is positive.
- ^g Breath alcohol testing is acceptable as an alternative to urine testing.
- ^h Digital ECGs will be captured on Day -1; predose on Day 1; at 1, 2 (± 15 min); 4, 6, 8, and 12 (± 30 min); and 24 hours (± 60 min, except Day 12) postdose on each day of dosing (Days 1 through 12); additionally at 0.5 hours (± 15 min) post dose on Day 9 and Day 41; predose, 1, 2 hours (± 15 min) and 4 hours (± 30 min) postdose at the weekly visits during the at-home dosing period (Day 20, Day 27, Day 34); 24 hours (± 60 min) after the last dose (Day 42); and at

the 7 to 14 days post last dose visit (V14). All ECGs should be printed. Whenever possible, meals should be scheduled such that at least 2 hours elapse between the meal and the next scheduled ECG time point.

- i On Day -1, a minimum of 4 hours of cardiac telemetry will be performed, and any rhythm disturbance is to be recorded in the eCRF. Throughout the inpatient period, cardiac telemetry will be monitored continuously as tolerated, ie, balanced in consideration of potential skin abrasion AEs.
- j Vital Signs Schedule: On Day 1 and the first day of each new dose level, vital signs are to be recorded predose, and at 15, 30, 60 and 90 minutes postdose; 2, 4, 6, 8, and 12 hours postdose, as well as before the mid-day meal and before the evening meal (approximately 5 minutes before each meal), and at 24 hours postdose (prior to next dose). Thereafter (but not on up-titration days), vital signs will be recorded on each inpatient day at 4, 12, and 24 hours postdose (prior to next dose or the morning of final discharge). During the at-home dose administration period, at weekly clinic visits, vital signs are to be recorded predose, and at 15, 30, 60 and 90 minutes postdose; then at 2 and 4 hours postdose. Also, vital signs are to be taken at all PK time points.
- k Subjects will return the accelerometer when they return to the clinic for inpatient admission on Day -2.

l PK Sampling Schedule for MED10382:

Day 1 (V4.1): Predose and 2 hours (± 15 min) postdose.

Day 5 (V5.1): Predose and 2 hours (± 15 min) postdose.

Day 9 (V6.1): Predose and 0.5, 1, 2 hours (± 15 min); 4, 6, 8, and 12 hours (± 30 min) postdose.

Day 10 (V6.2): 24 hours (± 60 min) post Day 9 dose (prior to Day 10 dose).

Day 13 (V7): Predose.

Day 20 (V8): Predose.

Day 27 (V9): Predose.

Day 34 (V10): Predose.

Day 41 (V12): 24 hours (± 60 min) post Day 40 dose (prior to Day 41 dose); then 0.5, 1, 2 hours (± 15 min); 4, 6, 8, and 12 hours (± 30 min) postdose.

Day 42 (V13): 24 hours (± 60 min) post Day 41 dose.

- m MMT Schedule: Following a minimum 8-hour fast and after collection of the 2-hour postdose PK sample (except on Day -1), blood samples for the tests indicated will be taken immediately prior to the subject drinking 1 entire can of Ensure Plus as a standardized meal (ie, “0 minutes”). On Day -1, and Day 41, blood samples for the tests indicated will additionally be taken at 15, 30, 45, 60, 90, 120, 180, and 240 minutes (± 5 min) after consumption of the standardized meal. On Day 13, Day 20, Day 27, and Day 34, blood samples for the tests indicated will additionally be taken at 30, 60, 120, and 240 minutes (± 5 min) after consumption of the standardized meal.

- ⁿ Using the glucometer (ie, by finger-prick), during the in-clinic dosing period and except for Day -1, the PD glucose will be taken 15 minutes (\pm 10 minutes) prior to and 2 hours (\pm 10 minutes) after breakfast, mid-day, and evening meals, and prior to going to bed. The time of the meal start will be recorded in the eCRF every day the subject is an inpatient. For Day -1, PD glucose will be taken only at 15 minutes (\pm 10 minutes) before the evening meal. For the at-home dosing period, PD glucose samples are to be taken at home with the standardized glucometer (a) prior to breakfast (ie, fasting)/prior to self-dosing, (b) approximately 2 hours after the mid-day meal, (c) within 15 minutes prior to the evening meal, and (d) approximately every other day at bedtime.
- ^o ADA Sampling Schedule: Day 1 (V4.1) predose; Day 13 (V7) predose; Day 27 (V9) predose; Day 41 (V12) predose; and 7 to 14 days after administration of the last dose in the study.
- ^p Injection Site Assessment Schedule: On Day 1 and the first day of each new dose level, the injection site will be assessed postdose at 4, 12, and 24 hours (prior to next dose). Thereafter (but not on up-titration days), the injection site will be assessed predose on the morning of every inpatient day and on the morning of final discharge. At weekly clinic visits during the at-home self-administration period, the injection site will be assessed predose in the morning.
- ^q MRI will only be conducted if MRI is available to the site and the subject is suitable for and consents to scan.
- ^r Predose MRI scan may be done anytime between Day -7 to Day -1, as determined by site feasibility. This may require a separate visit at the subject's discretion if not carried out on Day -2 or Day -1.
- ^s Postdose MRI scan may be done on Day 39, 40, 41, or 42.
- ^t The P/MSS is to be completed by the subject within 30 minutes (\pm 10 minutes) prior to starting the MMT and within 30 minutes (\pm 10 minutes) after collection of the final MMT glucose metabolism panel blood sample for the inpatient period of the study and at the weekly site visits during the outpatient period.
- ^u Sample to be taken following a minimum of 8 hours fasting.

Table 4.2.2-5 Schedule of Treatment Period Procedures: Cohort 4 Self-administration Dosing Period Detail

| | Visit Number Location | V7 | | V8 | | V9 | | V10 | | V11 | |
|---------------------------------|--------------------------|----------------|-------|----------------|-------|----------------|-------|----------------|-------|-------------|--------|
| | | Clinic | Home | Clinic | Home | Clinic | Home | Clinic | Home | Home | Clinic |
| Procedure / Study Day | | 13 | 14-19 | 20 (±1 day) | 21-26 | 27(±1 day) | 28-33 | 34(±1 day) | 35-39 | 40 (±1 day) | |
| Admit to clinic | | | | | | | | | | | X |
| Targeted physical examination | | X | | | | | | | | | |
| Body weight ^a | | X | | X | | X | | X | | | |
| Collect blood for: | | | | | | | | | | | |
| Hematology panel (predose) | | X | | X | | X | | X | | | |
| Serum chemistry panel (predose) | | X ⁿ | | X ⁿ | | X ⁿ | | X ⁿ | | | |
| Amylase and lipase (predose) | | X | | X | | X | | X | | | |

Table 4.2.2-5 Schedule of Treatment Period Procedures: Cohort 4 Self-administration Dosing Period Detail

| | Visit Number Location | V7 | | Home | V8 | | Home | V9 | | Home | V10 | | V11 | |
|---|--------------------------|--------|-------|------|----------------|-------|------|------------|---|------|------------|-------|-------------|--------|
| | | Clinic | | | Clinic | | | Clinic | | | Clinic | | Home | Clinic |
| Procedure / Study Day | | 13 | 14-19 | | 20 (±1 day) | 21-26 | | 27(±1 day) | | | 34(±1 day) | 35-39 | 40 (±1 day) | |
| Lactate (predose) | | X | | | X | | | X | | | X | | | |
| HbA1c (predose) | | X | | | X | | | X | | | X | | | |
| Fructosamine (predose) | | X | | | X | | | X | | | X | | | |
| Fasting lipid panel (predose before breakfast) | | X | | | X | | | X | | | X | | | |
| Collect urine sample for: | | | | | | | | | | | | | | |
| Urinalysis (dipstick; at clinic visits only) | | X | | | X | | | X | | | X | | | |
| Urinary Ketostix (at home only) ^b | | | X | | | X | | | X | | | X | | |
| Pregnancy test (if applicable) | | | | | X | | | X | | | X | | | X |
| ECG ^c | | X | | | X | | | X | | | X | | | |
| Telemetry | | X | | | | | | | | | | | | |
| Vital signs (BP, pulse, body temperature, RR) ^d | | X | | | X | | | X | | | X | | | X |
| 24-hour ABPM ^e | | X | D14 | | X | D21 | | X | | D28 | X | D35 | | X |
| Subject completes Daily Diary | | | X | | X | X | | X | | X | X | X | | |
| Staff review Daily Diary with subject | | | | | X | | | X | | | X | | | |
| Staff train subject in Daily Diary completion (refer to Section 4.3.12.3) | | X | | | | | | | | | | | | |
| Accelerometer receipt/exchange/collection | | X | | | X | | | X | | | X | | | X |
| Compliance/accountability for outpatient doses | | | | | X | | | X | | | X | | | X |
| IP administration by subject at the study site | | X | | | X | | | X | | | X | | | |
| IP administration once daily by subject at home | | | X | | | X | | | | X | | X | X | |

Table 4.2.2-5 Schedule of Treatment Period Procedures: Cohort 4 Self-administration Dosing Period Detail

| | Visit Number Location | V7 | | Home | V8 | | Home | V9 | | Home | V10 | | V11 | |
|--|--------------------------|--------|-------|------|----------------|-------|------|------------|---|------|------------|----------------|----------------|----------------|
| | | Clinic | | | Clinic | | | Clinic | | | Clinic | | Home | Clinic |
| Procedure / Study Day | | 13 | 14-19 | | 20 (±1 day) | 21-26 | | 27(±1 day) | | | 34(±1 day) | 35-39 | 40 (±1 day) | |
| PK for MEDI0382 ^f | | X | | | X | | | X | | | X | | | |
| PK for metformin (prior to MEDI0382 dose) | | X | | | X | | | X | | | X | | | |
| MMT ^g | | X | | | X | | | X | | | X | | | |
| Blood samples for glucose and insulin ^g | | X | | | X | | | X | | | X | | | |
| Record start time of mid-day and evening meals | | | X | | | X | | | X | | | X | | X |
| PD samples for glucose ^h | | | X | | | X | | | X | | | X | | |
| ADA ⁱ | | X | | | | | | X | | | | | | |
| ██████████ | | ████ | | | ████ | | | ████ | | | ████ | | | |
| AEs/SAEs | | X | | | X | | | X | | | X | | X | |
| Injection site assessment ^j | | X | | | X | | | X | | | X | | X | |
| MRI ^k | | | | | | | | | | | | X ^l | X ^l | X ^l |
| ██████████ | | ████ | | | ████ | | | ████ | | | ████ | | | |
| C-SSRS | | ████ | | | ████ | | | ████ | | | ████ | | | ████ |
| Concomitant medications | | X | | | X | | | X | | | X | | X | X |
| Discharge from clinic | | X | | | | | | | | | | | | |

ABPM = ambulatory blood pressure monitoring; ADA = antidrug antibody; AE = adverse event; BP = blood pressure; C-SSRS = Columbia-Suicide Severity Rating Scale; D = day; ECG = electrocardiogram; ██████████ HbA1c = glycated hemoglobin; IP = investigational product; min = minutes; MMT = mixed-meal test; MRI = magnetic resonance imaging; PD = pharmacodynamic(s); PK = pharmacokinetic(s); ██████████ RR = respiration rate; SAE = serious adverse event; V = Visit.

Note: Whenever vital signs, ECGs, and blood draws are scheduled for the same nominal time, the ECG should occur first, then vital signs, and blood draws should occur last. The timing of the ECGs and/or vital signs should be such that it allows the blood draw (eg, for PK and PD) to occur as close as possible to the scheduled time. Ten minutes of supine rest should precede these assessments.

- ^a Body weight should be taken in the morning before breakfast.
- ^b The subject should do a Ketostix test daily on non-clinic-visit days; the subject will indicate whether the result was negative or positive in the Daily Diary, and will be instructed to call the clinic if the result is positive.
- ^c Digital ECGs will be captured predose, 1, 2 hours (\pm 15 min) and 4 hours (\pm 30 min) postdose at the weekly visits during the at-home dosing period (starting with Day 13, then Day 20, Day 27, and Day 34). All ECGs should be printed. Whenever possible, meals should be scheduled such that at least 2 hours elapse between the meal and the next scheduled ECG time point.
- ^d Vital Signs Schedule: At clinic visits, vital signs are to be recorded predose, and at 15, 30, 60 and 90 minutes postdose; then 2 and 4 hours postdose.
- ^e Subjects will be fitted with the ABPM device whilst at the clinical unit, which may involve practice inflations. The subject will then wear the monitor/cuff for approximately 24 hours (including overnight at home) and will remove the device at home at the end of the 24 hour period. Subjects will return the device to the clinic.
- ^f PK Sampling Schedule for MED10382: Predose on Days 13, 20, 27, and 34.
- ^g MMT Schedule: Following a minimum 8-hour fast and after collection of the PK sample, a blood sample for the tests indicated will be taken immediately prior to the subject drinking 1 entire can of Ensure Plus as a standardized meal (ie, “0 minutes”). Blood samples for the tests indicated will additionally be drawn at 30, 60, 120, and 240 minutes (\pm 5 min) after consumption of the standardized meal.
- ^h PD glucose samples are to be taken at home with the standardized glucometer (a) prior to breakfast (ie, fasting)/prior to self-dosing (b) approximately 2 hours after the mid-day meal, (c) within 15 minutes prior to the evening meal, and (d) approximately every other day at bedtime..
- ⁱ ADA Sampling Schedule: Predose on Days 13 and 27.
- ^j Injection Site Assessment Schedule: At weekly clinic visits during the at-home self-administration period, the injection site will be assessed predose in the morning (except Day 40).
- ^k MRI will only be conducted if MRI is available to the site and the subject is suitable for and consents to scan
- ^l Postdose MRI scan may be done on Day 39, 40, 41, or 42.
- ^m [REDACTED]
- ⁿ Sample to be taken following a minimum of 8 hours fasting.

| Table 4.2.2-6 Schedule of Treatment Period Procedures: Cohort 5 Overview | | | | | | | | | | | | | | | | | | |
|--|-----------------------|----------------|----------------|------------|----------------|------------|----------------|--------|-----------------------|--------|------------------|------------|----|-----------------------|----|-------------------|-------|----|
| Dose Level | | 100 µg | | | | 150 µg | | 200 µg | | 300 µg | | | | | | | | |
| Visit Number | Residential Inpatient | | | Outpatient | V3 | Outpatient | | | Residential Inpatient | | | Outpatient | | Residential Inpatient | | Outpatient | | |
| | -2 | -1 | 1 | 2 | | 3 | 4-5 | V4 | 7-10 | 11 | 12-15 | 16 | 17 | 18 | 19 | | 20-21 | V6 |
| Study Day | | | | | | | | | | | | | | | | | | |
| Procedure | | | | | | | | | | | | | | | | | | |
| Verify eligibility criteria | | X | | | | | | | | | | | | | | | | |
| Admit to clinic | X | | | | | | | | | | X ^{a,b} | | | | | X ^{a, b} | | |
| Discharge home | | | | | X ^a | | | | | | | | | X ^a | | | X | |
| Outpatient clinic visit | | | | | | | | | X ^{a,b} | | X ^{a,b} | | | | | | | X |
| Medical and disease history | X | | | | | | | | | | | | | | | | | |
| Targeted physical examination | X | | | | | | | | X | | X | | | | | X | | X |
| Body weight ^c | X | | | | | | | | X | | X | | | | | X | | X |
| Randomization | | X _d | X ^d | | | | | | | | | | | | | | | |
| Hematology panel (predose as applicable) | X | | X | | | | X | | X | | X | | | | | X | | X |
| Serum chemistry panel (predose as applicable) | X | | X ^r | X | X | | X ^r | | X ^r | | X | X | X | X | X | X ^r | | X |
| Amylase and lipase (predose) | | | X | | | | X | | X | | X | X | X | X | | X | | |
| Lactate (predose as applicable) | | | X | | | | X | | X | | X | X | X | X | | X | | |
| HbA1c (predose as applicable) | X | | | | | | | | X | | X | X | X | X | | X | | |
| Fructosamine (predose as applicable) | X | | | | | | | | | | | | | | | X | | |

| Table 4.2.2-6 Schedule of Treatment Period Procedures: Cohort 5 Overview | | | | | | | | | | | | | | | | | | | |
|--|-----------------------|--------|---|---|------------|--------|----|------------|------|--------|-----------------------|----|----|-----------------------|-------|-----------------------|----|------------|--------------------------|
| Dose Level | | 100 µg | | | | 200 µg | | | | 300 µg | | | | Residential Inpatient | | Outpatient | | Outpatient | |
| Visit Number | Residential Inpatient | | | | Outpatient | | V3 | Outpatient | | | Residential Inpatient | | | 19 | 20-21 | Residential Inpatient | | V7 | |
| | -2 | -1 | 1 | 2 | 3 | 4-5 | | 6 | 7-10 | 11 | 12-15 | 16 | 17 | | | 18 | 22 | | 23 |
| Study Day | | | | | | | | | | | | | | | | | | | |
| Fasting lipid profile (before breakfast and predose as applicable) | | X | | | | | | | | | | | | | | | X | | 7-14 days post last dose |
| ██████████ | █ | | | | | | | | | | | | | | | | █ | | |
| Optional future genetic research ^e | X | | | | | | | | | | | | | | | | | | |
| Optional future non-genetic research ^e | X | | | | | | | | | | | | | | | | X | | |
| Urinalysis (dipstick) | X | | X | X | X | | X | | X | | | X | | X | X | | X | | X |
| Urinary Ketostix ^f | | | | | | X | | X | | X | | X | | | | X | | | |
| Pregnancy test | X | | | | | | | | X | | | X | | X | | | | | X |
| Drug and alcohol screen ^g | X | | | | | | | | | | X | | | | | | | | |
| ██████████ | | █ | | | | | | | | | | █ | | | | | | | █ |
| ECG ^h | | X | X | X | X | X | | X | | X | | X | X | X | X | | X | | X |
| Telemetry ⁱ | | X | X | X | X | X | | | | | | X | X | X | X | | X | | |
| Vital signs (BP, pulse, body temperature, RR) ^j | X | X | X | X | X | | X | | X | | | X | X | X | X | | X | | X |
| 24-hour ABPM ^o | X | | | | | | | | | | | X | | | | | X | | |
| Subject completes Daily Diary | | | | | X | X | X | X | X | X | | | | | X | X | | | |
| Staff review Daily Diary with subject | | | | | | | X | | X | | X | | | | | X | | | |

| Table 4.2.2-6 Schedule of Treatment Period Procedures: Cohort 5 Overview | | | | | | | | | | | | | | | | | | | | |
|---|--|-----------------------|----|---|------------|----|------------|----|------|-----------------------|-------|----|------------|----|-----------------------|-------|----|----|---|--|
| Dose Level | | 100 µg | | | | | 150 µg | | | 200 µg | | | 300 µg | | | | | | | |
| | | Residential Inpatient | | | Outpatient | | Outpatient | | | Residential Inpatient | | | Outpatient | | Residential Inpatient | | | | | |
| Visit Number | | V2 | | | | V3 | | V4 | | | | V5 | | | | V6 | | | | |
| Study Day | | -2 | -1 | 1 | 2 | 3 | 4-5 | 6 | 7-10 | 11 | 12-15 | 16 | 17 | 18 | 19 | 20-21 | 22 | 23 | Outpatient V7 7-14 days post last dose | |
| Train subject on self-administration, at-home dose preparation and glucometer and diary use as required (refer to Section 4.3.12) | | X | | X | X | X | | X | | X | | | | X | X | | | | | |
| IP administration by staff ^q | | | | X | | | | | | | | | | | | | | | | |
| IP administration by subject ^q | | | | | X | X | X | X | X | X | X | X | X | X | X | X | X | | | |
| PK for MEDI0382 ^k | | | | X | | | | X | | X | | X | X | X | | | X | | | |
| PK for metformin (prior to MEDI0382 dose as applicable) | | | | | | | | | | | | X | | | | | X | | | |
| MMT ^l | | | X | | | | | | | | | X | | | | | X | | | |
| Record start time of breakfast, mid-day, and evening meals | | | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | | | |
| PD samples for glucose ^m | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | | | |
| ADA | | | | X | | | | | | X | | | | | | | | | X | |
| AEs/SAEs | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | |
| Injection site assessment ⁿ | | | | X | X | X | | X | | X | | X | X | X | X | | X | | X | |
| P/MSS ^p | | | X | | | | | | | | | | | | | | | | X | |
| C-SSRS | | | X | | | | | | | | | | | | | | | | X | |
| Concomitant medications | | | | | | | | | | | | | | | | | | | X | |
| Collected on an ongoing basis throughout study | | | | | | | | | | | | | | | | | | | | |

ABPM = ambulatory blood pressure monitoring; ADA = antidrug antibody; AE = adverse event; BP = blood pressure; C-SSRS = Columbia-Suicide Severity Rating Scale; [REDACTED] ECG = electrocardiogram; eCRF = electronic case report form; HbA1c = glycated hemoglobin; IP = investigational product; min = minutes; MMT = mixed-meal test; [REDACTED] PD = pharmacodynamic(s); PK = pharmacokinetic(s); P/MSS = Physical/Mental State Scale; RR = respiration rate; SAE = serious adverse event; V = Visit.

Note: Whenever vital signs, ECGs, and blood draws are scheduled for the same nominal time, the ECG should occur first, then vital signs, and blood draws should occur last. The timing of the ECGs and/or vital signs should be such that it allows the blood draw (eg, for PK and PD) to occur as close as possible to the scheduled time. Ten minutes of supine rest should precede these assessments.

- ^a Dosing to take place in the clinic
- ^b Instruct subject to arrive fasted for a minimum of 8 hours
- ^c Except Day -2, body weight measurement should be taken in the morning before breakfast.
- ^d Randomization may occur on either Day -1 or Day 1.
- ^e There are separate consent forms for the genetic future research sample and the non-genetic future research sample. Only sample(s) for which the subject has consented will be taken.
- ^f The subject should do a Ketostix test daily on non-clinic-visit days during the at-home self-administration period; the subject will indicate whether the result was negative or positive in the Daily Diary, and be instructed to call the clinic if the result is positive.
- ^g Breath alcohol testing is acceptable as an alternative to urine testing.
- ^h Digital ECGs will be captured on;

Day -1: No specific time point

Day 1: Predose, 1, 2 (\pm 15 min); 4, 6, 8, and 12 (\pm 30 min) hours postdose

Day 2: Predose, 1, 2 (\pm 15 min); 4, 6, 8, and 12 (\pm 30 min) hours postdose

Day 3: Predose, 1, 2 (\pm 15 min); hours postdose

Day 6: Predose, 1, 2 (\pm 15 min); 4, 6 (\pm 30 min); hours postdose

Day 11: Predose, 1, 2 (\pm 15 min); 4, 6 (\pm 30 min); hours postdose

Day 16: Predose, 1, 2 (\pm 15 min); 4, 6, 8, and 12 (\pm 30 min) hours postdose

Day 17: Predose, 1, 2 (\pm 15 min); 4, 6, 8, and 12 (\pm 30 min) hours postdose

Day 18: Predose, 1, 2 (\pm 15 min); 4, 6, 8, and 12 (\pm 30 min); hours postdose

Day 19: Predose, 1, 2 (\pm 15 min) hours postdose

Day 22: Predose, 1, 2 (\pm 15 min); 4, 6, 8, and 12 (\pm 30 min) and 24 (\pm 60 min) hours postdose

7-14 days post last dose visit; No specific timepoint

24-hour postdose samples may be taken in the next calendar day. Whenever possible, meals should be scheduled such that at least 2 hours elapse between the meal and the next scheduled ECG time point.

ⁱ On Day -1, a minimum of 4 hours of cardiac telemetry will be performed, and any rhythm disturbance is to be recorded in the eCRF. Throughout the inpatient period, cardiac telemetry will be monitored continuously as tolerated, ie, balanced in consideration of potential skin abrasion AEs.

^j Vital Signs Schedule:

Day -2: No timepoint specified

Day -1: No timepoint specified

Day 1: predose, and at 15, 30, 60, and 90 minutes postdose; 2, 4, 6, 8, and 12 hours postdose

Day 2: predose, 4 and 12 hour postdose

Day 3: predose and 2 hours postdose.

Day 6: predose, and at 15, 30, 60 and 90 minutes postdose; then at 2 and 4 hours postdose.

Day 11: predose, and at 15, 30, 60 and 90 minutes postdose; then at 2 and 4 hours postdose.

Day 16: predose, and at 15, 30, 60, and 90 minutes postdose; 2, 4, 6, 8, and 12 hours postdose

Day 17: predose, and at 15, 30, 60, and 90 minutes postdose; 2, 4, 6, 8, and 12 hours postdose

Day 18: predose, and at 15, 30, 60, and 90 minutes postdose; 2, 4, 6, 8, and 12 hours postdose

Day 19: predose, and at 15, 30, 60 and 90 minutes postdose; then at 2 hours postdose

Day 22: predose, and at 15, 30, 60 and 90 minutes postdose; 2, 4, 6, 8, and 12 hours postdose

7-14 days post last dose: No timepoint specified

^k PK Sampling Schedule for MED10382::

Day 1 (V): Predose

Day 6 (V): Predose

Day 11 (V): Predose

Day 16 (V): Predose and 0.5, 1, 2 hours (± 15 min); 4, 6, 8, and 12 hours (± 30 min) postdose.

Day 17 (V): 24 hours (± 60 min) post Day 16 dose (prior to Day 17 dose).

Day 18 (V): Pre-dose

Day 22 (V): Predose and 0.5, 1, 2 hours (± 15 min); 4, 6, 8, and 12 hours (± 30 min) postdose

Day 23 (V): 24 hours (± 60 min) post Day 22 dose

^l MMT Schedule: Following a minimum 8-hour fast and after collection of the 2-hour postdose PK sample (except on Day -1), blood samples for the tests indicated will be taken immediately prior to the subject drinking 1 entire can of Ensure Plus as a standardized meal (ie, “0 minutes”). On Day -1, Day 16,

and Day 22, blood samples for the tests indicated will additionally be taken at 15, 30, 45, 60, 90, 120, 180, and 240 minutes (± 5 min) after consumption of the standardized meal.

- ^m Using the glucometer (ie, by finger-prick), during a full in-patient day in the clinic, the PD glucose will be taken 15 minutes (± 10 minutes) prior to and 2 hours (± 10 minutes) after breakfast, mid-day, and evening meals, and prior to going to bed. The time of the meal start will be recorded in the eCRF every day the subject is an inpatient.. For the at-home dosing period, PD glucose samples are to be taken at home with the standardized glucometer (a) prior to breakfast (ie, fasting)/prior to self-dosing, (b) approximately 2 hours after the mid-day meal, (c) within 15 minutes prior to the evening meal, and (d) bedtime. On days where patients are both in clinic and at home the 4 point monitoring sequence should be followed
- ⁿ Injection Site Assessment Schedule: On Day 1 and the first day of each new dose level, the injection site will be assessed postdose at 4, hours. Thereafter (but not on up-titration days), the injection site will be assessed predose on the morning of every inpatient day and on the morning of final discharge. Subjects will not need to assess injection site reactions, but to report anything unusual to site staff.
- ^o ABPM device will be fitted at a convenient time on the day stated and worn for 24 hours per period. On Day 22, the ABPM device should be fitted as soon as possible after the subject arrives on the unit that morning. Subjects will be given training on how to fit and wear the ABPM device during the day and overnight whilst sleeping
- ^p The P/MSS is to be completed by the subject within 30 minutes (± 10 minutes) prior to starting the MMT and within 30 minutes (± 10 minutes) after collection of the final MMT glucose metabolism panel blood sample for the inpatient period of the study and at the weekly site visits during the outpatient period.
- ^q Subject will dose themselves on the days indicated as long as the investigator is satisfied the subject is competent to do so, This may involve supervision and or assistance being given whilst in clinic, particularly on up-titration days. If not capable of accurately dosing themselves, subjects will be dosed at the unit each day or a trained health care professional will attend the home of the subject according to their preference.
- ^r Sample to be taken following a minimum of 8 hours fasting.

-Cohort 6

| Table 4.2.2-7 Schedule of Treatment Period Procedures: Cohort 6 Overview | | | | | | | | | | | | | | | | | | | |
|--|----|----------------|----------------|---|-----------------------|-----|--|------------------|----------------|------|--|--|-----------------------|----|----|----------------|------------|------------------|----|
| Dose Level | | | | | 100 µg | | | | 200 µg | | | | 300 µg | | | | | | |
| | | | | | Residential Inpatient | | | | Outpatient | | | | Residential Inpatient | | | | Outpatient | | |
| Visit Number | V2 | | | | | | | | V3 | | | | V4 | | | | V5 | | |
| Study Day | -2 | -1 | 1 | 2 | 3 | 4-5 | | | 6 | 7-10 | | | 11 | 12 | 13 | 14 | 15-16 | 17 | 18 |
| Procedure | | | | | | | | | | | | | | | | | | | |
| Verify eligibility criteria | | X | | | | | | | | | | | | | | | | | |
| Admit to clinic | X | | | | | | | | | | | | X ^{a,b} | | | | | X ^{a,b} | |
| Discharge home | | | | | X ^a | | | | | | | | | | | X ^a | | | X |
| Outpatient clinic visit | | | | | | | | X ^{a,b} | | | | | | | | | | | |
| Medical and disease history | X | | | | | | | | | | | | | | | | | | X |
| Targeted physical examination | X | | | | X | | | | X | | | | X | | | | | X | |
| Body weight ^c | X | | X | | | | | X | X | | | | X | | | | | X | |
| Randomization | | X ^d | X ^d | | | | | | | | | | | | | | | | |
| Hematology panel (predose as applicable) | X | | X | | | | | | X | | | | X | | | | | X | |
| Serum chemistry panel (predose as applicable) | X | | X ^r | X | x | | | | X ^r | | | | X ^r | X | X | X | X | X ^r | |
| Amylase and lipase (predose) | | | X | | | | | | X | | | | X | X | X | X | | X | |
| Lactate (predose as applicable) | | | X | | | | | | X | | | | X | X | X | X | | X | |
| HbA1c (predose as applicable) | X | | | | | | | | | | | | | | | | | X | |

| Table 4.2.2-7 Schedule of Treatment Period Procedures: Cohort 6 Overview | | | | | | | | | | | | | | | | | | | |
|--|----|-----------------------|---|---|---|-----|------------|------|----|-----------------------|----|----|------------|----|----|--------------------------|-----------------------|--|----|
| Dose Level | | 100 µg | | | | | 200 µg | | | 300 µg | | | | | | | | | |
| | | Residential Inpatient | | | | | Outpatient | | | Residential Inpatient | | | Outpatient | | | | Residential Inpatient | | |
| Visit Number | V2 | | | | | V3 | | | V4 | | | V5 | | | | V6 | | | V7 |
| Study Day | -2 | -1 | 1 | 2 | 3 | 4-5 | 6 | 7-10 | 11 | 12 | 13 | 14 | 15-16 | 17 | 18 | 7-14 days post last dose | | | |
| Fructosamine (predose as applicable) | X | | | | | | | | | | | | | X | | | | | |
| Fasting lipid profile (before breakfast and predose as applicable) | | X | | | | | | | | | | | | X | | | | | |
| ██████████ | █ | | | | | | | | | | | | | | █ | | | | |
| Optional future genetic research ^e | X | | | | | | | | | | | | | | | | | | |
| Optional future non-genetic research ^e | X | | | | | | | | X | | | | | X | | | | | |
| Urinalysis (dipstick) | X | | X | X | X | | X | | X | X | X | X | | X | | | | | |
| Urinary Ketostix ^f | | | | | | X | | X | | | | | X | | | | | | |
| Pregnancy test | X | | | | | | X | | X | | X | | | | | | | | |
| Drug and alcohol screen ^g | X | | | | | | | | X | | | | | | | | | | |
| ██████████ | | █ | | | | | | | █ | | | | | | | | | | |
| ECG ^h | | X | X | X | X | | X | | X | X | X | X | | X | | | | | |
| Telemetry ⁱ | | X | X | X | X | | | | x | X | X | X | | X | | | | | |
| Vital signs (BP, pulse, body temperature, RR) ^j | X | X | X | X | X | | X | | X | X | X | X | | X | | | | | |
| 24-hour ABPM ^o | X | | | | | | | | X | | | | | | | | | | |
| Subject completes Daily Diary | | | | | X | X | X | X | | | | X | X | | | | | | |

| Table 4.2.2-7 Schedule of Treatment Period Procedures: Cohort 6 Overview | | | | | | | | | | | | | | | | | | | | |
|--|---|-----------------------|----|---|---|------------|-----|-----------------------|---|------------|----|----|-----------------------|----|------------|-------|-----------------------|----|----|--------------------------|
| Dose Level | | 100 µg | | | | 200 µg | | 300 µg | | | | | | | | | | | | |
| | | Residential Inpatient | | | | Outpatient | | Residential Inpatient | | Outpatient | | | Residential Inpatient | | Outpatient | | Residential Inpatient | | | |
| Visit Number | | -2 | -1 | 1 | 2 | 3 | 4-5 | V3 | 6 | 7-10 | V4 | 11 | 12 | 13 | 14 | 15-16 | V6 | 17 | 18 | 7-14 days post last dose |
| Staff review Daily Diary with subject | | | | | | | | X | | | X | | | | X | | | | | |
| Train subject on self-administration at-home dose | | | | | | | | | | | | | | | | | | | | |
| preparation and glucometer and diary use as required (refer to Section 4.3.12) | | | X | X | X | X | | X | | | | | | X | X | | | | | |
| IP administration by staff ^q | | | | X | | | | | | | X | | | | | | | | | X |
| IP administration by subject ^q | | | | | X | X | X | X | X | X | | | | X | X | X | | | | |
| PK for MEDI0382 ^k | | | | X | | | | X | | | X | | X | X | | | X | | | |
| PK for metformin (prior to MEDI0382 dose as applicable) | | | | | | | | | | | X | | | | | | X | | | |
| MMT ^l | | | X | | | | | | | | X | | | | | | X | | | |
| Record start time of breakfast, mid-day, and evening meals | | | | X | X | X | X | X | X | X | X | X | X | X | X | X | | | | |
| PD samples for glucose ^m | | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | | | |
| ADA | | | | X | | | | | | | X | | | | | | | | | X |
| AEs/SAEs | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Injection site assessment ⁿ | | | | X | X | X | | X | | | X | X | X | X | X | | | X | | X |
| P/MSS ^p | | X | | | | | | | | | | | | | | | | | | X |

| Table 4.2.2-7 Schedule of Treatment Period Procedures: Cohort 6 Overview | | | | | | | | | | | | | | | | |
|--|--|----|-----------------------|---|---|------------|---|------|-----------------------|----|----|------------|-------|-----------------------|----|--------------------------|
| | | | 100 µg | | | 200 µg | | | 300 µg | | | | | | | |
| | | | Residential Inpatient | | | Outpatient | | | Residential Inpatient | | | Outpatient | | Residential Inpatient | | |
| Visit Number | | V2 | | | | | | V3 | V4 | | | | V5 | | V6 | |
| Study Day | -2 | -1 | 1 | 2 | 3 | 4-5 | 6 | 7-10 | 11 | 12 | 13 | 14 | 15-16 | 17 | 18 | 7-14 days post last dose |
| C-SSRS | | X | | | | | | | | | | | | | | X |
| Concomitant medications | Collected on an ongoing basis throughout study | | | | | | | | | | | | | | | X |

ABPM = ambulatory blood pressure monitoring; ADA = antidrug antibody; AE = adverse event; BP = blood pressure; C-SSRS = Columbia-Suicide Severity Rating Scale; [REDACTED] ECG = electrocardiogram; eCRF = electronic case report form; HbA1c = glycated hemoglobin; IP = investigational product; min = minutes; MMT = mixed-meal test; [REDACTED]; PD = pharmacodynamic(s); PK = pharmacokinetic(s); [REDACTED] RR = respiration rate; SAE = serious adverse event; V = Visit.

Note: *Whenever vital signs, ECGs, and blood draws are scheduled for the same nominal time, the ECG should occur first, then vital signs, and blood draws should occur last. The timing of the ECGs and/or vital signs should be such that it allows the blood draw (eg, for PK and PD) to occur as close as possible to the scheduled time. Ten minutes of supine rest should precede these assessments.*

- ^a Dosing to take place in the clinic
- ^b Instruct subject to arrive fasted for a minimum of 8 hours
- ^c Except Day -2, body weight measurement should be taken in the morning before breakfast.
- ^d Randomization may occur on either Day -1 or Day 1.
- ^e There are separate consent forms for the genetic future research sample and the non-genetic future research sample. Only sample(s) for which the subject has consented will be taken.
- ^f The subject should do a Ketostix test daily on non-clinic-visit days during the at-home self-administration period; the subject will indicate whether the result was negative or positive in the Daily Diary, and be instructed to call the clinic if the result is positive.
- ^g Breath alcohol testing is acceptable as an alternative to urine testing.
- ^h Digital ECGs will be captured on;
Day -1: No specific time point
Day 1: Predose, 1, 2 (± 15 min); 4, 6, 8, and 12 (± 30 min) hours postdose
Day 2: Predose, 1, 2 (± 15 min); 4, 6, 8, and 12 (± 30 min) hours postdose
Day 3: Predose, 1, 2 (± 15 min) hours postdose
Day 6: Predose, 1, 2 (± 15 min); 4, 6 (± 30 min) hours postdose

Day 11; Predose, 1, 2 (\pm 15 min); 4, 6, 8, and 12 (\pm 30 min) hours postdose

Day 12; Predose, 1, 2 (\pm 15 min); 4, 6, 8, and 12 (\pm 30 min) hours postdose

Day 13; Predose, 1, 2 (\pm 15 min); 4, 6, 8, and 12 (\pm 30 min) hours postdose

Day 14; Predose, 1, 2 (\pm 15 min) hours postdose

Day 17; predose, and at 15, 30, 60 and 90 minutes postdose; 2, 4, 6, 8, and 12 hours postdose

7-14 days post last dose visit; No specific timepoint

24-hour postdose samples may be taken in the next calendar day. Whenever possible, meals should be scheduled such that at least 2 hours elapse between the meal and the next scheduled ECG time point.

ⁱ On Day -1, a minimum of 4 hours of cardiac telemetry will be performed, and any rhythm disturbance is to be recorded in the eCRF. Throughout the inpatient periods, cardiac telemetry will be monitored continuously as tolerated, ie, balanced in consideration of potential skin abrasion AEs.

^j Vital Signs Schedule:

Day -2: No timepoint specified

Day -1: No timepoint specified

Day 1: predose, and at 15, 30, 60, and 90 minutes postdose; 2, 4, 6, 8, and 12 hours postdose

Day 2: predose, 4 and 12 hour postdose

Day 3: predose 2 and 4 hours postdose.

Day 6: predose, and at 15, 30, 60 and 90 minutes postdose; then at 2 and 4 hours postdose.

Day 11: predose, and at 15, 30, 60, and 90 minutes postdose; 2, 4, 6, 8, and 12 hours postdose

Day 12: predose, and at 15, 30, 60, and 90 minutes postdose; 2, 4, 6, 8, and 12 hours postdose

Day 13: predose, and at 15, 30, 60, and 90 minutes postdose; 2, 4, 6, 8, and 12 hours postdose

Day 14: predose, and at 15, 30, 60 and 90 minutes postdose; then at 2 and 4 hours postdose

Day 17: predose, and at 15, 30, 60 and 90 minutes postdose; then at 2 and 4 hours postdose

7-14 days post last dose: No timepoint specified

^k PK Sampling Schedule for MEDI0382::

Day 1 (V); Predose

Day 6 (V); Predose

Day 11 (V); Predose and 0.5, 1, 2 hours (\pm 15 min); 4, 6, 8, and 12 hours (\pm 30 min) postdose.

Day 12 (V); 24 hours (\pm 60 min) post Day 11 dose

Day 13 (V); Predose

Day 17 (V); Predose and 0.5, 1, 2 hours (\pm 15 min); 4, 6, 8, and 12 hours (\pm 30 min) postdose.

Day 18 (V); 24 hours (\pm 60 min) post Day 17 dose.

^l MMT Schedule: Following a minimum 8-hour fast and after collection of the 2-hour postdose PK sample (except on Day -1), blood samples for the tests indicated will be taken immediately prior to the subject drinking 1 entire can of Ensure Plus as a standardized meal (ie, “0 minutes”). On Day -1, Day 11, and Day 17, blood samples for the tests indicated will additionally be taken at 15, 30, 45, 60, 90, 120, 180, and 240 minutes (\pm 5 min) after consumption of the standardized meal.

^m Using the glucometer (ie, by finger-prick), during a full in-patient day in the clinic, the PD glucose will be taken 15 minutes (\pm 10 minutes) prior to and 2 hours (\pm 10 minutes) after breakfast, mid-day, and evening meals, and prior to going to bed. The time of the meal start will be recorded in the eCRF every day the subject is an inpatient. For the at-home dosing period, PD glucose samples are to be taken at home with the standardized glucometer (a) prior to

breakfast (ie, fasting)/prior to self-dosing, (b) approximately 2 hours after the mid-day meal, (c) within 15 minutes prior to the evening meal, and (d) at bedtime. On days where patient is in the unit and at home, the 4 point monitoring schedule should be followed.

- ⁿ Injection Site Assessment Schedule: On Day 1 and the first day of each new dose level, the injection site will be assessed postdose at 4, hours. Thereafter (but not on up-titration days), the injection site will be assessed predose on the morning of every inpatient day and on the morning of final discharge. Subjects will not need to assess injection site reactions, but to report anything unusual to site staff.
- ^o ABPM device will be fitted at a convenient time on the day stated and worn for 24 hours and subjects with receive training from study site staff on how to fit and wear the device during the day and whilst sleeping. On Day 17, the ABPM device should be fitted as soon as possible after the subject arrives on the unit that morning
- ^p The P/MSS is to be completed by the subject within 30 minutes (+ 10 minutes) prior to starting the MMT and within 30 minutes (+ 10 minutes) after collection of the final MMT glucose metabolism panel blood sample for the inpatient period of the study and at the weekly site visits during the outpatient period.
- ^q Subject will dose themselves on the days indicated as long as the investigator is satisfied the subject is competent to do so, This may involve supervision and or assistance being given whilst in clinic. If not capable of accurately dosing themselves, subjects will be dosed at the clinical unit each day.
- ^r Sample to be taken following a minimum of 8 hours fasting

4.2.3 Follow-up Period

Table 4.2.3-1 shows procedures to be conducted during the follow-up period. Assessments should be performed in the order shown in the table.

Table 4.2.3-1 Schedule of Follow-up Procedures: All Cohorts

| Study Period | Follow-up |
|--|---|
| Visit Number | End of Study Visit (Visit Number Varies by Cohort) |
| Procedure / Study Day | 28 (± 2) Days Post Last Dose |
| Targeted physical examination | X |
| Pregnancy test (if applicable) | X |
| ECG ^a | X |
| Vital signs (BP, pulse, body temperature, RR) ^a | X |
| Body weight | X |
| MEDI0382 ADA ^b | X |
| Assessment of AEs/SAEs | X |
| Concomitant medications | X |

AE = adverse event; ADA = antidrug antibody; BP = blood pressure; ECG = electrocardiogram; RR = respiration rate; SAE = serious adverse event.

^a Prior to discharge from the clinic, subjects should be assessed with respect to QT interval, HR and BP. If, after a period of 10 minutes supine rest, any of these parameters for an individual subject are outside the limits specified in the protocol exclusion criteria, or if in the opinion of the investigator any of these parameters are clinically significantly different versus baseline measures on an individual subject basis, the findings should be discussed with the medical monitor prior to the subjects' release. Measurements may be re-assessed for confirmation.

^b If this sample is ADA positive, the subject will be asked to return to provide another sample at approximately 3 months after the end of study visit (post-study sample). If the sample taken at 3 months is ADA positive, the subject will be asked to return to provide a sample in another 3 months (ie, 6 months after the end of study visit).

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.

4.2.4 Early Discontinuation 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.

- Targeted physical examination
- ECG

- Vital signs
- Body weight
- PK for MEDI0382 and for metformin
- Lactate
- MEDI0382 ADA
- Assessment of AEs/SAEs
- Injection site assessment
- C-SSRS (Cohort 4, 5, and 6 only)
- Concomitant medications
- Pregnancy test (Cohort 4, 5, and 6 only)

4.3 Description of Study Procedures

4.3.1 Efficacy

4.3.1.1 Mixed-meal Test

Refer to Section [4.3.7](#).

4.3.1.2 Weight

Weight will be measured at the time points specified in the schedules of procedures by cohort(s), after the subject has toileted and removed bulky clothing including shoes.

Whenever possible, the same (properly calibrated) scale should be used for each measurement for any given subject.

4.3.2 Medical History, Physical Examination, Electrocardiograms, and Vital Signs

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, gastrointestinal, renal, hepatic, neurological, endocrine, lymphatic, hematologic, immunologic, dermatological, psychiatric, genitourinary, drug and surgical history, or 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, throat; respiratory; cardiovascular; gastrointestinal; 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 electronic case report form (eCRF).

The full physical examination including structured neurological examination is required at screening. Targeted examinations (evaluation of selective body systems at the judgement of the physician or qualified designee based on subject presentation) are sufficient for the remaining time points.

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 at the times specified in the study procedures table. Injection site reactions may include (but are not limited to) local erythema, pain, tenderness, induration, swelling, pruritus, ulceration and pigmentation.

4.3.2.3 Electrocardiograms

Electrocardiography will be used in this study to monitor cardiac safety. Digital ECG [dECG]/paper printout will be used for each subject at each time point. Telemetry will also be utilized, to improve capture of any potential arrhythmias. 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. Electrocardiograms will be recorded after the subject has rested for 10 minutes in the supine position. Where significant skin irritation exists in response to telemetry electrode placement, subjects may be permitted to discontinue telemetry during stable dosing after 48 hours recording, although re-application of telemetry is to be encouraged for 48 hours after dose up-titration in this situation.

The following variables will be reported: RR, PR, QRS and QT intervals. Derived parameters (such as HR, QTcF and others as applicable) will be calculated.

12-lead Electrocardiograms

Electrocardiograms will be digitally recorded and printed on paper according to the schedules specified for each cohort. Digital ECGs will be captured as triplicate measures in a single recording. Printed ECGs will be reviewed by the investigator for assessments of subject eligibility related to the ECG criteria and assessment of AEs. The printed ECGs will be used for the real time bedside ECG assessment made by the investigator, and at minimum, a single representative ECG should be printed and archived in the subject's file.

The investigator may record 12-lead ECGs at other time points if there are any abnormal findings or if the investigator considers it is required for any other safety reason.

Digital ECGs will be collected according to the schedules specified for each cohort. These will be submitted to the sponsor (or designee) and to the ECG vendor. The ECG vendor will perform the dECG analysis and interpretation in this study using their methodology for dECG analysis. If the central readers pick up an abnormality that the clinician may have missed, they will notify the investigator who will review the ECG and report any AEs as necessary.

Telemetry

Telemetry will be used to continuously monitor HR and rhythm activity as a real-time safety measure. Telemetry will be monitored as tolerated (ie, balanced in consideration of potential skin abrasion AEs). Telemetry measurements using 3 leads will be continuous during the inpatient treatment period as specified in the schedules by cohort(s). Any significant abnormality in telemetry before dosing should be documented in the eCRF as part of the subject's medical history, and abnormalities after dosing should be reported as AEs. Significant abnormalities include atrial or VT lasting for more than 3 beats, or symptomatic heart block (ie, pulse < 40 bpm accompanied by symptomatic hypotension for at least 10 minutes). Any clinically significant change noted on telemetry will be followed up by performing and printing a 12-lead dECG.

4.3.2.4 Vital Signs

Vital sign measurements (BP, pulse, body temperature, and respiration rate) will be obtained after the subject has rested in the supine position for at least 10 minutes at the time points specified in the schedules of procedures for each cohort (for time points where ECG recording precedes vital sign measurement, the 10 minute rest in the supine position prior to the ECG suffices for the rest prior to vital sign measurement). Route of body temperature measurement will be according to local custom.

During the at-home self-administration dosing period for Cohorts 4, 5, and 6, ambulatory BP and HR monitoring will be used for the 24-hour period after receipt of the SC dose at the clinic visit.

Prior to discharge from the unit, subjects should be assessed with respect to QT interval, HR and BP. If, after a period of 10 minutes supine rest, any of these parameters for an individual subject are outside the limits specified in the protocol exclusion criteria, or if in the opinion of the investigator any of these parameters are clinically significantly different versus baseline measures on an individual subject basis, the findings should be discussed with the medical monitor prior to the subject's release. Measurements may be re-assessed for confirmation.

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 will be performed in a licensed central or licensed local clinical laboratory. Abnormal laboratory results considered to be clinically significant should be repeated as soon as possible (preferably within 24 to 48 hours).

The following clinical laboratory tests will be performed (please refer to time points in the schedules of procedures by cohort[s]):

Serum Chemistry Panel

- | | |
|-------------------------------|------------------------------|
| • Calcium | • Alkaline phosphatase (ALP) |
| • Chloride | • Total bilirubin |
| • Potassium | • Gamma glutamyl transferase |
| • Sodium | • Creatinine |
| • Bicarbonate* | • Blood urea nitrogen |
| • AST | • Glucose |
| • ALT | • Albumin |
| • Magnesium (Cohorts 5 and 6) | |

Notes for serum chemistries: Tests for AST, ALT, ALP, and total bilirubin must be conducted concurrently and assessed concurrently. * may be measured via serum chemistry sample of blood gas analyzer per local procedures.

Hematology Panel

- White blood cell count with differential
- Red blood cell count
- Hematocrit
- Hemoglobin
- Platelet count
- Mean corpuscular volume
- Mean corpuscular hemoglobin concentration

Coagulation Panel

- Prothrombin time (screening only)
- Activated partial thromboplastin time (screening only)

Urinalysis

- Color
- Appearance
- Specific gravity
- pH
- Protein
- Glucose
- Ketones
- Leucocyte esterase
- Bilirubin
- Urobilinogen
- Nitrite
- Urine microscopy and urine casts (as required)
- Urine culture (as required)
- Urine drug and alcohol screen ^a (screening and Day -2 for all cohorts; at the weekly site visits for Cohort 4 and just prior to initiation of the 300 µg dose for Cohorts 5 and 6 at the discretion of the investigator)

- Blood

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

Note: Urinalysis for specific gravity, pH, protein, glucose, ketones, blood, leucocyte esterase, bilirubin, urobilinogen, and nitrite may be performed at the site using a licensed test (dipstick).

Other Tests

- Calcitonin (screening only), TSH (screening only), pancreatic amylase, lipase
- Blood lactate
- HbA1c
- [REDACTED]
- Anti-drug antibodies
- Total immunoglobulin (Ig) and subsets (Ig A/E/G/M)
- Follicle-stimulating hormone (for females at screening only)
- Urine pregnancy test (females only)
- Hepatitis B surface antigen, hepatitis C antibody (screening only)
- HIV-1, -2 antibodies (screening only)
- Glucose metabolism panel for MMT for Cohort 1 to 4: Timed glucose, insulin, pro-insulin, c-peptide, GLP-1, glucagon, and GIP
- Glucose metabolism panel for MMT for Cohorts 5 and 6; Timed glucose and insulin
- Fructosamine (Cohorts 4, 5, and 6 only)
- [REDACTED]

- [REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]

4.3.4 Estimate of Volume of Blood to Be Collected

The estimated volume of blood to be collected from each subject over the entire course of their participation in the study is 371 mL for Cohort 1, 490 mL for Cohort 2, 445 mL for Cohort 3, 553 mL for Cohort 4, 425 mL for Cohort 5, and 405 mL for Cohort 6. Additional blood samples may be collected at the discretion of the investigator in the event of abnormal laboratory findings or an adverse event.

4.3.5 Glucometer Blood Glucose Readings during the Inpatient Period

At study start, each subject in every cohort will be issued a standardized glucometer. Subjects will be encouraged to follow their normal practice with respect to finger-prick blood testing for glucose at normal testing frequency and include extra finger-prick tests if at any time they feel unwell and feel the symptoms may be due to hypo- or hyperglycemia during the inpatient period. If the investigator/site staff feel that a subject could be experiencing hypo- or hyperglycemia, blood glucose should be tested with the standardized glucometer issued to that subject. Any glucometer blood glucose values of concern should be reported as AEs. The PD glucose measurements will be taken with the glucometer (15 minutes [\pm 10 minutes] prior to and 2 hours [\pm 10 minutes] after breakfast, mid-day, and evening meals, and prior to going to bed, and for which start time of meal is recorded) and recorded. Other inpatient glucometer blood glucose readings are for “real time” safety purposes, and will only be captured if reported as AEs.

4.3.6 Pharmacokinetic Evaluation and Methods

Separate PK samples will be collected to measure MEDI0382 concentration and metformin concentration. The PK sampling times and windows for collection are specified in the schedules of procedures by cohort(s). 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. A sample schedule for Day 1 that depicts the relationship of the MEDI0382 PK sampling times relative to dosing and meals is provided in [Table 4.3.8-1](#) together with PD sampling times.

4.3.7 Pharmacodynamic Evaluation and Methods

Mixed-meal Test

Following a minimum 8-hour overnight fast and after collection of the 2-hour postdose PK blood sample (as applicable), the subject will undergo a MMT. For the MMT, the subject will consume a standardized meal (Ensure Plus, a nutritional supplement containing the components of fat, carbohydrate and protein, which make up a standard MMT) within 5 minutes, and timed serial blood samples will be obtained for measurement of glucose and parameters related to glucose metabolism through 240 minutes after consumption of the standardized meal (with no additional food intake during this time). The MMT procedures will be performed at the time points specified in the schedules of procedures by cohort(s). The time points are also summarized in Section 3.1.1.

The timed pre- and post-MMT blood sample collections are for measurement of a panel of glucose metabolism markers: glucose, insulin, pro-insulin, c-peptide, GLP-1, glucagon, and GIP as indicated by the footnotes in the example schedule for PK and PD/efficacy in Table 4.3.8-1. Glucose measurements from these pre- and post-MMT samples will be used for the primary efficacy assessment (Cohort 4). All MMT test results will be used to generate PD profiles. For Cohorts 5 and 6, only glucose and insulin will be measured.

Blood will be drawn within 15 minutes before consuming the standardized meal (ie, “0 minutes”), and at 15, 30, 45, 60, 90, 120, 180, and 240 minutes (± 5 minutes) after consumption (except at the weekly visits for Cohort 4, during which the time points will be abbreviated to include 0, 30, 60, 120, and 240 minutes [± 5 minutes])). Blood sampling should occur as close as possible to the specified times for the MMT. Sampling ± 5 minutes of the specified time will not be considered a protocol deviation but the exact time of sampling should be recorded.

4.3.8 Combined Pharmacokinetic and Pharmacodynamic Blood Sampling Example Schedule

Table 4.3.8-1 Example Schedule for MEDI0382 PK and for PD Blood Sample Collections on Day 7 (Cohort 1), Day 11 (Cohort 2), Day 15 (Cohort 3), and Day 41 (Cohort 4), Day 22 (Cohort 5), and Day 17 (Cohort 6)

| Example Clock Time | Time Relative to Dosing | MEDI0382 PK Sample | Time Relative to MMT | PD Sample |
|--|---|--------------------|--|------------------|
| Overnight (minimum 8-hour fast) | | | | |
| 5:55 ^a | Predose | X | | |
| 6:00 | Administer IP | | | |
| 6:30 | 0.5 hour postdose | X | | |
| 7:00 | 1 hour postdose | X | | |
| 8:00 | 2 hours postdose | X | | |
| 8:15 | | | 15 minutes before breakfast | X ^b |
| 8:25 | | | Within 15 min before ingesting Ensure Plus (MMT) | X ^c |
| 8:30 | Ensure Plus after collection of the 2-hour post dose PK sample (Ensure Plus to be consumed within 5 minutes); actual start time to be recorded in eCRF Or Breakfast | | | |
| 8:45 | | | 15 minutes | X ^c |
| 9:00 | | | 30 minutes | X ^c |
| 9:15 | | | 45 minutes | X ^c |
| 9:30 | | | 60 minutes | X ^c |
| 10:00 | 4 hours postdose | X | 90 minutes | X ^c |
| 10:30 | | | 120 minutes | X ^{b,c} |
| 11:30 | | | 180 minutes | X ^c |
| 12:00 | 6 hours postdose | X | | |
| 12:30 | | | 240 minutes | X ^{b,c} |
| 12:45 | Mid-day Meal (after collection of the 240-minute MMT sample; actual start time to be recorded in eCRF) | | | |
| 14:00 | 8 hours postdose | X | | |
| 14:45 | | | | X ^b |
| 15:00 | | | 2 hours after mid-day meal | X ^b |
| 18:00 | 12 hours postdose | X | | |
| 18:15 | | | Within 15 minutes before evening meal | X ^b |

Table 4.3.8-1 Example Schedule for MEDI0382 PK and for PD Blood Sample Collections on Day 7 (Cohort 1), Day 11 (Cohort 2), Day 15 (Cohort 3), and Day 41 (Cohort 4), Day 22 (Cohort 5), and Day 17 (Cohort 6)

| Example Clock Time | Time Relative to Dosing | MEDI0382 PK Sample | Time Relative to MMT | PD Sample |
|---|---|--------------------|------------------------------|----------------|
| 18:30 | Evening Meal (actual start time to be recorded in eCRF) | | | |
| 20:30 | | | | X ^b |
| Pre bedtime | | | | X ^b |
| Overnight (minimum 8 hours of fasting) | | | | |
| 5:55 (next day) | 24 hours postdose | X | After a minimum 8-hours fast | X ^b |

eCRF = electronic case report form; GIP = gastric inhibitory peptide; GLP-1 = glucagon-like peptide-1; IP = investigational product; min = minutes; MMT = mixed-meal test; PD = pharmacodynamics(s); PK = pharmacokinetic(s).

Notes: For instances in which a PK and PD blood sample are required at the same clock time, every effort should be made to take the samples using a single venipuncture.

^a This is an example schedule. Actual start time may vary, but the timing relative to dosing and timing relative to MMT should be maintained.

^b Using the glucometer (ie, by finger-prick); for PD glucose only.

^c For the complete glucose metabolism panel (glucose, insulin, pro-insulin, c-peptide, GLP-1, glucagon, and GIP). Note: On MMT days not listed in the title of this table, components of the panel are to be drawn as specified in the schedules of procedures by cohort.

Note that ECGs and vital signs immediately precede PK sample times (refer to schedules of assessments by cohort). Whenever possible, it is preferable to have meals consumed after ECGs or to perform ECGs ≥ 1.5 hours after a meal, to avoid the influence of food intake on HR, T-wave morphology, and QT assessment.

4.3.9 Immunogenicity Evaluation and Methods

Antidrug antibody sampling will occur at the time points specified in the schedules of procedures by cohort(s). A screening assay will be used to determine ADA-positive samples. This will be in the form of a traditional ligand-binding “bridging” assay using electrochemiluminescence. Any positive samples will be tested in a confirmatory assay whereby the specificity of the ADA response will be confirmed as either positive or negative with respect to MEDI0382. Cross reactivity of ADA-positive samples to GLP-1 and glucagon may also be assessed in the confirmatory assay. Titer evaluation will be performed on samples that are confirmed positive for ADA. For subjects with a positive ADA result, a qualitative analysis of incretin hormone levels in response to MMT (ie, glucagon, GLP-1,

[REDACTED]

4.3.10.6 Magnetic Resonance Imaging of the Liver/Abdomen (Cohort 4)

At study sites that have the capacity and if subject is suitable and has consented, MRI of the liver/abdomen will be performed at the time points specified in the schedules of procedures for Cohort 4 only. Detailed instructions will be provided in the MRI manual. Subject suitability to be scanned will be determined against local criteria at the scanning site.

[REDACTED] [REDACTED]

4.3.11.1 Columbia-Suicide Severity Rating Scale (Cohorts 4, 5, and 6)

The C-SSRS is a 2-page validated questionnaire that assesses suicidal ideation and behavior. The Baseline Form will be used on Day -1, and the Since Last Visit Form will be used at the time points shown in the schedules of procedures for Cohorts 4, 5, and 6 to assess change from baseline ([Appendix 4](#)). Site staff will complete the assessment with the subject in a private, quiet place.

[REDACTED] [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

4.3.12 Training of Cohorts 4, 5, and 6 Subjects for At-home Activities

4.3.12.1 Training for Self-administration and At-home Preparation of Investigational Product

Cohort 4

While the subject is still an inpatient at the unit, qualified study site personnel will train the subject about the technique of SC abdominal self-administration for each dose administration at dose level 1 and dose level 2 as shown in [Table 4.2.2-4](#) (8 doses total). Beginning with the first dose at dose level 3, while the subject is still an inpatient undergoing up-titration (5 doses), qualified site personnel will work daily with the subject to train

him/her how to prepare their daily dose and the subject will administer his or her own dose under their watchful supervision.

Cohorts 5 and 6

While the subject is still an inpatient at the clinic, qualified site personnel will train the subject about the technique of SC abdominal self-administration during the initial days 3 days of inpatient dosing, beginning with the first dose. Qualified site personnel will work daily with the subject to train him/her how to prepare their daily dose and the subject will administer his or her own dose under their watchful supervision.

Subjects will be given an instructions sheet for self-administration and at-home preparation of investigational product while in residence at the clinic.

4.3.12.2 Training during the Inpatient Period for Using the Standardized Glucometers during the Inpatient and Outpatient Periods

In Clinic

At the beginning of the study, a standardized glucometer will be provided to each subject in all cohorts. This glucometer will be used for the PD glucose samples. Site staff will make a point of explaining how the glucometer should be used for the purposes of this study (refer to Section 4.3.5), and allow the subject to demonstrate that he or she uses it properly (under watchful supervision) before the subject is discharged from the clinic after the inpatient up-titration period.

At Home

Blood glucose measurements are to be taken with the standardized glucometer supplied for this study (a) prior to breakfast (ie, fasting)/prior to self-dosing, (b) approximately 2 hours after the mid-day meal, (c) within 15 minutes prior to the evening meal, and (d) approximately every other day at bedtime (every bedtime for Cohort 5 and 6). Meal start times are to be recorded in the Daily Diary (see Section 4.3.12.3).

At the weekly site visit, relevant data (eg, blood glucose values, dates and times) will be collected by site staff.

4.3.12.3 Training for Completing the Daily Diaries during the At-home Self-administration Period

Before discharge from the unit, at the time points indicated in the overview schedule of procedures for Cohorts 4, 5, and 6, each subject in these cohorts will be trained on how to

complete the Daily Diary. At the time points indicated in the at-home schedule of procedures for Cohort 4, each subject will be given a Daily Diary for the next week to be completed at home, and each subject in Cohorts 5 and 6 will be given a Daily Diary to complete according to the schedule outlined in Section 4.2.2. Subjects will be encouraged to complete the Daily Diary as accurately as possible.

The following entries will be made daily into the Daily Diary and collected and reviewed by site staff at the appropriate visits:

- Date
- Confirmation that the acceptable temperature was maintained
- Unique kit number of dose
- Time of self-dose administration
- Start time of each meal
- Daily Ketostix[®] result (negative or positive) (Note: In case a Ketostix [ketone] test result is positive, the subject will be instructed to call the site)
- Any new medications or changes to standard medications (Note: Subjects will be instructed to contact the site in the event of any new medications or changes to medication)
- Any symptoms experienced (Note: For data capture purposes, this information will be captured in a comment field. Subjects will be instructed to contact the site in the event of any symptoms being experienced. Based on the information provided by the subject, the investigator will report any AEs, what action was taken, and if no action was taken, why no action was taken)

If the subject forgets to fill in any requested information, it will not be considered a protocol deviation.

4.3.12.4 Training for Application and Wearing of ABPM Device

Subjects will be given training at their local study site about 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 and the device will be fitted to the non-dominant arm of the subject, with the bladder placed over the artery and an initial test reading performed. The subjects will be advised that for the first reading the device will inflate to a pressure of 180 mm Hg, and 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 how to wear the device during the day and at night while sleeping, and what to expect in terms of frequency of readings during the day (every 15 minutes) and overnight (every 30 minutes). During ABPM, systolic BP, diastolic BP, pulse pressure, HR and mean arterial pressure readings will be recorded over a period of 24 hours.

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:

1. 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)
2. Subject enrollment is unsatisfactory
3. Non-compliance that might significantly jeopardize the validity or integrity of the study
4. Sponsor decision to terminate development
5. Sponsor decision 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 Institutional Review Board (IRB) / 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 IRBs/IECs when applicable) will be obtained prior to resuming the study.

4.5 Investigational Products

4.5.1 Identity of Investigational Product(s)

4.5.1.1 Identity of Investigational Product(s)

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

Table 4.5.1.1-1 Identification of Investigational Products

| Investigational Product | Manufacturer | Concentration and Formulation as Supplied |
|-------------------------|--------------|---|
| MEDI0382 | MedImmune | 2 mg/mL liquid formulation |
| Placebo | MedImmune | Solution |

Note: Diluent (solution manufactured by MedImmune) will be provided to sites for use in the event that a dose level requires dilution).

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

Investigational product will be supplied to the site as blinded kits each containing 1 vial. These kits will each contain a unique identifying number, which will appear on both the vial and kit label.

For in-clinic dosing: investigational product kits (ie, containing 1 vial) will be dispensed via the IXRS.

For Cohorts 4, 5 and 6 for the in-home dosing: investigational product will be provided to the subject in a container with sufficient vials that have 1.3 mL of liquid product in each. The kit must be stored in the original container in the refrigerator at all times and must not exceed 25°C. In addition, sufficient syringes, needles, wipes, gloves and one container for used equipment will also be provided.

In the event that a subject is deemed not competent to perform at home dosing, the investigational product kit will be stored by the site and utilized there for subject administration.

The unique identifying number on MEDI0382 and matching placebo vial and kit labels will be random, to maintain the blind of MEDI0382 and placebo investigational product.

4.5.1.2 Investigational Product Handling

In-clinic Investigational Product Handling

Investigational product should be stored at 2°C to 8°C in the original container.

Investigational products do not contain preservatives and any unused portion must be discarded. Preparation of syringes for dose administration is to be performed aseptically.

Total in-use storage time from needle puncture of the investigational product vial to start of administration should not exceed 4 hours at room temperature or 24 hours at 2°C to 8°C. If storage time exceeds these limits, a new dose must be prepared from new vials.

At-home Investigational Product Handling

The entire carton of investigational product should be stored in the refrigerator and must not exceed 25°C. Subjects should be asked to ensure they have a normal domestic refrigerator at home, which should be between 4°C and 8°C.

The subject is to remove from the refrigerator only the 1-vial kit required for their daily dose. All other kits are to be kept in the outer carton in the refrigerator until required. The subject is to make sure that the temperature does not exceed 25°C. The subject is to avoid the risk of freezing the investigational product by carefully placing the investigational product within their refrigerator, and is not to use investigational product if it has been frozen. The subject is not to administer investigational product if the time outside of the refrigerator has exceeded 1 day; if storage time exceeds this limit, a new dose must be prepared from a new vial. After use, the subject is to retain the vial during the at-home self-administration period for return to the site (along with any unused vials) for accountability at the weekly visit. Investigational product should be protected from heat and sunlight. The needle should always be removed and safely discarded after each use.

4.5.1.3 Investigational Product Inspection

Investigational Product Inspection

Each vial selected for dose preparation should be inspected. 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 for further instructions (Section 4.5.1.7).

4.5.1.4 Dose Preparation Steps

In-clinic Dose Preparation Steps

The final delivery volume and concentration for each dose level are described in [Table 4.5.1.4-1](#) and [Table 4.5.1.4-2](#).

Cohorts 1-3 Dose Preparation Steps

Table 4.5.1.4-1 Cohorts 1–3 MEDI0382 and Placebo Dose Preparation

| Dose Level | Formulation Stock Concentration (mg/mL) | Volume of Injection (mL) |
|-------------------|---|--------------------------|
| 100 µg or placebo | 0.2 | 0.5 |
| 150 µg or placebo | 0.2 | 0.75 |
| 200 µg or placebo | 0.2 | 1.0 |

Calculations for dose preparation for Cohorts 1-3 are as follows:

1. Investigational product is supplied in 3 mL glass vials at a nominal concentration of 2 mg/mL.
2. Determine from [Table 4.5.1.4-1](#) the correct dose level and injection volume.
3. For doses of 100, 150, and 200 µg, a 10-fold diluted stock concentration of 0.2 mg/mL will be prepared.
4. To make a 10-fold diluted MEDI0382, it is recommended to take 0.2 mL of MEDI0382 Drug Product using a needle and 1 mL syringe, add it into a sterile empty vial, followed by addition of 1.8 mL of diluent using a needle and 1 mL syringe into the same vial. The vial should be mixed by swirling gently to make a homogenous final admixture.

The volume to be delivered will be withdrawn using a 1 mL syringe, and then connected to a fresh 30G needle prior to administration.

No incompatibilities between MEDI0382 and plastics tested during the compatibility study (ie, polypropylene) syringe, or needle have been observed. (Syringe sizes, vial sizes and other consumables may be altered at the discretion of the sponsor, please refer to the investigational product manual).

Cohort 4 Dose Preparation Steps

Table 4.5.1.4-2 Cohort 4 MEDI0382 and Placebo Dose Preparation

| Dose Level | Formulation Stock Concentration (mg/mL) | Volume of Injection (mL)/ (U)* |
|-------------------------------------|---|-----------------------------------|
| Initial Dose; 100 µg or placebo | 2 | 0.05 (5) |
| Titration Dose 1; 150 µg or placebo | 2 | 0.075 (7.5) |
| Titration Dose 2; 200 µg or placebo | 2 | 0.1 (10) |

U = units

* The 0.3 mL syringe is marked in “units” where each unit = 0.01 mL, so 0.05 mL = 5 units; 0.075 mL = 7.5 units; 0.1 mL = 10 units.

Calculations for dose preparation for Cohort 4 are as follows:

- Investigational product is supplied in 3 mL glass vials at a nominal concentration of 2 mg/mL.
- Determine from [Table 4.5.1.4-2](#) the correct dose level and injection volume.

The volume to be delivered will be withdrawn using a 0.3 mL insulin syringe. Please note, dilution of investigational product will not be required for Cohort 4.

Please refer to subject at-home dosing instructions and investigational product manual for more information.

Cohort 5 Dose Preparation Steps

Table 4.5.1.4-3 Cohort 5 MEDI0382 and Placebo Dose Preparation

| Dose Level | Formulation Stock Concentration (mg/mL) | Volume of Injection (mL)/ (U)* |
|-------------------------------------|---|-----------------------------------|
| Initial Dose; 100 µg or placebo | 2 | 0.05 (5) |
| Titration Dose 1; 150 µg or placebo | 2 | 0.075 (7.5) |
| Titration Dose 2; 200 µg or placebo | 2 | 0.1 (10) |
| Titration Dose 3; 300 µg or placebo | 2 | 0.15 (15) |

U = units

* The 0.3 mL syringe is marked in “units” where each unit = 0.01 mL, so 0.05 mL = 5 units; 0.075 mL = 7.5 units; 0.1 mL = 10; 0.15 mL = 15 units.

Calculations for dose preparation for Cohort 5 are as follows:

- Investigational product is supplied in 3 mL glass vials at a nominal concentration of 2 mg/mL.
- Determine from [Table 4.5.1.4-3](#) the correct dose level and injection volume.

The volume to be delivered will be withdrawn using a 0.3 mL insulin syringe. **Please note, dilution of investigational product will not be required for Cohort 5.**

Please refer to subject at-home dosing instructions and investigational product manual for more information.

Cohort 6 Dose Preparation Steps

Table 4.5.1.4-4 Cohort 6 MEDI0382 and Placebo Dose Preparation

| Dose Level | Formulation Stock Concentration (mg/mL) | Volume of Injection (mL)/ (U)* |
|-------------------------------------|---|-----------------------------------|
| Initial Dose; 100 µg or placebo | 2 | 0.05 (5) |
| Titration Dose 2; 200 µg or placebo | 2 | 0.1 (10) |
| Titration Dose 3; 300 µg or placebo | 2 | 0.15 (15) |

U = units

* The 0.3 mL syringe is marked in “units” where each unit = 0.01 mL, so 0.05 mL = 5 units; 0.075 mL = 7.5 units; 0.1 mL = 10; 0.15 mL = 15 units.

Calculations for dose preparation for Cohort 6 are as follows:

- Investigational product is supplied in 3 mL glass vials at a nominal concentration of 2 mg/mL.
- Determine from [Table 4.5.1.4-4](#) the correct dose level and injection volume.

The volume to be delivered will be withdrawn using a 0.3 mL insulin syringe. **Please note, dilution of investigational product will not be required for Cohort 6.**

Please refer to subject at-home dosing instructions and investigational product manual for more information.

At-home Dose Preparation Steps

No dilution steps for preparation of investigational product will be performed by the subject at home. Specific dose preparation instructions will be provided to subjects on an instruction sheet (see Section 4.5.1.5).

4.5.1.5 Treatment Administration

If diluent is required: investigational product should be removed from the refrigerator for at least 30 minutes and a maximum of 2 hours for temperature equilibration. If no diluent is required, 15 minutes is recommended for temperature equilibration.

In-clinic Treatment Administration

The first day of dosing is considered Day 1. On the day of each dose, following an overnight fast for a minimum of 8 hours, investigational product will be administered as soon as is practicable after rising. For Cohorts 1-3, investigational product will be administered by SC injection in the lower abdomen utilizing a 1 mL syringe and a 30G needle. For Cohorts 4, 5, and 6 a 0.3 mL insulin syringe will be utilized during the in-clinic treatment period. Please refer to the investigational product manual.

At-home Treatment Administration

Each subject will be provided with an at-home dosing instructions sheet. The sheet will also include storage conditions and dose preparation information.

A once-daily dose is to be self-administered by SC injection as soon as practicable upon waking each morning prior to breakfast. Refer to Section 4.3.12.3 about training the subject for at-home self-administration. For Cohorts 4, 5, and 6 a 0.3 mL insulin syringe will be utilized during the at-home treatment period. Please refer to the investigational product manual.

The investigational product is packaged in a carton with sufficient vial kits. Each vial contains 1 mL of liquid product with adequate overfill. The carton must be stored in the refrigerator.

4.5.1.6 Monitoring of Dose Administration

Monitoring of In-clinic Dose Administration

As with any exogenous peptide delivered subcutaneously, allergic reactions to dose administration are possible. Therefore, appropriate drugs and medical equipment to treat acute anaphylactic reactions must be immediately available, and study personnel must be trained to recognize and treat anaphylaxis and in basic life support techniques and acute care for life-threatening emergencies. During the 24-hour post dosing period, vital signs will be periodically assessed (see Section 4.3.2.4), and the site of administration will be checked for signs of injection site reaction (see Section 4.3.2.2).

Monitoring of At-home Dose Administration

Subjects will be instructed on how and what to record daily for each dose self-administered in the Daily Diary (see Section 4.3.12.3).

4.5.1.7 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 labeled 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 should continue to take their metformin therapy at their regular dose prescribed, and any other medication prescribed for the treatment of comorbidities associated with T2DM. Subjects may also continue to take their regular prescribed daily dose of statin during the study. MedImmune will not provide metformin or statin.

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 fulfill GMP Annex 13 requirements for labeling. Label text will be translated into local languages, as required.

4.5.4 Storage

Store investigational product at the clinical site at 2°C to 8°C. Investigational product taken home by the subject must be stored in a refrigerator and must not exceed 25°C. Testing of the investigational product for photosafety is not applicable because the investigational product will not be topically or locally applied, nor does it partition into the skin. Furthermore, the investigational product is a peptide comprised of natural amino acids and thus is not expected to undergo photodegradation to form toxic metabolites.

4.5.5 Treatment Compliance

Investigational product will be administered by study site personnel, who will monitor compliance during the inpatient period. Compliance during the at-home dosing period for Cohorts 4, 5, and 6 will be monitored via Daily Diary entries, returned vials, and PK data.

4.5.6 Accountability

In-clinic Accountability

The investigator's or site's designated investigational product manager is required to maintain accurate investigational product accountability records. 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.

Accountability for Doses Administered by the Subject during the At-home Self-administration Period

Subjects will be instructed to return each used vial and any unused vials to the site along with the Daily Diaries containing dosing information when they return for their weekly visits.

4.6 Treatment Assignment and Blinding

4.6.1 Methods for Assigning Treatment Groups

An IXRS will be used for randomization to a treatment group and assignment of blinded 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 blinded investigational product kit number to the subject.

For Cohorts 1, 2, and 3, nine subjects in each cohort will be randomized in a 2:1 ratio to receive MEDI0382 or placebo. For Cohort 4, approximately 48 subjects will be randomized in a 1:1 ratio to receive MEDI0382 or placebo. For Cohorts 5 and 6, 16 subjects in each cohort will be randomized in a 3:1 ratio to receive MEDI0382 or placebo. The IXRS will assign a unique randomization code and treatment arm for the subject.

4.6.2 Methods for Ensuring Blinding

This is a double-blind study in which MEDI0382 and placebo are identically labeled and indistinguishable in appearance. As such, the pharmacist, the subject, and the investigator staff who are involved in the treatment or clinical evaluation of the subjects will NOT be aware of the treatment received (International Council for Harmonisation [ICH] E9). The sponsor will not be blinded to treatment allocation to allow for evaluation of data for dose escalation decisions (including safety, PK and PD data) and 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. The medical monitor from the CRO will remain blinded throughout the study, and will review blinded AEs and may be asked questions around clarification of the information by the site. In the event that 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*.

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.

4.7 Restrictions during the Study and Concomitant Treatment(s)

The investigator must be informed as soon as possible about any medication taken by the subject from the time of screening until the end of the clinical phase of the study (final 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 described in Section 4.7.2. Specifically, subjects should continue to take their metformin therapy at their regular dose prescribed, and any other medication prescribed for the treatment of comorbidities associated with T2DM. Subjects may also continue to take their regular prescribed dose of statin during the study. Statins are allowed in all cohorts. Subjects should receive full supportive care during the study in accordance with their institutional guidelines. In the event of nausea or vomiting subjects should be encouraged to reduce oral intake of food until symptoms pass. In the event that symptoms do not improve, subjects should be offered a centrally acting anti-emetic such as a 5HT-3 antagonist in the first instance, rather than a prokinetic agent such as domperidone or metoclopramide. Hormone replacement therapy and agents for benign prostatic hyperplasia are also permitted.

4.7.2 Prohibited Concomitant Medications

Other than the medications described above, use of the following medications are restricted, generally speaking, from the time specified in the entry criteria until after the final follow-up visit:

- Use of other concomitant medications, including over-the-counter medications, herbal supplements, multivitamins, and vitamins containing selenium, that are thought to play a role in control of body weight or appetite, is prohibited from 1 week prior to Day 1 until after the final follow-up visit. Subjects must be instructed not to take any medications, including over-the-counter products, without first consulting with the investigator.
- Use of any other GLP-1 agonist is prohibited.
- Systemic corticosteroids are prohibited within 28 days prior to screening and throughout the study, except if needed to treat a generalized allergic reaction or anaphylaxis as defined in [Appendix 3](#). (Inhaled, intranasal, topical, and intra-articular corticosteroids are permitted.) Systemic corticosteroid use should first be discussed with and permitted by the medical monitor.
- Use of DPPIV inhibitor, sulphonylurea, or SGLT2 inhibitor is prohibited during the study (see inclusion criterion [5b](#), [5c](#), and [5d](#) for explanation of washout period).
- Compounds known to prolong the QTc interval are prohibited. Refer to <https://www.crediblemeds.org/healthcare-providers/>.
- Use of antihypertensives, while strongly discouraged, is not strictly prohibited. Stable antihypertensive therapy (initiated 2 months before screening) is acceptable; however, antihypertensive therapy cannot be initiated during the screening period.

4.8 Statistical Evaluation

4.8.1 General Considerations

Data will be provided in listings and tabular summaries. Categorical data will be summarized by the number and percentage of subjects in each category. Continuous variables will be summarized by descriptive statistics, including mean, standard deviation, median, minimum, and maximum. Baseline values will be defined as the last assessment prior to the first administration of investigational product. Additional details will be described in the statistical analysis plan.

Analysis Populations

The Intent-to-treat (ITT) Population includes all subjects who are randomized and receive any investigation product analyzed according to the initial randomization.

The As-treated Population includes all subjects who received the actual investigational product. All subjects who received investigational product will be analyzed for safety.

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.

The PD Population includes all subjects who participated in at least 1 MMT (ie, gave at least 1 post-MMT PD blood sample).

4.8.2 Sample Size and Power Calculations

The sample size of 6 subjects in the MEDI0382 group and 3 subjects in the placebo group for Cohorts 1, 2, and 3 was empirically determined to obtain adequate safety and tolerability evaluation. Under a two-sided 10% significance level, a sample size of 44 evaluable subjects (22 per arm) for Cohort 4 will provide 80% power to detect weight loss of 1.5 kg versus placebo (assuming a standard deviation of 1.9 kg), and 98% power to detect a 20% relative reduction in MMT glucose AUC (up to 240 minutes post-MMT) versus placebo at the end of treatment (assuming a coefficient of variation [CV] of 17%). (Internal data from another investigational agent for T2DM showed a CV of 17% for 24-hour glucose AUC, and the CV for glucose AUC [up to 240 minutes post-MMT] is expected to be similar.) The sample size for Cohort 4 is adjusted to 48 subjects (24 per arm) to account for a 10% drop-out rate. For Cohorts 5 and 6, under a one-sided 2.5% significance level the combination of 24 subjects in the MEDI0382 and 8 subjects in placebo from both cohorts will provide 80% power to rule out more than 20% of MEDI0382 subjects having > 5 mm Hg increase from baseline in diastolic BP on the seventh day of the 300 µg dose level (Day 22 visit of Cohort 5 and Day 17 visit of Cohort 6) relative to that of placebo subjects under the assumption that both placebo and MEDI0382 subjects have a true rate of 1% with > 5 mm Hg increase from baseline in diastolic BP. Moreover, under a one-sided 2.5% significance level, this sample size will provide 88% power to rule out > 20 bpm pulse rate increase from baseline on the seventh day of the 300 µg dose level in MEDI0382 subjects relative to that of placebo subjects with assumed standard deviation of 15 bpm. The assumed standard deviation is a relatively conservative estimation based on a liraglutide publication ([Lovshin et al, 2015](#)).

4.8.3 Efficacy

4.8.3.1 Primary Efficacy Analysis

For evaluation of the impact on glucose control and weight after multiple doses of MEDI0382 compared to placebo:

The percent change in MMT glucose AUC (up to 240 minutes post-MMT) and change in weight from baseline to the end of treatment in Cohort 4 will be compared between MEDI0382 and placebo groups using an analysis of covariance by adjusting for baseline measurement and treatment group. A missing measurement at the end of treatment will be replaced with the last available measurement. The comparison will be conducted at a two-

sided significance level of 0.1. Those analyses will be conducted using the ITT Population in Cohort 4.

4.8.3.2 Secondary Efficacy Analysis

Change from baseline in HbA1c and fructosamine, and percent change from baseline (Day - 1) in 24-hour glucose AUC post-MMT through end of treatment in Cohort 4, and percent change in MMT glucose AUC (up to 240 minutes post-MMT), and change in weight from baseline through end of treatment in all cohorts will be analyzed similarly to the primary efficacy endpoints.

The 24-hour glucose AUC analyses will include glucose measures from the pre-/post-MMT glucose metabolism panel as well as serum chemistry glucose levels and PD glucose samples, where those results are from unique time points.

4.8.4 Safety

Safety analyses will be based on the As-treated Population. For each cohort, AEs including injection site reactions, clinical chemistry and hematology; and vital signs, ECGs, and ADAs (see Section 4.8.5) will be collected.

Adverse events will be coded using the most updated Medical Dictionary for Regulatory Activities (MedDRA) version. The type, incidence, severity and relationship to investigational product of each AE will be summarized by MedDRA System Organ Class and Preferred Term. Specific AEs will be counted once for each subject for calculating percentages. In addition, if the same AE occurs multiple times within a particular subject, the highest severity and level of relationship observed will be reported.

Electrocardiogram parameters will be assessed using telemetry and 12-lead electrocardiography, and the data will be descriptively summarized. Initial safety assessment will be based on paper ECG copies at the site.

HR and BP during the at-home self-administration period for Cohorts 4, 5, and 6, as measured by the ABPM, will be summarized and listed separately from vital signs data. In addition, HR and diastolic BP in Cohorts 5 and 6 will be compared between MEDI0382 and placebo groups using an analysis of covariance by adjusting for baseline measurement.

Descriptive statistics for the C-SSRS score will be generated at time points specified in the schedules of procedures for Cohort 4.

Other safety endpoints will be summarized descriptively and/or listed as appropriate.

4.8.5 Pharmacokinetics/Immunogenicity

Pharmacokinetic parameters such as C_{max} , T_{max} , AUC, elimination half-life, and accumulation ratio will be estimated from plasma concentration-time data for MEDI0382 if data permit. Descriptive statistics will be generated for PK parameters for the MEDI0382 group in each cohort. Subjects who have at least one measurable concentration time point of investigational product will be used for this analysis.

With respect to metformin PK, changes in metformin levels over time will be evaluated, as will any association between baseline metformin dose and change in metformin levels over time in the clinical study. In the event that a reduction in metformin levels is seen in Cohorts 1-3, an exploratory analysis will be performed to examine the relationship between changes in metformin level and glucose control over time.

The incidence and impact of ADA to MEDI0382 will be evaluated. The number and percentage of subjects with confirmed positive serum antibodies to MEDI0382 will be reported by cohort. If warranted by the data, the association of ADA positivity with observed PK data and safety may be explored.

Data on titers and cross reactivity to GLP-1 and glucagon (if applicable) will be listed.

4.8.6 Pharmacodynamics Analyses

Similar analysis will be used for comparing change in beta cell function and insulin sensitivity between MEDI0382 and placebo. Beta cell function will be derived using the Homeostasis Model Assessment (HOMA) calculation from fasting glucose and insulin data, and insulin sensitivity will be derived from MMT data using the HOMA-2 IR algorithm and the modified Matsuda index calculation.

The level of glucose, insulin, pro-insulin, c-peptide, GLP-1, glucagon, and GIP from immediately prior to the MMT to 240 minutes and (for glucose only) 24 hours after the MMT will be collected. Descriptive statistics including mean, standard deviation, median, minimum and maximum will be generated for these variables for MEDI0382 in each cohort separately and the placebo group, which includes all subjects in the placebo group across cohorts.

4.8.7 Subject Diaries and Glucometer Blood Glucose (Cohorts 4, 5, and 6)

Data from Daily Diaries of subjects in Cohorts 4, 5, and 6, as well as blood glucose measurements taken by the subject at home with the glucometer during the at-home self-administration period, will be summarized and/or listed as appropriate.

4.8.8 Exploratory Analyses

[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED] Change from baseline to Week 4 in liver fat (%), liver volume (L), visceral adipose tissue (L), subcutaneous adipose tissue (L), liver diffusion, sagittal diameter (image based), and transversal diameter (image based), as determined by MRI, will be summarized descriptively.

4.8.9 Dose Escalation Committee

A DEC will be formed for the purpose of data review and safety monitoring, and for decisions on cohort progression as outlined in the DEC Charter.

The unblinded members of the DEC are the MedImmune medical monitor, sponsor patient safety study representative, and the MedImmune PK study representative. The coordinating investigator will remain blinded. The committee will meet at the earliest practicable time point following availability of PK, safety, and MMT glucose data from each completed cohort to determine if dose escalation can proceed. The rules for dose escalation are discussed in Section 3.1.3.

For each dose escalation decision, blinded safety data and summary-level (ie, blinded) PK and PD data will be reviewed at the first session of the DEC meeting. If a safety signal is detected from blinded data review, or if the PK or PD profile warrants evaluation of subject-level data, then the MedImmune DEC members will review the unblinded safety data and/or unblinded PK/PD data in a second separate meeting session. If review of unblinded data is not necessary, the second session of the DEC meeting will not occur.

As sponsor of this study, MedImmune will be unblinded to treatment allocation. Appropriate measures will be in place to ensure that the coordinating investigator remains blinded to study treatment during this process (eg, separate dial-in numbers for the meeting sessions, distribution of unblinded data to MedImmune DEC members only after a determination that it is needed).

4.8.10 Interim Analysis

An interim analysis of the safety and PD data will be conducted after the last subject of Cohort 4 has completed dosing. PK data will be analyzed if available at the time of analysis.

5 ASSESSMENT OF SAFETY

5.1 Definition of Adverse Events

The ICH Guideline for Good Clinical Practice 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-treatment-emergent AE 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 pre-existing 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 AESI is one of scientific and medical interest specific to understanding of the investigational product and may require close monitoring and collecting additional information by the investigator. 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.

Please refer to the Investigator's Brochure for a discussion of potential risks. The following AESIs have been identified specifically for this protocol and are to be reported as described in Section 5.4 and Section 5.5:

- Any arrhythmia deemed by the investigator to be clinically significant
- Any vomiting

Risk mitigation strategies for arrhythmias are built into the study design, ie, extensive time points for manual collection of vital signs, ECGs, as well as continuous telemetry during the inpatient period, and 24-hour ABPM (Cohorts 4, 5, and 6) during the at-home self-administration period. Subjects with significant vomiting should be monitored for electrolytes.

See Section 3.1.4 for a discussion of GI tolerability and other mitigating strategies, eg, potential adjustments to planned dose escalations.

Hepatic function abnormality meeting the definition of Hy's law is also considered an AESI. See Section 5.6.2 for the definition and reporting of AESIs of hepatic function abnormality.

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. Adverse events 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 (see Section 5.5). See Section 5.2 for the definition of SAEs. See [Appendix 2](#) for guidelines for assessment of severity (grade) and relationship. If an AE evolves into a condition that meets the regulatory definition of “serious,” it will be reported on the SAE Report Form.

Subcutaneous injection of biological products is commonly associated with injection site reactions. The investigator is advised to carefully examine symptoms of adverse reactions observed during or shortly after exposure to MEDI0382. Reactions occurring at the time of or shortly after subsequent injections of investigational product are to be judged by the investigator at his/her own discretion. For the investigator’s convenience and in order to facilitate consistency in judgments a copy of the National Institute of Allergy and Infectious Diseases and Food Allergy and Anaphylaxis Network guidance for anaphylaxis diagnosis is provided in [Appendix 3](#).

5.4.1 Time Period for Collection of Adverse Events

Adverse events will be collected from time of signature of informed consent throughout the treatment period and including the follow-up period (28 [\pm 2] days after the last study dose for each cohort).

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.

5.5 Reporting of Serious Adverse Events

All SAEs have to be reported, whether or not considered causally related to the investigational product, or to the study procedure(s). All SAEs will be recorded in the eCRF.

If any SAE occurs during the course of the study, the investigator or other site personnel will inform the appropriate sponsor representative(s) within one 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 the necessary information is provided to the sponsor 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 or she becomes aware of it.

Once the investigator or other site personnel indicate an AE is serious in the electronic data capture (EDC) system, an automated email alert is sent to inform 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 is defined as a subject receiving a dose of investigational product in excess of that specified in the Investigator's Brochure, unless otherwise specified in this protocol.

- 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, or 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 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 $\geq 3 \times \text{ULN}$ together with total bilirubin $\geq 2 \times \text{ULN}$ may need to be reported as SAEs. Please refer to [Appendix 6](#) 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 are not allowed to be included in this study. Should a pregnancy still occur, the investigational product should be discontinued immediately and the pregnancy reported to the sponsor.

5.6.3.2 Paternal Exposure

Should the investigator become aware of a pregnancy in the partner of a male study subject who has received investigational product, then the investigator or other site personnel will inform 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 to the sponsor's patient safety data entry site within 1 or 5 calendar days for SAEs (see Section [5.5](#)) and within 30 days for all other pregnancies. The same timelines apply when the outcome information is available.

The pregnancy reporting module in the eCRF is used to report the pregnancy and the pregnancy outcome module is used to report the outcome of the pregnancy.

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 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:

- 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 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 clinical study protocol and the Clinical Study Agreement, the terms of clinical study protocol shall prevail with respect to the conduct of the study and the treatment of subjects, and in all other respects, 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/assessment, 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 (Section 4.1.5) or the subject was lost to follow-up.

The end of the study (“study completion”) is defined as the date of the last protocol-specified visit/assessment for the last subject in the study.

6.4 Data Management

MedImmune Data Management will be accountable for the data management of this study according to the Data Management Plan.

An electronic-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 of 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 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 clinical study protocol, 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/Good Clinical Practice, and applicable regulatory requirements.

7.2 Subject Data Protection

The ICF will incorporate (or, in some cases, be accompanied by a separate document incorporating) wording that complies with relevant data protection and privacy legislation.

Subjects have the option of providing samples for future genetic research and/or future non-genetic research (refer also to Section 7.4). MedImmune will not provide individual genotype results to subjects, any insurance company, any employer, their family members, general physician or any other third party, unless required to do so by law.

Extra precautions are taken to preserve confidentiality and prevent genetic data being linked to the identity of the subject. In exceptional circumstances, however, certain individuals might see both the genetic data and the personal identifiers of a subject. For example, in the case of a medical emergency, a MedImmune medical monitor or an investigator might know a subject's identity and also have access to his or her genetic data. Also regulatory authorities may require access to the relevant files, though the subject's medical information and the genetic files would remain physically separate.

7.3 Ethics and Regulatory Review

An IRB/IEC should approve the final study protocol, including the final version of the ICF and any other written information and/or materials to be provided to the subjects. The investigator will ensure the distribution of these documents to the applicable IRB/IEC, and to the study site staff.

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

The IRB/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 re-approved by the IRB/IEC annually.

Before enrolment of any subject into the study, the final study protocol is approved by the national regulatory authority or a notification to the national regulatory authority is done, according to local regulations. The ICFs will be approved by the IRB/IEC.

MedImmune will handle the distribution of any of these documents to the national regulatory authorities.

MedImmune will provide regulatory authorities, IRB/IEC and principal investigators with safety updates/reports according to local requirements, including suspected unexpected serious adverse reactions, where relevant.

7.4 Informed Consent

There will be 3 ICFs for this study: a mandatory general ICF, an optional ICF for samples for future genetic research, and an optional ICF for samples for future non-genetic research. 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 that each subject is given the opportunity to ask questions and allowed time to consider the information provided
- Ensure each subject provides signed and dated informed consent before conducting any procedure specifically for the study
- Ensure the original, signed Informed Consent Form(s) is/are stored in the investigator's Study File
- Ensure a copy of the signed ICF(s) is/are 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 informed consent form that is approved by an IRB/IEC

If subjects consent, optional blood samples for future genetic research or future non-genetic research (2 additional separate consent forms) will be collected and may be used to study disorders of metabolism or related complications. Provision of consent to provide blood

samples for future genetic or future non-genetic research is not a requirement to participate in the study.

7.5 Changes to the Protocol and Informed Consent Form

Study procedures will not be changed without the mutual agreement of the coordinating 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 where required in a new version of the study protocol.

The amendment is to be approved by the relevant IRB/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 IRB/IEC see Section 7.3.

If a protocol amendment requires a change to a site's Informed Consent Form, MedImmune and the site's IRB/IEC are to approve the revised Informed Consent Form before the revised form is used.

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

7.6 Audits and Inspections

Authorized representatives of MedImmune, a regulatory authority, or an IRB/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 data were recorded, analyzed, and accurately reported according to the protocol, Good Clinical Practice, guidelines of ICH, and any applicable regulatory requirements. The investigator will contact MedImmune immediately if contacted by a regulatory agency about an inspection at the site.

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9 CHANGES TO THE PROTOCOL


All changes described below have been incorporated into the current version of the protocol

9.1 Amendment 8, 23Sep2016

This amendment has been implemented in order to add Part C to the study, including the addition of 2 cohorts (Cohorts 5 and 6) to assess the safety and tolerability of the MEDI0382 300 µg dose and to explore the optimal up-titration. Text revisions resulting from this amendment are incorporated in the body of Protocol Amendment 8. Changes to the protocol are summarized below:

1. Protocol Synopsis (Study Design and Investigational Product, Dosage, and Mode of Administration), Section 3.1.1 (Overview), Section 3.1.2 (Treatment Regimen): Text was added to include Part C of the study and to describe the details of Cohorts 5 and 6 in terms of number of subjects, treatment duration and dosages, and up-titration schedule. The study schematic (Figure 3.1.1-1) was updated to include Part C.
2. Section 1.5 (Rationale for Conducting the Study), [REDACTED]
3. Protocol Synopsis (Study Endpoints), Section 2.2.2 (Secondary Endpoints), Section 3.1.1 (Overview), Section 4.3.7 (Pharmacodynamic Evaluation and Methods), Section 4.3.11.1 (Columbia-Suicide Severity Rating Scale): Text was added to specify that the C-SSRS score is an endpoint for Cohorts 5 and 6, in addition to Cohort 4; PD endpoints for Cohorts 5 and 6 are insulin and glucose only; terminal half-life and accumulation ratio are PK endpoints for Cohorts 1 to 3 only.
4. Protocol Synopsis (Study Endpoints), Section 2.2.2 (Secondary Endpoints: “Percent change from baseline in MMT glucose AUC (up to 240 minutes post-MMT) to end of

treatment” and “Change from baseline in body weight in kg to end of treatment” added as secondary endpoints.

5. 
6. Protocol Synopsis (Study Design), Section 3.1.1 (Overview), Section 4.1.1 (Number of Subjects): Number of subjects is increased from 75 to 107 because of the addition of 32 subjects in Part C.
7. Protocol Synopsis (Study Design), Section 3.1.1 (Overview): Text was added to describe the inpatient periods and clinic visits for Cohorts 5 and 6 – subjects will have an initial inpatient period ending on Day 3 followed by at-home self-administration of investigational product with a clinic visit at each dose up-titration step until initiation of the 300 µg dose. Subjects will have a second inpatient period for the initiation of the 300 µg dose ending on the fourth day at that dose followed by another inpatient period on the last day of dosing to collect the final endpoints, with at-home self-administration of investigational product in between.
8. Protocol Synopsis (Study Design) and Section 3.1.1 (Overview): Text was added concerning the timing of the MMT procedures for Cohorts 5 and 6 - at baseline (Day -1) and at the start (Day 16 for Cohort 5 and Day 11 for Cohort 6) and end (Day 22 for Cohort 5 and Day 17 for Cohort 6) of the 300 µg dosing schedule.
9. Protocol Synopsis (Study Design), Section 3.1.1 (Overview): Text was added to make clear that, for Cohorts 4, 5, and 6, the last PK sample will be collected 24 hours after the last dose.
10. Protocol Synopsis (Statistical Analysis Plan) and Section 4.8.2 (Sample Size and Power Calculations): Text was added to provide details of the sample size calculation resulting in 32 subjects in total in Cohorts 5 and 6.
11. Protocol Synopsis (Statistical Analysis Plan): ‘Cohort 4’ was removed from the description of the analysis of efficacy endpoints because, with the addition of 2 secondary endpoints, the analysis no longer applies to Cohort 4 only.
12. Section 3.1.1 (Overview), Section 4.2.1 (Enrollment/Screening Period), Section 5.3 (Definition of Adverse Events of Special Interest): Text was added to specify 24-hour ABPM is applicable to Cohorts 5 and 6, in addition to Cohort 4.
13. Section 3.1.1 (Overview): Text was added to add Cohorts 5 and 6 to the measuring of body weight during the outpatient periods, and at the 28-day End of Study Visit.
14. Section 3.1.3 (Cohort Progression), Section 4.6.1 (Methods for Assigning Treatment Groups): Text was amended to clarify that the randomization ratio is 3:1 (active: placebo) for Cohorts 5 and 6, while remaining unchanged at 2:1 for Cohorts 1 to 3 and at 1:1 for Cohort 4.
15. Section 3.1.1 (Cohort Progression): Text was added to describe the sentinel dosing approach for Cohorts 5 and 6 that will review 3 subjects in each cohort with 7 days of dosing at the 300 µg dose before additional subjects are dosed at this level, and that the cohorts will run concurrently.

16. Section 3.1.3.2 (Cardiac Stopping Criteria): Text was added to the definition of hypertension for safety purposes - "or an increase in resting supine diastolic BP > 20 mm Hg or above 100 mm Hg and persisting for at least 10 minutes".
17. Section 3.1.4 (Management of Toxicities and Dose Modification): Text was added to include the 5-day up-titration periods for Cohorts 5 and 6, 1 day longer than the up-titration periods in Cohorts 2 to 4. In the event of unacceptable nausea and vomiting in 3 or more subjects, a provision was added to switch remaining Cohort 6 subjects to Cohort 5 up-titration schedule after discussion with the medical monitor.
18. Section 4.1.2 (Inclusion Criteria): Criteria 7, ability to self-administer daily SC injections, was made applicable to Cohorts 5 and 6, in addition to Cohort 4. Normal saline will be an alternative to placebo for the self-injection during the screening period for Cohorts 5 and 6.
19. Section 4.1.3 (Exclusion Criteria): Criteria 15b text was added to remove the systolic BP criteria for subjects aged 60 and over, and to use systolic BP < 90 mm Hg or ≥ 140 mm Hg for all subjects in Cohorts 5 and 6.
20. Section 4.1.3 (Exclusion Criteria): Criteria 22b was added for Cohorts 5 and 6, to additionally exclude subjects with a history of transient ischemic attack within the previous 12 months.
21. Section 4.1.6 (Discontinuation of Investigational Product): Criteria 7 was added for safety purposes, because a higher dose of MEDI0382 will be used in Cohorts 5 and 6 - "Subject develops a resting supine systolic BP of ≥ 180 mm Hg or a resting supine diastolic BP of ≥ 100 mm Hg sustained for more than 10 minutes, or a sustained resting tachycardia which is symptomatic and requires urgent medical intervention".
22. Section 4.2.1 (Enrollment/Screening Period): A row was added to Table 4.2.1-1 to check ability to self-administer investigational product for Cohorts 4, 5, and 6.
23. Section 4.2.2 (Randomized Treatment Period): In Table 4.2.2-4 (Cohort 4) the C-SSRS assessment on Day 41 was removed because it was not needed. It is being done already on the evening of Day 40. There was also a footnote change to remove the 24-hour ECG reading on Day 12, because it is already being done on Day 13.
24. Section 4.2.2 (Randomized Treatment Period): In Table 4.2.2-5 (Cohort 4) the 24-hour ABPM assessment on Day 40 was moved from 'Home' to 'Clinic'.
25. Section 4.2.2 (Randomized Treatment Period): Table 4.2.2-6, Schedule of Treatment Period Procedures for Cohort 5, and Table 4.2.2-7, Schedule of Treatment Period Procedures for Cohort 6, were added to provide full details of the assessments for these new cohorts.
26. Section 4.2.3 (Follow-up Period): Table 4.2.3-1 title changed from 'Cohorts 1 through 4' to 'All Cohorts', to add Cohorts 5 and 6.
27. Section 4.2.4 (Early Discontinuation or Unscheduled Study Visit): Pregnancy test made applicable to Cohorts 5 and 6, in addition to Cohort 4. Also, C-SSRS made applicable to Cohorts 5 and 6 as well as Cohort 4.
28. Section 4.3.2.4 (Vital Signs): Ambulatory BP and HR monitoring during the outpatient periods made applicable to Cohorts 5 and 6, in addition to Cohort 4.
29. Section 4.3.3 (Clinical Laboratory Tests): Urine drug and alcohol screen prior to initiation of the 300 μ g dose for Cohorts 5 and 6 added to the urinalysis tests. Magnesium

was added to the serum chemistry panel because vomiting may lead to electrolyte disturbances, including hypomagnesemia, which may predispose to cardiac arrhythmia. If hypomagnesemia were to arise it should be treated and, in the unlikely event of an arrhythmia or ECG changes occurring, it would be important to know the serum levels of magnesium for root cause analysis of the event.

30. Synopsis (Study Endpoints), Section 4.3.3 (Clinical Laboratory Tests), Section 4.3.10.4 (Fasting Lipid Profile), Section 4.3.10.5 (Non-alcoholic Steatohepatitis Biomarkers): Text was added to make clear that fructosamine, [REDACTED] [REDACTED] s are applicable to Cohorts 5 and 6 in addition to Cohort 4. To provide more flexibility, beta-hydroxybutyrate may be done by point-of-care capillary blood ketone testing as per local procedures.
31. [REDACTED]
32. Section 4.3.3 (Clinical Laboratory Test) and 4.3.7 (Pharmacodynamic Evaluation and Methods); Text was added to make clear that only timed glucose and insulin are included in the glucose metabolism panel for MMT for Cohorts 5 and 6.
33. Section 4.3.4 (Estimate of Volume of Blood to be Collected): Blood collection volumes were added for Cohorts 5 and 6.
34. Section 4.3.8 (Combined PK and PD Blood Sampling Example Schedule): Day 22 (Cohort 5) and Day 17 (Cohort 6) added to the title of Table 4.3.8-1.
35. Section 4.3.12.1 (Training for Self-Administration and At-Home Preparation of Investigational Product): Text was added to make sure that subjects in Cohorts 5 and 6 are given training to self-administer the investigational product.
36. Section 4.3.12.2 (Training during the Inpatient Period for Using the Standardized Glucometers during the Inpatient and Outpatient Periods): Text was added to make blood glucose measurements every bedtime for Cohorts 5 and 6.
37. Section 4.3.12.3 (Training for Completing the Daily Diaries during the At-home Self-administration Period): Text was added to include a Daily Diary for Cohorts 5 and 6.
38. Section 4.3.12.4 (Training for Application and Wearing of ABPM Device): This section has been added to make sure that subjects in Cohorts 5 and 6 are given training with the ABPM device.
39. Section 4.5.1.1 (Identity of Investigational Products): Text was revised to reflect the addition of Cohorts 5 and 6.
40. Section 4.5.1.2 (Investigational Product Handling): Text was added to instruct the subject to use their refrigerator, which should be between 4°C and 8°C, and to avoid the risk of freezing the investigational product by careful placement within their refrigerator. The requirement for the subject to record storage temperatures in the Daily Diary was removed.
41. Section 4.5.1.4 (Dose Preparation Steps), Section 4.5.1.5 (Treatment Administration): Table 4.5.1.4-3 and text were added to describe Cohort 5 MEDI0382 and placebo dose preparation. Similarly, Table 4.5.1.4-4 and text were added to describe Cohort 6 MEDI0382 and placebo dose preparation.
42. Section 4.5.1.5 (Treatment Administration): Text was added to recommend 15 minutes for temperature equilibration if no diluent is used. Cohorts 5 and 6 were added.

43. Section 4.5.5 (Treatment Compliance): Text was added to include Cohorts 5 and 6 in the monitoring of at-home doses via Daily Diaries, returned vials, and PK data.
44. Section 4.6.1 (Methods for Assigning Treatment Groups): Cohorts 5 and 6 were added to provide number of subjects and randomization ratio.
45. Section 4.8.3.1 (Primary Efficacy Analysis): 'Day -1' removed as the definition of baseline for change in weight.
46. Section 4.8.3.1 (Secondary Efficacy Analysis): 'Day-2' removed as the definition of baseline and 'percent change in MMT glucose AUC (up to 240 minutes post-MMT) and change in weight from baseline through end of treatment in all cohorts' was added to state the analysis for these new secondary endpoints.
47. Section 4.8.4 (Safety): Analysis of ABPM measures of HR and BP for Cohorts 5 and 6 added.
48. Section 4.8.7 (Subject Diaries and Glucometer Blood Glucose) and Section 4.8.8 (Exploratory Analyses): Text added to include Cohorts 5 and 6 in addition to Cohort 4.
49. Section 4.8.10 (Interim Analysis): Text was added to include an interim analysis after the last subject in Cohort 4 has completed dosing.
50. Section 8 (References): Details of Davies et al 2015 were added.

9.2 Amendment 7, 25Aug2016

This amendment has been implemented in response to requests made from the Bundesinstitut fuer Arzneimittel und Medizinprodukte (BfArM; received 24Aug2016). Revisions have been made to two sections of the protocol, as outlined below:

1. Section 4.1.4 (Subject Enrollment and Randomization): Text was reverted to specify that subjects may be rescreened only once.
2. Section 4.1.7 (Replacement of Subjects): Text was reverted to state that additional subjects may be screened and available to ensure that a sufficient number of subjects are randomized into each cohort.

9.3 Amendment 6, 21Jul2016

Text revisions resulting from this amendment are incorporated in the body of Protocol Amendment 6. Major changes to the protocol are summarized below:

1. Protocol Synopsis (Study Endpoints), Section 2.2.3 (Exploratory Endpoints) and Section 4.3.3 (Clinical Laboratory Tests): [REDACTED]
[REDACTED] Relevant text was revised to reflect this.
2. Protocol Synopsis (Study Design), Section 3.1.1 (Overview): The text was changed from "approximately 10 study sites" to "approximately 12 study sites" to reflect current projections. Text was changed from "48 subjects" to "approximately 48 subjects".

3. Protocol Synopsis (Study Design), Section 3.1.1 (Overview), Figure 3.1.1-1 (Study Flow Diagram), Section 3.1.2 (Treatment Regimen), [REDACTED], [REDACTED], Section 4.5.4 (Dose Preparation Steps), Table 4.5.1.4-1 (Cohort 1-3 MEDI0382 and Placebo Dose Preparation): Text was revised to clarify that 200 µg MEDI0382 is the maximum dose in the study. The study flow diagram and tables were updated to align with this.
4. Protocol Synopsis (Study Design), Section 3.1.1 (Overview) and Table 4.2.2-4 (Schedule of Treatment Period Procedures: Cohort 4 Overview): Text was revised to widen the window for predose MRI scan from Day -2 or Day -1 to anytime between Day -7 to Day -1 to provide greater flexibility for subject scheduling. Table footnote text was updated for consistency and to clarify that the predose MRI may require a separate visit, at the subject's discretion, if not carried out on Day -2 or Day -1.
5. Protocol Synopsis (Study Design), Section 3.1.1 (Overview), Table 4.2.2-4 (Schedule of Treatment Period Procedures: Cohort 4 Overview) and Section 4.3.5 (Glucometer Blood Glucose Readings during the Inpatient Period): Text was revised and table footnote text was updated to clarify that PD glucose will be taken at specified timepoints ± 10 minutes during Day -1 and the in-clinic dosing period to provide greater flexibility for procedure scheduling.
6. Protocol Synopsis (Study Design), Section 2.2.3 (Exploratory Endpoints), Table 4.2.2-4 (Schedule of Treatment Period Procedures: Cohort 4 Overview), Table 4.2.2-5 (Schedule of Treatment Period Procedures: Cohort 4 Self-administration Dosing Period Detail) and Section 4.3.10.6 (Magnetic Resonance Imaging of the Liver/Abdomen [Cohort 4]): Text was updated to clarify that MRI scans will occur only if MRI is available to the site and the subject is suitable for and consents to scan. Text in Section 4.3.10.6 was revised to clarify that subject suitability to be scanned will be determined against local criteria at the scanning site.
7. Protocol Synopsis (Study Design), Section 3.1.1 (Overview), Table 4.2.2-4 (Schedule of Treatment Period Procedures: Cohort 4 Overview) and Table 4.2.2-5 (Schedule of Treatment Period Procedures: Cohort 4 Self-administration Dosing Period Detail): Text was updated to clarify that postdose MRI scan may be done on Day 39, 40, 41, or 42 and tables were updated to correct a previous oversight. The text "as determined by site feasibility" was removed.
8. [REDACTED]
9. Section 4.1.3 (Exclusion Criteria): Criterion 11 was updated to clarify glomerular filtration rate should be estimated according to Modification in Renal Disease using MDRD Study Equation IDMS-traceable (SI units). Criterion 35 was revised to remove the text "Cohort 4 only if the site has access to MRI" to correct a previous oversight. Criterion 36 was removed as subject suitability for MRI will be determined against local criteria at the scanning site (Section 4.3.10.6).
10. Section 4.1.4 (Subject Enrollment and Randomization): Text was revised to clarify that subjects may be rescreened more than once based on principal investigator judgment to aid recruitment.

11. Section 4.1.7 (Replacement of Subjects) and Section 4.6.1 (Methods for Assigning Treatment Groups): Text was revised to clarify that additional subjects can be screened and randomized to ensure that a sufficient number of subjects complete each cohort. Relevant text was changed from “48 subjects will be randomized” to “approximately 48 subjects will be randomized” to align with this.

13. Table 4.2.2-4 (Schedule of Treatment Period Procedures: Cohort 4 Overview), Table 4.2.2-5 (Schedule of Treatment Period Procedures: Cohort 4 Self-administration Dosing Period Detail): Tables were updated to correct an oversight in Columbia-Suicide Severity Rating Scale scheduling and to include a pregnancy test (if applicable) at clinic visits 8, 9, 10, and 11. Footnote text was revised to change P/MSS completion from “within 30 minutes” of specified time to “within 30 minutes (+10 minutes)” of specified time to provide greater flexibility for procedure scheduling. Footnote text was updated to specify that blood samples for the serum chemistry panel should be taken following a minimum of 8 hours fasting on Day 1 (V4.1), Day 6 (V5.2), Day 13 (V7), Day 20 (V8), Day 27 (V9), Day 34 (V10) and Day 42 (V13) to allow for analysis of fasting plasma glucose.
14. Table 4.2.2-5 (Schedule of Treatment Period Procedures: Cohort 4 Self-administration Dosing Period Detail): Footnote text was updated to clarify when subjects will be fitted with the ambulatory blood pressure monitoring device, the duration of monitoring and when the device will be removed. The timeframe for subjects to return the device to the clinic was removed to provide greater flexibility for procedure scheduling.
15. Table 4.2.3-1 (Schedule of Follow-up Procedures: Cohorts 1 through 4) and Section 4.2.4 (Early Discontinuation for Unscheduled Visit): Table was revised to include a pregnancy test (if applicable) during the follow-up period and text was revised to add a pregnancy test to the list of assessments performed for subjects who prematurely discontinue from the study or for subjects who require an unscheduled study visit to correct a previous oversight.
16. Section 4.3.3 (Clinical Laboratory Tests): Serum chemistries panel note was updated to clarify that bicarbonate may be measured via serum chemistry sample of blood gas analyzer per local procedures.
17. Section 4.3.4 (Estimate of Volume of Blood to Be Collected): The estimated blood sample volume for Cohort 4 was increased to 553 mL to reflect the addition of CK18, P1NP and ProC3 as serum markers of oxidative stress and liver fibrosis.
18. Section 4.3.11.1 (Columbia-Suicide Severity Rating Scale [Cohort 4]): Text was revised to clarify that site staff will complete the assessment with the subject in a private, quiet place.
19. Section 4.3.12.3 (Training for Completing the Daily Diaries during the At-home Self-administration Period): Text was updated to be consistent with device instructions and to clarify that subjects will be instructed to contact the site in the event of new medications, a change in medications or if they experience any symptoms.
20. Section 4.5.1.4 (Dose Preparation Steps), Table 4.5.1.4-1 (Cohort 1 – 3 MEDI0382 and Placebo Dose Preparation) and Table 4.5.1.4-2 (Cohort 4 MEDI0382 and Placebo Dose

Preparation): Text was updated to provide instructions for Cohort 4. Tables were updated/inserted to clarify the dose preparation for Cohorts 1-3 and Cohort 4.

21. Section 4.5.1.5 (Treatment Administration): Text was updated to clarify that diluent is not required for Cohort 4 and that a 0.3 mL insulin syringe will be utilized during the in-clinic and at-home treatment periods.

9.4 Amendment 5, 27Apr2016

This amendment has been implemented in response to requests made from the Bundesinstitut fuer Arzneimittel und Medizinprodukte (BfArM; received 13Apr2016). Revisions have been made to several sections of the protocol, as outlined below:

1. Protocol Synopsis (Study Design), Section 3.1.1 (Overview): The text was changed from “up to 10 study sites” to “approximately 10 study sites” to reflect current projections.
2. Protocol Synopsis (Study Design), Section 3.1.1 (Overview), Section 4.3.2.3 (Electrocardiograms), Section 4.3.2.3 (Telemetry), Table 4.2.2-3 (Schedule of Treatment Period Procedures: Cohort 3), Table 4.2.2-4 (Schedule of Treatment Period Procedures: Cohort 4 Overview): The study design was reverted to state that subjects will be admitted to and remain in the unit for all doses and all dose levels during the up-titration period as requested by the BfArM. Relevant text in Section 4.3.2.3, the telemetry footnote in Table 4.2.2-3 (Schedule of Treatment Period Procedures: Cohort 3) and Table 4.2.2-4 (Schedule of Treatment Period Procedures: Cohort 4 Overview) was modified to reflect the reversion in study design.
3. Protocol Synopsis (Target Subject Population), Section 3.2.2 (Rationale for Study Population), Section 4.1 (Subjects), Section 4.1.2 (Inclusion Criteria): The age range for inclusion in the study was changed from 18 through ≤ 69 years to 18 through ≤ 65 years, as requested by the BfArM, and relevant text was modified to reflect this change.
4. Section 3.2.2 (Rationale for Study Population), Section 4.1.2 (Inclusion Criteria): The upper range of screening HbA1c was changed from 9.0% to 8.5%, as requested by the BfArM.
5. Section 4.1.3 (Exclusion Criteria): The exclusion criterion of “fasting blood glucose ≥ 200 mg/dL (11.11 mmol/L)” was reinstated as requested by the BfArM.
6. Section 4.1.3 (Exclusion Criteria): The upper range of abnormal systolic BP was decreased by 10 mm Hg for both age groups (< 60 years old, ≥ 60 years old), and the upper range of abnormal diastolic BP was decreased by 10 mm Hg as requested by the BfArM.

9.5 Amendment 4, 18Mar2016

Text revisions resulting from this amendment are incorporated in the body of Protocol Amendment 4. Major changes to the protocol are summarized below.

1. [REDACTED], Section 1.5 (Rationale for Conducting the Study), [REDACTED], and Section 3.2.3 (Rationale for Endpoints): [REDACTED]
[REDACTED] In Section 3.2.1, under “Starting Dose and Criteria for Dose Escalation”, the median of $AUC_{(0-inf)}$ was updated from “152.2 ng•hr/mL” to “155.9 ng•hr/mL” and the range of half-life (hours) was updated from “(10.1-13.2)” to “(10.1-18.3)”. [REDACTED]
[REDACTED]
2. Protocol Synopsis (Objectives; Target Subject Population), Section 2.1.3 (Exploratory Objectives), Section 3.2.3 (Rationale for Endpoints), Section 4.1.2 (Inclusion Criteria), Section 4.5.2 (Additional Study Medications), Section 4.7.1 (Permitted Concomitant Medications): The inclusion criterion, requiring that subjects in Cohort 4 must be taking ≥ 10 mg daily dose of a statin for a period of at least 4 weeks prior to screening, was removed; text was modified in relevant sections to reflect this change and to clarify that statins are permitted (but not required). The requirement for statin therapy in Cohort 4 was originally introduced to evaluate the possible therapeutic benefit of MEDI0382 on lipids when prescribed in addition to statin therapy. The effect of MEDI0382 on lipid parameters in addition to statin therapy will now be evaluated later in the clinical development program. The removal of this requirement is expected to have no effect on the study conduct or the safety profile of MEDI0382 and is implemented to facilitate study recruitment.
3. Protocol Synopsis (Objectives; Study Endpoints; Study Design), Section 2.1.3 (Exploratory Objectives), Section 2.2.3 (Exploratory Endpoints), Section 3.1.1 (Overview), Section 3.2.3 (Rationale for Endpoints), Table 4.2.2-4 (Schedule of Treatment Period Procedures: Cohort 4 Overview), Table 4.2.2-5 (Schedule of Treatment Period Procedures: Cohort 4 Self-administration Dosing Period Detail), Section 4.3.10 (Exploratory Endpoints Evaluations and Methods [REDACTED] Magnetic Resonance Imaging]), Section 4.8.8 (Exploratory Analyses): Exploratory objectives to explore the effect of MEDI0382 on the volume and fat/water content of the liver and on visceral and subcutaneous fat were added. Endpoints of change from baseline to Week 4 in liver fat (%), liver volume (L), visceral and subcutaneous adipose tissue (L), liver diffusion, and sagittal and transversal diameter (image based) were added for Cohort 4; text was added to specify that endpoints are to be measured by MRI of the liver/abdomen at sites that have the capacity to perform the procedure. The MRI assessment was added to the schedules of treatment procedures for Cohort 4 (Tables 4.2.2-4 and Table 4.2.2-5) and described in new Section 4.3.10.6 (Magnetic Resonance Imaging of the Liver/Abdomen [Cohort 4]). The exploratory objectives/endpoints were added as there is potential to see changes in liver, visceral, and subcutaneous fat content over the course of the study and will provide information on the potential profile of MEDI0382 in treating NASH. The MRI assessment is non-invasive and is not associated with any risk to study subjects.

4. Protocol Synopsis (Study Design), Section 3.1.1 (Overview), Section 4.3.2.3 (Electrocardiograms), Table 4.2.2-3 (Schedule of Treatment Period Procedures: Cohort 3), Table 4.2.2-4 (Schedule of Treatment Period Procedures: Cohort 4 Overview): The study design was changed to allow subjects in Cohorts 3 and 4 to discontinue telemetry and return home (at the discretion of the investigator) after remaining in the unit for at least 48 hours after dose initiation and dose up titration. The telemetry footnote in Table 4.2.2-3 (Schedule of Treatment Period Procedures: Cohort 3) and Table 4.2.2-4 (Schedule of Treatment Period Procedures: Cohort 4 Overview) was modified to reflect the change in study design. Continuous telemetry measurement is most important during treatment initiation and during dose titration. This is because nausea and vomiting may impact HR and BP and are most likely to be seen before steady state is established/re-established. For MEDI0382, this is predicted to occur within 48 hours post dose initiation or up titration. Given that subjects taking part in this study are extensively screened for cardiovascular disease, the risk of significant arrhythmia once steady state is achieved is thought to be negligible. For this reason, in the opinion of the sponsor, discontinuation of telemetry monitoring outside of these 48-hour periods does not pose an increased safety risk and, as such, may be permitted at the investigator's discretion based on tolerability assessments (ie, skin irritation at the site of telemetry electrode placement) and/or to allow subjects the option of home visits during the inpatient study period (ie, subjects are required to return to the unit for daily dosing and study assessments during the inpatient study period in Cohort 3 and the initial inpatient study period in Cohort 4).
5. Protocol Synopsis (Study Design), Section 3.1.1 (Overview), Section 4.1.2 (Inclusion Criteria), Table 4.2.1-1 (Schedule of Screening Procedures): The screening window was changed from 42 days to 60 days to facilitate study recruitment. Given patients with early diabetes are relatively stable with respect to metabolic parameters and co-morbidities, a minimal number of subjects are likely to be excluded at Day -1, and the longer screening window will allow more time for subjects to plan for the prolonged in-house stay. As eligibility is rechecked on Day -1, there is no increased risk to subjects.
6. Figure 3.1.1-1 (Study Flow Diagram): The figure was updated for clarity and to reflect changes in study design.
7. Section 3.1.3.1 (Progression of Cohorts within this MAD Study): The requirement that regulatory approval be obtained "prior to initiating enrollment" in order to proceed with Cohort 4 was changed to "prior to initiating dosing" so that screening activities can occur prior to receiving approval of the Part A (Cohorts 1-3) data submission package. This is to allow subjects to plan for both the prolonged inpatient stay associated with Cohort 4 and the subsequent outpatient dosing period by confirming provisional participation as soon as possible.
8. Protocol Synopsis (Target Subject Population), Section 3.2.2 (Rationale for Study Population), Section 4.1 (Subjects), Section 4.1.2 (Inclusion Criteria): The age range for inclusion in the study was changed from 18 through ≤ 65 years to 18 through ≤ 69 years, and relevant text was modified to reflect this change. The increase in age range from 65 to 69 years is likely to be associated with only a small increase in prevalent cardiovascular disease. According to recent UK epidemiology data, prevalence of ischemic heart disease in a modern day European population remains at less than 10% up to age 74 years (see [Bhatnagar et al, 2015](#)). Given the extensive cardiovascular screening

procedures, alteration of the age range is not expected to impact subject safety in this clinical study and is implemented to facilitate study recruitment.

9. Section 3.2.2 (Rationale for Study Population), Section 4.1.2 (Inclusion Criteria): The lower range of screening HbA1c was changed from 7.0% to 6.5%. As a GLP-1 agonist, MEDI0382 is expected to enhance insulin release only in the presence of hyperglycemia without increasing the risk of hypoglycemia. This change is not expected to impact the scientific validity of the study or subject safety and is implemented to facilitate study recruitment.
10. Section 3.2.2 (Rationale for Study Population), Section 4.1.2 (Inclusion Criteria): The upper range of screening HbA1c was changed from 8.5% to 9.0%. HbA1c is recognized as a poor predictor of ischemic cardiovascular disease (see [Olsson et al, 2015](#)). As such, an increase of 0.5% in the upper limit to 9.0% is not expected to impact significantly on cardiovascular disease prevalence within the study population or represent any incremental safety risk and is implemented to facilitate study recruitment.
11. Protocol Synopsis (Target Study Population), Section 4.1 (Subjects), Section 4.1.2 (Inclusion Criteria), and Section 4.7.2 (Prohibited Concomitant Medications): Text was added to the inclusion criterion for HbA1c that subjects who are taking sulphonylurea or SGLT2 inhibitors may be eligible to enter the study following a 4-week sulphonylurea or SGLT2 inhibitor washout period. The study population and prohibited concomitant medications were updated to reflect the change in inclusion criteria. Neither sulphonylurea or SGLT2 inhibitors are associated with pleiotrophic effects on beta cells. Hence a 4-week washout period is considered adequate with respect to study entry. The dose of sulphonylurea is capped at 50% of the licensed dose to avoid enrolling subjects to the study who have limited beta cell reserve.
12. Section 4.1.3 (Exclusion Criteria): The exclusion criterion of “history of cancer, with the exception of non-melanoma skin cancer” was changed to “history of cancer within the last 10 years, with the exception of non-melanoma skin cancer” to facilitate study recruitment.
13. Section 4.1.3 (Exclusion Criteria): The exclusion criterion of “fasting blood glucose ≥ 200 mg/dL (11.11 mmol/L)” was removed, because the inclusion criterion for HbA1c is sufficient to exclude subjects with poor glycemic control.
14. Section 4.1.3 (Exclusion Criteria): The upper range of abnormal systolic BP was increased by 10 mm Hg for both age groups. The upper range of abnormal diastolic BP was increased by 10 mm Hg. Glucagon is mechanistically expected to drive natriuresis, and GLP-1 agonism is associated with modest reduction in BP; therefore, at steady state, GLP-1/glucagon agonists should not lead to hypertension. Data for BP and pulse rate changes from Cohort 1 used for the DEC meeting show that MEDI0382 has a benign effect on BP and an effect on pulse rate similar to that seen with short-term liraglutide use.





[Redacted text line]

[Redacted text block]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]



15. Section 4.1.3 (Exclusion Criteria): Text was added to the note for vital signs criteria that subjects who fail BP screening at the clinic may be eligible to enter the study based on results of 24-hour ABPM to be recommended at the investigator's discretion. Guidelines on BP management recognize the fact that blood pressures measured at the clinic may not be predictive of actual BP control. For this reason, ABPM is recommended with respect to BP assessment, where available, for subjects entering the study with BP above the entry threshold as measured at the clinic in order to rule out "white coat" hypertension (see [National Institute for Health and Clinical Excellence \[2013\]](#)).
16. Section 4.1.3 (Exclusion Criteria): A note was added to the exclusion criteria concerning QRS duration to allow subjects with QRS duration > 120 msec in the presence of right bundle branch block, which is not in the opinion of the investigator associated with significant respiratory or cardiovascular disease, to be enrolled in the study. As right bundle branch block (in contrast to left bundle branch block) is recognized as a normal ECG variant and is not associated with underlying respiratory and cardiovascular disease, this should not preclude entry to the study.
17. Section 4.1.3 (Exclusion Criteria): Additional exclusion criteria regarding subject's use of weight loss diets/agents, and conditions where MRI is contraindicated were added for Cohort 4 only if the site has access to an MRI scanner.

18. Tables 4.2.2-1 (Schedule of Treatment Period Procedures: Cohort 1), 4.2.2-2 (Schedule of Treatment Period Procedures: Cohort 2), 4.2.2-3 (Schedule of Treatment Period Procedures: Cohort 3), 4.2.2-4 (Schedule of Treatment Period Procedures: Cohort 4 Overview), and Section 4.6.1 (Methods for Assigning Treatment Groups): In table footnotes pertaining to randomization, the requirement that “dosing must occur within 10 hours of randomization” was removed; the relevant text in Section 4.6.1 (Methods for Assigning Treatment Groups) was deleted. This requirement posed a logistical burden to the sites and is deemed unnecessary as randomizations are planned across sites.
19. Section 4.3.2.3 (Electrocardiograms): The printing of paper ECGs was modified from “all occasions when a digital ECG is sampled” to “at minimum, a single representative ECG should be printed and archived in the subject’s file” to reduce the administrative burden on sites.
20. Section 4.3.3 (Clinical Laboratory Tests): Clinical laboratory testing for [REDACTED] anti-drug antibodies, and Ig and subsets (Ig A/E/G/M) were added under “Other Tests” to correct an oversight in the original protocol and for consistency with the tables of study procedures provided in Section 4.2 (Schedule of Study Procedures).
21. Section 4.5.1.4 (Dose Preparation Steps): Text that syringe sizes, vial sizes and other consumables may be altered at the discretion of the sponsor was added so that similar changes to consumables will not require an administrative change or an amendment to the protocol.

9.6 Administrative Change 1, 05Nov2015

1. Section 4.5.1.4 (Dose Preparation Steps): The specific requirement for 3 cc vials was removed, as these are not feasible for use at sites.
1. Section 4.5.1.4 (Dose Preparation Steps): Dilution of MEDI0382 with MEDI0382 placebo was changed to dilution of MEDI0382 with diluent (solution manufactured by MedImmune) to be consistent with the footnote in Table 4.5.1.4-1 (MEDI0382 and Placebo Dose Preparation).
2. Section 4.5.1.4 (Dose Preparation Steps) and Section 4.5.1.5 (Treatment Administration): The requirement to use a 29G needle for treatment administration was changed to 30G needle, because 29G needles are not available to the sites.

9.7 Amendment 3, 10Oct2015

This amendment has been implemented in response to requests made from the Bundesinstitut fuer Arzneimittel und Medizinprodukte (BfArM; received 08Oct2015). Revisions have been made to several sections of the protocol, as outlined below:

1. Protocol Synopsis, Section 3.1.2 (Treatment Regimen), Section 3.1.3.1 (Progression of Cohorts within this MAD Study), [REDACTED], Section 4.5.1.4 (Dose Preparation Steps [In-clinic Dose Preparation Steps]) were amended to reflect a reduction in the maximum dose to be administered in this study from 400 to 300 µg/day as requested by the BfArM.

2. [REDACTED]
3. Section 4.1.3 (Exclusion Criteria), a criterion excluding subjects with a history of lactic acidosis or ketoacidosis was added as requested by the BfArM.
4. Protocol Synopsis, Section 3.1.1 (Overview), Table 4.2.2-1 (Schedule of Treatment Period Procedures: Cohort 1), Table 4.2.2-2 (Schedule of Treatment Period Procedures: Cohort 2), Table 4.2.2-3 (Schedule of Treatment Period Procedures: Cohort 3), Table 4.2.2-4 (Schedule of Treatment Period Procedures: Cohort 4 Overview), Section 4.3.5 (Glucometer Blood Glucose Readings during the Inpatient Period), and Table 4.3.8-1 (Example Schedule for MEDI0382 PK and for PD Blood Sample Collections on Day 7 [Cohort 1], Day 11 [Cohort 2], Day 15 [Cohort 3], and Day 41 [Cohort 4]) were amended to include collection of finger prick glucose samples 15 minutes prior to and 2 hours after breakfast and before going to bed in addition to the measures taken before and after the mid-day and evening meals to increase glucose monitoring as requested by the BfArM.
5. Table 4.2.2-1 (Schedule of Treatment Period Procedures: Cohort 1), Table 4.2.2-2 (Schedule of Treatment Period Procedures: Cohort 2), and Table 4.2.2-3 (Schedule of Treatment Period Procedures: Cohort 3), the footnotes describing the timing of ECG capture were corrected to be consistent with the measurements indicated in the tables.
6. Table 4.5.1.4-1 (MEDI0382 and Placebo Dose Preparation), the volume of injection was reduced consistent with the reduction in dose from 400 to 300 µg.
7. Section 4.5.1.4 (Dose Preparation Steps [In-clinic Dose Preparation Steps]) and Section 4.5.1.5 (Treatment Administration [In-clinic Treatment Administration]) the needle gauge was amended from 27G to 29G to reduce the chance of discomfort for the subjects.

9.8 Amendment 2; 14Aug2015

This amendment has been implemented to meet the requirements of the regulatory agency whereby data from the SAD study are summarized to support initiation of the MAD study. Revisions to several sections of the protocol, as outlined below, reflect changes in the MAD study taking into account these SAD data where appropriate.

In addition, the current eligibility criteria are considered unduly restrictive and do not accurately represent the expected benefit/risk profile for MEDI0382. These eligibility criteria also raise significant concerns around the ability to recruit subjects to the study. The current Leipzig (LIFE) Heart Study (courtesy of [REDACTED]) contains data on 10,001 men and women, including 337 individuals with T2DM in the 27-65 years age group. These data imply that approximately 1% of the current T2DM population in Germany is eligible to enter the study with the current inclusion/exclusion criteria. This is further supported by data from Vision practices within the United Kingdom Clinical Practice Research Datalink study (www.cprd.com; accessed on 30Apr2015).

Modification of the eligibility criteria as detailed below is not anticipated to change the benefit-risk profile of MEDI0382; specifically the changes with respect to the anticipated cardiovascular risk profile of MEDI0382 have been considered. The action of MEDI0382 is designed to mimic the action of the naturally occurring peptide hormone oxyntomodulin, a peptide with both glucagon and GLP-1 agonist activity. Evidence to support a negative effect of glucagon or GLP-1 agonism on blood pressure does not exist. For dual GLP-1 and glucagon agonism, as exhibited by oxyntomodulin, no negative effects on pulse or blood pressure have been observed. As oxyntomodulin is the prototype naturally occurring model for MEDI0382, the benefit-risk profile for MEDI0382 with respect to cardiovascular disease is expected to be positive, driven by substantial weight loss against clinically insignificant effects on pulse and blood pressure.

Amendments to the eligibility criteria have been made as detailed below; the number of clinical sites has also been increased. Text revisions resulting from this amendment are incorporated in the body of Protocol Amendment 2. Changes to the protocol are summarized below.

- [REDACTED]
- [REDACTED]
- [REDACTED]
3. Synopsis (Objectives/Endpoints), Section 2.1.1 (Primary Objective), Section 2.2.1 (Primary Endpoints), and Section 4.8.3.1 (Primary Efficacy Analysis) were changed to specify that change from baseline in glucose and body weight will be evaluated rather than change from the first dose in an up-titration period, this will more accurately reflect the likely clinical use profile of MEDI0382.
 4. Synopsis (Objectives), Section 2.1.2 (Secondary Objectives), Section 2.2.2 (Secondary Endpoints), and Section 4.8.3.2 (secondary Efficacy Analysis) objective 1 and endpoint 1 were changed to specify that change from baseline rather than Day 1 will be used to evaluate glucose control. Given that subjects are admitted 2 days prior to administration of investigational product, baseline parameters are considered stable enough to represent a subjects' predose metabolic state accurately. In keeping with the sponsor's responsibility to reduce unnecessary collection of blood samples, collection of these parameters at Day 1 has now been rationalized.
 5. Synopsis (Objectives), Section 2.1.3 (Exploratory Objectives), Section 4.1.2 (Inclusion Criteria) were clarified to state that subjects should be treated with a daily dose of statin at baseline.
 6. Synopsis (Endpoints), Section 2.2.2 (Secondary Endpoints), Section 3.1.1 (Overview), Section 3.2.2 (Recruitment of Subjects with T2DM on Metformin), Section 3.2.3 (Rationale for Endpoints Supporting the Secondary Objectives of Safety/Tolerability and

PK/Immunogenicity), Table 4.2.2-1 (Schedule of Treatment Period Procedures: Cohort 1), Table 4.2.2-2 (Schedule of Treatment Period Procedures: Cohort 2), Table 4.2.2-3 (Schedule of Treatment Period Procedures: Cohort 3), and Table 4.2.2-4 (Schedule of Treatment Period Procedures: Cohort 4), Section 4.3.6 (Pharmacokinetic Evaluation and Methods) was amended to include measurement of metformin concentration. Measurement of metformin concentration at baseline ensures that any PK/PD interaction between metformin dosing and MEDI0382 can be adequately explored during this intensively monitored, early phase study in a safe, in house environment.

- [REDACTED]
8. Synopsis (Study Design) and Section 3.1.1 (Overview) the number of anticipated clinical sites anticipated to successfully recruit this study was increased from 8 to 10. In addition, the inclusion of overweight as well as obese subjects has been reflected due to the increased range for body weight eligibility.
 9. Synopsis, Section 3.1.1 (Overview), Figure 3.1.1-1 (Study Flow Diagram), Section 3.1.2 (Treatment Regimen), were amended to make the language describing the dosing in the 4 cohorts consistent throughout the protocol and to ensure it more accurately reflects the proposed dosing schedule for the MAD study.
 10. Synopsis, Section 3.1.1 (Overview) and Table 4.2.1-1 (Screening procedures) were amended to lengthen the screening period from 28 days to 42 days to ensure there is adequate time for subjects to complete a washout period within the screening period if required.
 11. Synopsis, Section 3.1.1 (Overview), Section 4.5.1.1 (Identity of Investigational Product), where subjects in Cohort 4 are not considered competent with regards to self-administration of investigational product, an option for them to continue to receive investigational product by a qualified study site professional has been added to ensure these subjects are able to continue in the study.
 12. Synopsis and Section 3.1.1 (Overview) were edited to clarify that subjects are admitted to the clinic 2 evenings before the receipt of investigational product.
 13. Synopsis, Section 3.1.1 (Overview), Table 4.2.2-1 (Schedule of Treatment Period Procedures: Cohort 1), Table 4.2.2-2 (Schedule of Treatment Period Procedures: Cohort 2), Table 4.2.2-3 (Schedule of Treatment Period Procedures: Cohort 3), and Table 4.2.2-4 (Schedule of Treatment Period Procedures: Cohort 4) the Day 1 assessment of MMT and blood samples for glucose metabolism panel were removed from the protocol.
- [REDACTED]
- [REDACTED]

- [REDACTED]
15. Section 3.1.3.1 (Progression of Cohorts) has been amended to include further details of when dose escalation will be stopped and the process leading to a stopping decision.
16. Section 3.1.3.2 (Cardiac Stopping Criteria) has been edited to clarify that pulse rate should be measured at 5 timepoints during the 10 minute period.
17. [REDACTED]
18. Section 3.2.2 (Rationale for Study Population) and Section 4.1.2 (Inclusion Criteria) the lower limit of HbA1c for Cohort 4 has been lowered from 7.5% to 7.0%. A different lower limit was originally proposed with respect to HbA1c for Cohorts 1-3 vs Cohort 4 to facilitate recruitment in the earlier cohorts and maximize the ability to demonstrate a reduction in blood glucose for Cohort 4. It has now become apparent that excellence in diabetes care within the German T2DM population means that maintaining the lower limit of HbA1c at 7.5% will significantly impair recruitment for the proposed study. In the opinion of the sponsor the reduction in the HbA1c limit at study entry does not impact on patient safety, as GLP-1 agonists when used in monotherapy or in combination with metformin are not associated with increased risk of hypoglycemia.
19. Section 4.1 (Subjects) clarified that the population is to have been treated with a stable dose of oral blood glucose lowering therapy for 3 months prior to screening.
20. Synopsis (Target Subject Population) and Section 4.1.2 (Inclusion Criteria) the acceptable BMI range has been changed from 30-35 kg/m² to 27-40 kg/m². Section 3.2.2 (Rationale for Study Population) has also been amended to include the rationale for inclusion of subjects in this BMI range. MedImmune considers the current BMI criteria (30-35 kg/m²) unduly restrictive. Approximately 44% of the T2DM population have a BMI between 30-40 kg/m² ([Daousi et al, 2006](#)) and with regards to cardiovascular disease, the greatest increase in prevalence in an unselected primary care population occurs at a BMI > 37.5 kg/m² in men and > 40 kg/m² in women ([McQuigg et al, 2008](#)). With the screening procedures in place, including medical history assessment, full physical examination, and ECG monitoring throughout the study, MedImmune believes that significant ischemic cardiovascular disease can be excluded while allowing for the broader BMI range at inclusion.
21. Section 4.1.2 (Inclusion Criteria) the requirement for subjects to be willing and able to complete and meet all eligibility requirements for randomization within 42 days after signing the informed consent form was added for clarity.
22. Section 4.1.3 (Exclusion Criteria) the exclusion of subjects with microalbuminuria (20-200 mg/L) has been removed from the protocol. MedImmune believes that the current exclusion of subjects with microalbuminuria is unnecessarily restrictive. Microalbuminuria screening has low accuracy to detect subjects with diabetic nephropathy; whereas, deterioration of glomerular filtration rate (GFR) appears at an earlier stage in the progression of diabetic nephropathy than albuminuria, and therefore represents a more reliable indicator of renal function impairment in diabetic kidney disease (exclusion criterion 12; [Rajic et al, 2003](#); [Baskar et al, 2006](#)). In addition,

multiple parameters of renal function will be closely monitored throughout the study in all cohorts, with serial measurements of urinary protein, pH, and specific gravity as well as serial measurements of relevant plasma parameters, including creatinine, blood urea nitrogen, and electrolytes.

In addition, a change in exclusion criteria to allow subjects with microalbuminuria (≤ 300 mg/L albumin) is likely to have a minimal impact on coronary disease in this study population ([Pugliese et al, 2014](#) and data from the CPRD vision practice data viewer accessed on 29May2015). Given the multiple screening assessments for cardiovascular disease, including medical history, complete physical examination, and ECG assessment, MedImmune believes that the change to include subjects with microalbuminuria up to 300 mg/L is appropriate and will not impact significantly on the cardiovascular risk profile of subjects included in this study.

23. Section 4.1.3 (Exclusion Criteria), criterion 11 was edited to correct an error.
24. Section 4.1.3 (Exclusion Criteria), criterion 14 was deleted to remove redundancy with criterion 18.
25. Section 4.1.6 (Discontinuation of Investigational Product) was edited to include both mg/dL and mmol/L units for glucose.
26. Section 4.1.7 (Replacement of Subjects) the provision for additional screened subjects to be available for randomization was included to ensure that sufficient numbers of subjects are randomized into each cohort.
27. Section 4.1.8 (Withdrawal of Informed Consent for Data and Biological Samples) the section describing Optional Samples Obtained for Future Genetic Research or Future Non-genetic Research was edited to reflect the current practice of the sponsor in handling these samples.
28. Table 4.2.1-1 (Schedule of Screening Procedures) was edited to reduce redundancy and the calculation of GFR was added to confirm eligibility.
29. Table 4.2.2-1 (Schedule of Treatment Period Procedures: Cohort 1), Table 4.2.2-2 (Schedule of Treatment Period Procedures: Cohort 2), Table 4.2.2-3 (Schedule of Treatment Period Procedures: Cohort 3), Table 4.2.2-4 (Schedule of Treatment Period Procedures: Cohort 4), and Section 4.6.1 Methods for Assigning Treatment Groups, randomization was changed to allow for randomization on either Day -1 or Day 1 with dosing to occur within 10 hours of randomization to allow adequate time on the day of dosing dose preparation.
30. Table 4.2.2-1 (Schedule of Treatment Period Procedures: Cohort 1), Table 4.2.2-2 (Schedule of Treatment Period Procedures: Cohort 2), Table 4.2.2-3 (Schedule of Treatment Period Procedures: Cohort 3), and Table 4.2.2-4 (Schedule of Treatment Period Procedures: Cohort 4) was edited to reduce redundancy, and a predose blood sample for evaluation of lactate and screening PD sample for glucose were added. A MEDI0382 PK dose sample at 48 hours post-final dose for Cohorts 1-3 was also added.
31. [REDACTED]
32. Section 4.2.4 (Early Discontinuation or Unscheduled Visit) was added to the protocol to detail the procedures to perform in the event a subject prematurely discontinues from the study or requires an unscheduled study visit.

33. Section 4.3.2.1 (Medical History and Physical Examination) was edited to make it clear the assessments to perform for a targeted physical examination (previously termed an abbreviated physical examination).
34. Section 4.3.2.2 (Assessment of the Injection Site) was edited to add more detail of the types or reactions that may occur.
35. Section 4.3.2.3 (Electrocardiograms) was edited to reflect the practice at clinical sites. The process to follow in the case of significant skin irritation was also added.
36. Section 4.3.4 (Estimate of Blood Volumes) was edited to reflect the changes in blood samples taken during the study.
37. Section 4.3.5 (Glucometer Blood Glucose Readings during the Inpatient Period) was edited for clarity.
38. Table 4.3.8-1 (Example Schedule for MEDI0382 PK and for PD Blood Sample Collections on Day 7 (Cohort 1), Day 11 (Cohort 2), Day 15 (Cohort 3), and Day 41 (Cohort 4) was edited to clarify that the time of collection is in relation to the MMT only.
39. Section 4.3.12.3 (Training for Completing the Daily Diaries during the At-home Self-administration Period) was edited to reflect the use of electronic diaries.
40. Section 4.5.1.1 (Identity of Investigational Product) was modified to reflect the kit supply for at-home dosing.
41. Section 4.5.1.2 (Investigational Product Handling) was edited to remove redundancy.
42. Section 4.5.1.4 (In-clinic Dose Preparation Steps), Table 4.5.1.4-1 (MEDI0382 and Placebo Preparation) were modified to reflect the change in dose selection for this study. The calculations for dose preparation were also amended accordingly.
43. Section 4.7.1 (Permitted Concomitant Medications) was amended to specify that hormone replacement therapy and agents for benign prostatic hyperplasia are permitted during the study.
44. Section 4.8.4 (Safety) was edited to emphasize that safety ECGs will be evaluated based on paper ECG copies at site.
45. Section 5.5 (Reporting of Serious Adverse Events), Section 5.6 (Other Events Requiring Immediate Reporting), Section 5.6.1 (Overdose), Section 5.6.2 (Hepatic Function Abnormality), and Section 5.6.3 (Pregnancy) have been modified to reflect a change in process of SAE reporting by the Sponsor and the implementation of electronic SAE reporting. Appendix 6 has been added to provide detail on the reporting of Hy's law cases in line with this updated process.
46. Section 8 (References) has been updated to include additional references included in this amendment.
47. Appendix 2 was revised to reflect current sponsor definitions for adverse event severity grading.

9.9 Amendment 1; 26Feb2015

Text revisions resulting from this amendment are incorporated in the body of Protocol Amendment 1. Changes to the protocol to enhance subject safety were made in response to

requests from the regulatory agency of the country in which the sponsor sought approval to conduct the study as well as the central ethics committee. Major changes to the protocol are summarized below.

1. Synopsis (under Study Design) and Section 3.1.1 (Overview) the number of anticipated study sites was changed from approximately 3 to 5 to “up to 8” to allow for the possibility of increasing the number of sites.

[REDACTED]

3. Section 3.1.3.2 (Progression of Cohorts within this MAD Study):
 - a. The following text was added for subject safety: A sentinel dosing approach is planned for Cohorts 1, 2, and 3. Only 2 subjects in a given cohort will be dosed on Day 1, and the randomization schedule will ensure that these consist of 1 active and 1 placebo subject. A time lag of ≥ 3 days will occur before additional subjects in the cohort are dosed. Dosing is proposed to continue based on a lack of significant safety findings in the first 2 subjects dosed. The overall randomization schedule will ensure a 2:1 randomization (active:placebo) for each cohort.
 - b. The bolded text in the following phrase was added for clarification: For progression from Cohort 1 to Cohort 2, and from Cohort 2 to Cohort 3, the decision whether or not to progress will be made by the Dose Escalation Committee.
 - c. Also, the relevant data will be summarized and provided to the appropriate regulatory body and central ethics committee.
 - d. And, approval to proceed with Cohort 4 will be obtained from the appropriate regulatory body prior to initiating enrollment.
 - e. Under the DEC recommendation options:
 - i. A bullet point was clarified. Expand “dosing” was clarified to say “expand “the number of patients dosed” at a particular dose level.
 - ii. And, a bullet point (a new option) was added as follows. “Escalate to the next cohort but extend the number of dosing days at a particular dose level before dose up-titration occurs.”
4. Section 3.1.3.3 (Cardiac Stopping Criteria): The bolded word “or” was added to the fourth bullet for clarity, ie, “In a subject receiving MEDI0382: hypertension, defined as an increase in resting supine systolic BP > 40 mm mercury (Hg) **or** above 180 mm Hg and persisting for at least 10 minutes.”

5. Section 3.1.4 (Management of Toxicities and Dose Modification): Significant vomiting was clarified as “3 or more episodes of vomiting on a single day or across 2 consecutive days, despite adjustment to diet having been made.”



7. Section 4.1.2 (Inclusion Criteria): A note was added to clarify Inclusion Criterion 9 (about contraception) reading “Male condom plus spermicide is only considered an effective contraceptive measure when used together with another method in Table 4.1.2-1. None of the methods in Table 4.1.2-1 are intended to be used alone.”
8. Section 4.1.3 (Exclusion Criteria): The exclusion criterion “Concurrent participation in another study of any kind is prohibited” was added.
9. Section 4.1.6 (Discontinuation of Investigational Product) was modified to add that an individual subject will not receive any further investigational product if that subject has more than 2 symptomatic hypoglycemic events (symptoms of hypoglycemia with documented finger prick glucose < 2.8 mmol/L); or persistent hyperglycemia (> 260 mg/dL measured with 2 laboratory fasting blood glucose samples more than 3 days apart).
10. Section 4.8.9 (Dose Escalation Committee): In the following sentence, “coordinating” investigator replaced “principal” investigator. The CRO medical monitor and the coordinating investigator will remain blinded.

Appendix 1 Signatures

Sponsor Signature(s)

A Phase 1/2, Randomized, Double-blind, Placebo-controlled, Multiple-ascending-dose Study to Evaluate the Efficacy, Safety, and Pharmacokinetics of MEDI0382 in Overweight and Obese Subjects with a History of Type 2 Diabetes Mellitus

I agree to the terms of this protocol.

Signature and date:

[REDACTED]

[REDACTED]

One MedImmune Way, Gaithersburg MD, 20878, USA

Telephone number: [REDACTED]

Signature of Coordinating Investigator

A Phase 1/2, Randomized, Double-blind, Placebo-controlled, Multiple-ascending-dose Study to Evaluate the Efficacy, Safety, and Pharmacokinetics of MEDI0382 in Overweight and Obese Subjects with a History of Type 2 Diabetes Mellitus

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 Council on Harmonisation (ICH) guidelines on Good Clinical Practice (GCP), any applicable laws and requirements, and any conditions required by a regulatory authority and/or Institutional Review Board/Independent Ethics Committee (IRB/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 IRB/IEC, and must be approved by the IRB/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 IRB/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): _____

Signature of Principal Investigator

A Phase 1/2, Randomized, Double-blind, Placebo-controlled, Multiple-ascending-dose Study to Evaluate the Efficacy, Safety, and Pharmacokinetics of MEDI0382 in Overweight and Obese Subjects with a History of Type 2 Diabetes Mellitus

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 Council on Harmonisation (ICH) guidelines on Good Clinical Practice (GCP), any applicable laws and requirements, and any conditions required by a regulatory authority and/or Institutional Review Board/Independent Ethics Committee (IRB/IEC).

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Signature and date: _____

Name and title: _____

Address including postal code: _____

Telephone number: _____

Site/Center Number (if available): _____

Appendix 2 Additional Safety Guidance

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 | An event of mild intensity 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 | An event of moderate intensity 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 | A severe 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 | An event, and/or its immediate sequelae, that is associated with an imminent risk of death. |
| Grade 5 | 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 nontreatment-emergent SAEs (ie, SAEs that occur prior to the administration of investigational product) as well as treatment-emergent SAEs. 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).

Appendix 3 National Institute of Allergy and Infectious Diseases and Food Allergy and Anaphylaxis Network Guidance for Anaphylaxis Diagnosis

Sampson HA, Muñoz-Furlong A, Campbell RL, Adkinson FN Jr, Bock SA, Branum A, et al. Second symposium on the definition and management of anaphylaxis: Summary report -- Second National Institute of Allergy and Infectious Diseases/Food Allergy and Anaphylaxis Network symposium. J Allergy Clin Immunol. 2006;117:391-7.

National Institute of Allergy and Infectious Diseases and Food Allergy and Anaphylaxis Network define anaphylaxis as a serious allergic reaction that is rapid in onset and may cause death. 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
 - Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced peak expiratory flow, hypoxemia)
 - 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):
 - Involvement of the skin-mucosal tissue (eg, generalized hives, itch-flush, swollen lips-tongue-uvula)
 - Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced peak expiratory flow, hypoxemia)
 - Reduced BP or associated symptoms (eg, hypotonia [collapse], syncope, incontinence)
 - Persistent gastrointestinal symptoms (eg, crampy abdominal pain, vomiting)
3. Reduced BP after exposure to known allergen for that patient (minutes to several hours):
 - Infants and children: low systolic BP (age specific) or greater than 30% decrease in systolic BP
 - Adults: systolic BP of less than 90 mm Hg or greater than 30% decrease from that person's baseline

Appendix 4 Columbia-Suicide Severity Rating Scale

COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS)

Baseline

Version 1/14/09

*Posner, K.; Brent, D.; Lucas, C.; Gould, M.; Stanley, B.; Brown, G.; Fisher, P.; Zelazny, J.;
Burke, A.; Oquendo, M.; Mann, J.*

Disclaimer:

This scale is intended to be used by individuals who have received training in its administration. The questions contained in the Columbia-Suicide Severity Rating Scale are suggested probes. Ultimately, the determination of the presence of suicidal ideation or behavior depends on the judgment of the individual administering the scale.

*Definitions of behavioral suicidal events in this scale are based on those used in **The Columbia Suicide History Form**, developed by John Mann, MD and Maria Oquendo, MD, Conte Center for the Neuroscience of Mental Disorders (CCNMD), New York State Psychiatric Institute, 1051 Riverside Drive, New York, NY, 10032. (Oquendo M. A., Halberstam B. & Mann J. J., Risk factors for suicidal behavior: utility and limitations of research instruments. In M.B. First [Ed.] Standardized Evaluation in Clinical Practice, pp. 103 -130, 2003.)*

For reprints of the C-SSRS contact Kelly Posner, Ph.D., New York State Psychiatric Institute, 1051 Riverside Drive, New York, New York, 10032; inquiries and training requirements contact posnerk@nyspi.columbia.edu

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| SUICIDAL IDEATION | | Lifetime: Time He/She Felt Most Suicidal |
|---|--|--|
| <p><i>Ask questions 1 and 2. If both are negative, proceed to "Suicidal Behavior" section. If the answer to question 2 is "yes", ask questions 3, 4 and 5. If the answer to question 1 and/or 2 is "yes", complete "Intensity of Ideation" section below.</i></p> | | |
| <p>1. Wish to be Dead Subject endorses thoughts about a wish to be dead or not alive anymore, or wish to fall asleep and not wake up. <i>Have you wished you were dead or wished you could go to sleep and not wake up?</i></p> <p>If yes, describe:</p> | | <p>Yes No</p> <p><input type="checkbox"/> <input type="checkbox"/></p> |
| <p>2. Non-Specific Active Suicidal Thoughts General, non-specific thoughts of wanting to end one's life/commit suicide (e.g., "I've thought about killing myself") without thoughts of ways to kill oneself/associated methods, intent, or plan. <i>Have you actually had any thoughts of killing yourself?</i></p> <p>If yes, describe:</p> | | <p>Yes No</p> <p><input type="checkbox"/> <input type="checkbox"/></p> |
| <p>3. Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act Subject endorses thoughts of suicide and has thought of at least one method during the assessment period. This is different than a specific plan with time, place or method details worked out (e.g., thought of method to kill self but not a specific plan). Includes person who would say, "I thought about taking an overdose but I never made a specific plan as to when, where or how I would actually do it... and I would never go through with it."</p> <p><i>Have you been thinking about how you might do this?</i></p> <p>If yes, describe:</p> | | <p>Yes No</p> <p><input type="checkbox"/> <input type="checkbox"/></p> |
| <p>4. Active Suicidal Ideation with Some Intent to Act, without Specific Plan Active suicidal thoughts of killing oneself and subject reports having <u>some intent to act on such thoughts</u>, as opposed to "I have the thoughts but I definitely will not do anything about them." <i>Have you had these thoughts and had some intention of acting on them?</i></p> <p>If yes, describe:</p> | | <p>Yes No</p> <p><input type="checkbox"/> <input type="checkbox"/></p> |
| <p>5. Active Suicidal Ideation with Specific Plan and Intent Thoughts of killing oneself with details of plan fully or partially worked out and subject has some intent to carry it out. <i>Have you started to work out or worked out the details of how to kill yourself? Do you intend to carry out this plan?</i></p> <p>If yes, describe:</p> | | <p>Yes No</p> <p><input type="checkbox"/> <input type="checkbox"/></p> |
| INTENSITY OF IDEATION | | |
| <p><i>The following features should be rated with respect to the most severe type of ideation (i.e., 1-5 from above, with 1 being the least severe and 5 being the most severe). Ask about time he/she was feeling the most suicidal.</i></p> <p>Most Severe Ideation: _____</p> <p style="text-align: center;">Type # (1-5) Description of Ideation</p> | | Most Severe |
| <p>Frequency <i>How many times have you had these thoughts?</i> (1) Less than once a week (2) Once a week (3) 2-5 times in week (4) Daily or almost daily (5) Many times each day</p> | | _____ |
| <p>Duration <i>When you have the thoughts, how long do they last?</i> (1) Fleeting - few seconds or minutes (4) 4-8 hours/most of day (2) Less than 1 hour/some of the time (5) More than 8 hours/persistent or continuous (3) 1-4 hours/a lot of time</p> | | _____ |
| <p>Controllability <i>Could/can you stop thinking about killing yourself or wanting to die if you want to?</i> (1) Easily able to control thoughts (4) Can control thoughts with a lot of difficulty (2) Can control thoughts with little difficulty (5) Unable to control thoughts (3) Can control thoughts with some difficulty (6) Does not attempt to control thoughts</p> | | _____ |
| <p>Deterrents <i>Are there things - anyone or anything (e.g., family, religion, pain of death) - that stopped you from wanting to die or acting on thoughts of committing suicide?</i> (1) Deterrents definitely stopped you from attempting suicide (4) Deterrents most likely did not stop you (2) Deterrents probably stopped you (5) Deterrents definitely did not stop you (3) Uncertain that deterrents stopped you (6) Does not apply</p> | | _____ |
| <p>Reasons for Ideation <i>What sort of reasons did you have for thinking about wanting to die or killing yourself? Was it to end the pain or stop the way you were feeling (in other words you couldn't go on living with this pain or how you were feeling) or was it to get attention, revenge or a reaction from others? Or both?</i> (1) Completely to get attention, revenge or a reaction from others (4) Mostly to end or stop the pain (you couldn't go on living with the pain or how you were feeling) (2) Mostly to get attention, revenge or a reaction from others (5) Completely to end or stop the pain (you couldn't go on living with the pain or how you were feeling) (3) Equally to get attention, revenge or a reaction from others and to end/stop the pain. (6) Does not apply</p> | | _____ |

| SUICIDAL BEHAVIOR (Check all that apply, so long as these are separate events; must ask about all types) | | | | Lifetime |
|---|---------------------------|---------------------------|-----------------------------|--|
| Actual Attempt: A potentially self-injurious act committed with at least some wish to die, as a result of act. Behavior was in part thought of as method to kill oneself. Intent does not have to be 100%. If there is any intent/desire to die associated with the act, then it can be considered an actual suicide attempt. There does not have to be any injury or harm , just the potential for injury or harm. If person pulls trigger while gun is in mouth but gun is broken so no injury results, this is considered an attempt. Inferring Intent: Even if an individual denies intent/wish to die, it may be inferred clinically from the behavior or circumstances. For example, a highly lethal act that is clearly not an accident so no other intent but suicide can be inferred (e.g., gunshot to head, jumping from window of a high floor/story). Also, if someone denies intent to die, but they thought that what they did could be lethal, intent may be inferred. Have you made a suicide attempt? Have you done anything to harm yourself? Have you done anything dangerous where you could have died? What did you do? Did you _____ as a way to end your life? Did you want to die (even a little) when you _____? Were you trying to end your life when you _____? Or did you think it was possible you could have died from _____? Or did you do it purely for other reasons / without ANY intention of killing yourself (like to relieve stress, feel better, get sympathy, or get something else to happen)? (Self-Injurious Behavior without suicidal intent) If yes, describe: | | | | Yes No <input type="checkbox"/> <input type="checkbox"/> Total # of Attempts _____ |
| Has subject engaged in Non-Suicidal Self-Injurious Behavior? | | | | Yes No <input type="checkbox"/> <input type="checkbox"/> |
| Interrupted Attempt: When the person is interrupted (by an outside circumstance) from starting the potentially self-injurious act (if not for that, actual attempt would have occurred). Overdose: Person has pills in hand but is stopped from ingesting. Once they ingest any pills, this becomes an attempt rather than an interrupted attempt. Shooting: Person has gun pointed toward self, gun is taken away by someone else, or is somehow prevented from pulling trigger. Once they pull the trigger, even if the gun fails to fire, it is an attempt. Jumping: Person is poised to jump, is grabbed and taken down from ledge. Hanging: Person has noose around neck but has not yet started to hang - is stopped from doing so. Has there been a time when you started to do something to end your life but someone or something stopped you before you actually did anything? If yes, describe: | | | | Yes No <input type="checkbox"/> <input type="checkbox"/> Total # of interrupted _____ |
| Aborted Attempt: When person begins to take steps toward making a suicide attempt, but stops themselves before they actually have engaged in any self-destructive behavior. Examples are similar to interrupted attempts, except that the individual stops him/herself, instead of being stopped by something else. Has there been a time when you started to do something to try to end your life but you stopped yourself before you actually did anything? If yes, describe: | | | | Yes No <input type="checkbox"/> <input type="checkbox"/> Total # of aborted _____ |
| Preparatory Acts or Behavior: Acts or preparation towards imminently making a suicide attempt. This can include anything beyond a verbalization or thought, such as assembling a specific method (e.g., buying pills, purchasing a gun) or preparing for one's death by suicide (e.g., giving things away, writing a suicide note). Have you taken any steps towards making a suicide attempt or preparing to kill yourself (such as collecting pills, getting a gun, giving valuables away or writing a suicide note)? If yes, describe: | | | | Yes No <input type="checkbox"/> <input type="checkbox"/> |
| Suicidal Behavior: Suicidal behavior was present during the assessment period? | | | | Yes No <input type="checkbox"/> <input type="checkbox"/> |
| Answer for Actual Attempts Only | | | | |
| | Most Recent Attempt Date: | Most Lethal Attempt Date: | Initial/First Attempt Date: | |
| Actual Lethality/Medical Damage: 0. No physical damage or very minor physical damage (e.g., surface scratches). 1. Minor physical damage (e.g., lethargic speech; first-degree burns; mild bleeding; sprains). 2. Moderate physical damage; medical attention needed (e.g., conscious but sleepy, somewhat responsive; second-degree burns; bleeding of major vessel). 3. Moderately severe physical damage; medical hospitalization and likely intensive care required (e.g., comatose with reflexes intact; third-degree burns less than 20% of body; extensive blood loss but can recover; major fractures). 4. Severe physical damage; medical hospitalization with intensive care required (e.g., comatose without reflexes; third-degree burns over 20% of body; extensive blood loss with unstable vital signs; major damage to a vital area). 5. Death | Enter Code | Enter Code | Enter Code | |
| Potential Lethality: Only Answer if Actual Lethality=0 Likely lethality of actual attempt if no medical damage (the following examples, while having no actual medical damage, had potential for very serious lethality: put gun in mouth and pulled the trigger but gun fails to fire so no medical damage; laying on train tracks with oncoming train but pulled away before run over). 0 = Behavior not likely to result in injury 1 = Behavior likely to result in injury but not likely to cause death 2 = Behavior likely to result in death despite available medical care | Enter Code | Enter Code | Enter Code | |

COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS)

Since Last Visit

Version 1/14/09

***Posner, K.; Brent, D.; Lucas, C.; Gould, M.; Stanley, B.; Brown, G.; Fisher, P.; Zelazny, J.;
Burke, A.; Oquendo, M.; Mann, J.***

Disclaimer:

This scale is intended to be used by individuals who have received training in its administration. The questions contained in the Columbia-Suicide Severity Rating Scale are suggested probes. Ultimately, the determination of the presence of suicidal ideation or behavior depends on the judgment of the individual administering the scale.

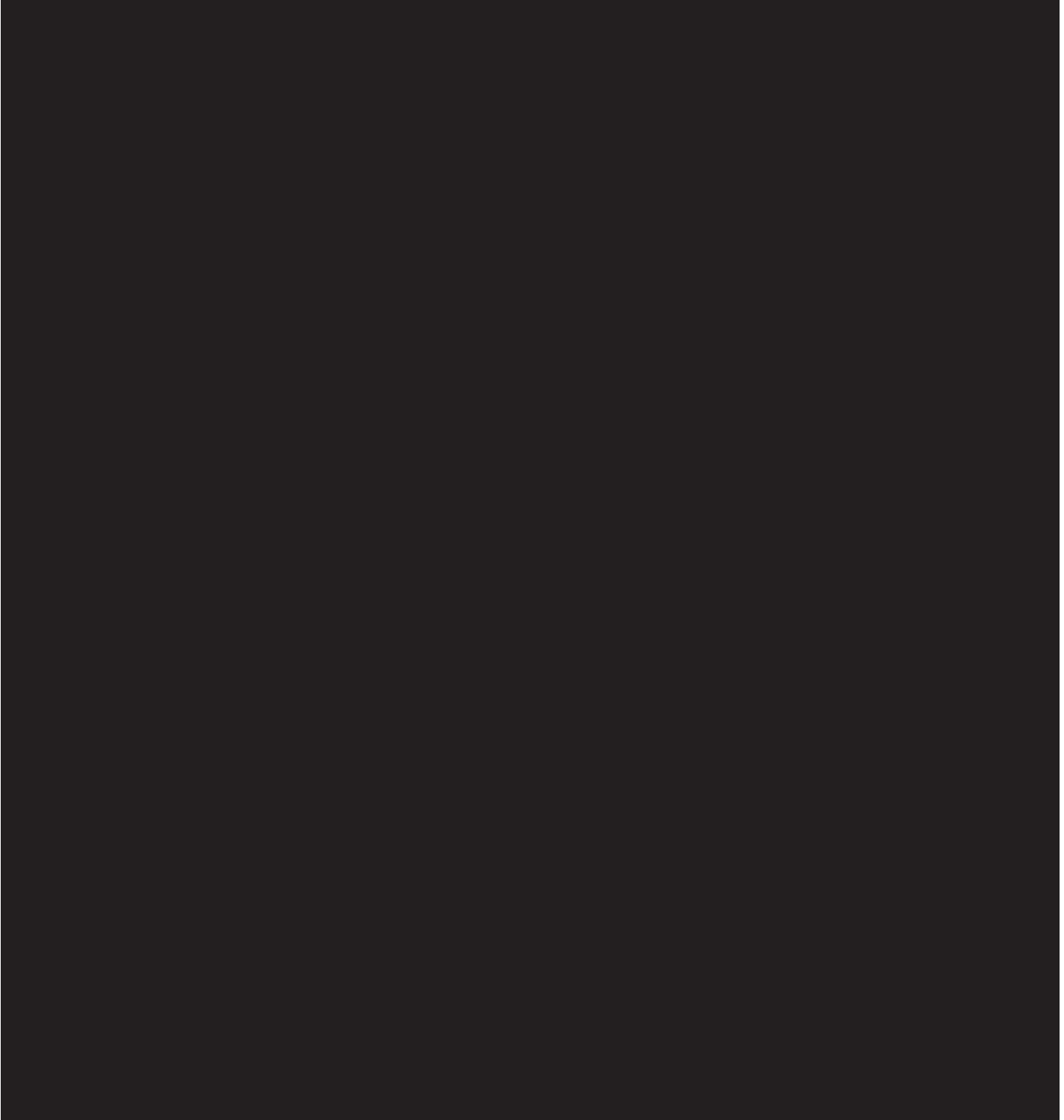
*Definitions of behavioral suicidal events in this scale are based on those used in **The Columbia Suicide History Form**, developed by John Mann, MD and Maria Oquendo, MD, Conte Center for the Neuroscience of Mental Disorders (CCNMD), New York State Psychiatric Institute, 1051 Riverside Drive, New York, NY, 10032. (Oquendo M. A., Halberstam B. & Mann J. J., Risk factors for suicidal behavior: utility and limitations of research instruments. In M.B. First [Ed.] Standardized Evaluation in Clinical Practice, pp. 103 -130, 2003.)*

For reprints of the C-SSRS contact Kelly Posner, Ph.D., New York State Psychiatric Institute, 1051 Riverside Drive, New York, New York, 10032; inquiries and training requirements contact posnerk@nyspi.columbia.edu

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| SUICIDAL IDEATION | | Since Last Visit | | |
|--|-------------------------|--|-------------------------|--|
| <p>Ask questions 1 and 2. If both are negative, proceed to "Suicidal Behavior" section. If the answer to question 2 is "yes", ask questions 3, 4 and 5. If the answer to question 1 and/or 2 is "yes", complete "Intensity of Ideation" section below.</p> | | | | |
| <p>1. Wish to be Dead Subject endorses thoughts about a wish to be dead or not alive anymore, or wish to fall asleep and not wake up. <i>Have you wished you were dead or wished you could go to sleep and not wake up?</i></p> <p>If yes, describe:</p> | | <p>Yes No</p> <p><input type="checkbox"/> <input type="checkbox"/></p> | | |
| <p>2. Non-Specific Active Suicidal Thoughts General, non-specific thoughts of wanting to end one's life/commit suicide (e.g., "I've thought about killing myself") without thoughts of ways to kill oneself/associated methods, intent, or plan during the assessment period. <i>Have you actually had any thoughts of killing yourself?</i></p> <p>If yes, describe:</p> | | <p>Yes No</p> <p><input type="checkbox"/> <input type="checkbox"/></p> | | |
| <p>3. Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act Subject endorses thoughts of suicide and has thought of at least one method during the assessment period. This is different than a specific plan with time, place or method details worked out (e.g., thought of method to kill self but not a specific plan). Includes person who would say, "I thought about taking an overdose but I never made a specific plan as to when, where or how I would actually do it...and I would never go through with it."</p> <p><i>Have you been thinking about how you might do this?</i></p> <p>If yes, describe:</p> | | <p>Yes No</p> <p><input type="checkbox"/> <input type="checkbox"/></p> | | |
| <p>4. Active Suicidal Ideation with Some Intent to Act, without Specific Plan Active suicidal thoughts of killing oneself and subject reports having some intent to act on such thoughts, as opposed to "I have the thoughts but I definitely will not do anything about them."</p> <p><i>Have you had these thoughts and had some intention of acting on them?</i></p> <p>If yes, describe:</p> | | <p>Yes No</p> <p><input type="checkbox"/> <input type="checkbox"/></p> | | |
| <p>5. Active Suicidal Ideation with Specific Plan and Intent Thoughts of killing oneself with details of plan fully or partially worked out and subject has some intent to carry it out. <i>Have you started to work out or worked out the details of how to kill yourself? Do you intend to carry out this plan?</i></p> <p>If yes, describe:</p> | | <p>Yes No</p> <p><input type="checkbox"/> <input type="checkbox"/></p> | | |
| INTENSITY OF IDEATION | | Most Severe | | |
| <p>The following features should be rated with respect to the most severe type of ideation (i.e., 1-5 from above, with 1 being the least severe and 5 being the most severe).</p> <p>Most Severe Ideation:</p> <table border="0"> <tr> <td>Type # (1-5)</td> <td>Description of Ideation</td> </tr> </table> | | Type # (1-5) | Description of Ideation | |
| Type # (1-5) | Description of Ideation | | | |
| <p>Frequency <i>How many times have you had these thoughts?</i> (1) Less than once a week (2) Once a week (3) 2-5 times in week (4) Daily or almost daily (5) Many times each day</p> | | — | | |
| <p>Duration <i>When you have the thoughts, how long do they last?</i> (1) Fleeting - few seconds or minutes (4) 4-8 hours/most of day (2) Less than 1 hour/some of the time (5) More than 8 hours/persistent or continuous (3) 1-4 hours/a lot of time</p> | | — | | |
| <p>Controllability <i>Could/can you stop thinking about killing yourself or wanting to die if you want to?</i> (1) Easily able to control thoughts (4) Can control thoughts with a lot of difficulty (2) Can control thoughts with little difficulty (5) Unable to control thoughts (3) Can control thoughts with some difficulty (6) Does not attempt to control thoughts</p> | | — | | |
| <p>Deterrents <i>Are there things - anyone or anything (e.g., family, religion, pain of death) - that stopped you from wanting to die or acting on thoughts of committing suicide?</i> (1) Deterrents definitely stopped you from attempting suicide (4) Deterrents most likely did not stop you (2) Deterrents probably stopped you (5) Deterrents definitely did not stop you (3) Uncertain that deterrents stopped you (6) Does not apply</p> | | — | | |
| <p>Reasons for Ideation <i>What sort of reasons did you have for thinking about wanting to die or killing yourself? Was it to end the pain or stop the way you were feeling (in other words you couldn't go on living with this pain or how you were feeling) or was it to get attention, revenge or a reaction from others? Or both?</i> (1) Completely to get attention, revenge or a reaction from others (4) Mostly to end or stop the pain (you couldn't go on living with the pain or how you were feeling) (2) Mostly to get attention, revenge or a reaction from others (5) Completely to end or stop the pain (you couldn't go on living with the pain or how you were feeling) (3) Equally to get attention, revenge or a reaction from others and to end/stop the pain (6) Does not apply</p> | | — | | |

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Appendix 6 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. 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 Hy's Law (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 adverse events (AE) and serious adverse events (SAE) 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) $\geq 3 \times$ upper limit of normal (ULN) together with total bilirubin (TBL) $\geq 2 \times$ 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 $\geq 3 \times$ ULN together with TBL $\geq 2 \times$ 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:

- $ALT \geq 3 \times ULN$
- $AST \geq 3 \times ULN$
- $TBL \geq 2 \times ULN$

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 Clinical Study Protocol.

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

FDA Guidance for Industry (issued July 2009) ‘Drug-induced liver injury: Premarketing clinical evaluation’:

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM174090.pdf>

| Document Name: d5670c00002-protocol-amendment-8 | | |
|--|---|------------------------------|
| Document Title: | d5670c00002-protocol-amendment-8 | |
| Document ID: | Doc ID-003324577 | |
| Version Label: | 1.0 Approved CURRENT LATEST | |
| Server Date (dd-MMM-yyyy HH:mm 'GMT'Z) | SignedBy | Meaning of Signature |
| 23-Sep-2016 15:36 GMT+0100 |  | Clinical Operations Approval |
| 23-Sep-2016 16:19 GMT+0100 |  | Medical Monitor Approval |
| 23-Sep-2016 16:37 GMT+0100 |  | Biostatistics Approval |
| 23-Sep-2016 16:51 GMT+0100 |  | Research Approval |
| 23-Sep-2016 17:27 GMT+0100 |  | Clinical Approval |
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Notes: (1) Document details as stored in ANGEL, an AstraZeneca document management system.