A Phase 2a Randomized, Blinded, Placebo-controlled Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Efficacy of MEDI0382 in Overweight/Obese Subjects with Type 2 Diabetes Mellitus

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

Medical Monitor: [redacted]

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PROTOCOL SYNOPSIS

TITLE

A Phase 2a Randomized, Blinded, Placebo-controlled Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Efficacy of MEDI0382 in Overweight/Obese Subjects with Type 2 Diabetes Mellitus

HYPOTHESES

Primary Hypothesis: Daily subcutaneous (SC) administration of ascending doses of MEDI0382, titrated weekly to the highest clinically tolerated dose (HCTD), will result in an acceptable safety/tolerability profile in overweight/obese subjects with type 2 diabetes mellitus (T2DM).

Secondary Hypothesis:

- Once daily SC administration of MEDI0382, titrated weekly to the HCTD, will have a predictable pharmacokinetic (PK) and immunogenic profile in overweight/obese subjects with T2DM.
- Administration of MEDI0382 titrated weekly to the HCTD, will result in clinically relevant improvement in blood glucose control in overweight/obese subjects with T2DM.
- Administration of MEDI0382 titrated weekly to the HCTD, will result in clinically relevant body weight loss versus placebo in overweight/obese subjects with T2DM.

OBJECTIVES AND ENDPOINTS

Primary Objective(s) and Associated Endpoints

Objective	Endpoint
Assess the safety and tolerability of MEDI0382 titrated up to the highest clinically tolerated dose (HCTD)	• Incidence of treatment-emergent adverse events (TEAEs) and treatment-emergent serious adverse events (TESAEs) through the end of the up-titration period (up to 8 weeks) and through the end of the follow-up period • Clinically important changes in 12-lead electrocardiogram (ECG), vital signs (including heart rate and blood pressure), physical examination, and clinical laboratory evaluations through the end of up-titration period (up to 8 weeks) and through the end of the follow-up period

Secondary Objective(s) and Associated Endpoints

Objective	Endpoint
To characterize the PK profile of MEDI0382 titrated up to the HCTD	• Area under the concentration-time curve (AUC) over a dosing duration (AUC_{tau}), maximum observed concentration (C_{max}), time to C_{max} (T_{max}), trough plasma concentration (C_{trough}), and accumulation ratio (C_{min} [R_0])
To characterize the immunogenicity of MEDI0382 titrated up to the HCTD	• Anti-drug antibodies (ADAs) to MEDI0382 at baseline through end of study

[redacted]	• [redacted]
To assess the effects of MEDI0382, titrated up to the HCTD, on additional measures of glucose control	• Change in fasting plasma glucose from Day -1 versus each week of the up-titration period, the end of the up-titration period, and the end of the treatment extension period • Change in HbA1c from Day -1 to the end of the treatment extension period
To assess the effects of MEDI0382, titrated up to the HCTD, on body weight	• Percentage and absolute change in body weight from baseline to the end of the up-titration period and the end of the treatment extension • Percentage and absolute change in body weight from baseline to the end of each week of the up-titration period • Proportion of subjects achieving > 5% body weight loss from baseline to the end of the treatment extension period.

[redacted]

STUDY DESIGN

This is a randomized, blinded, placebo-controlled study designed to evaluate the safety, tolerability, PK and efficacy of ascending doses of MEDI0382 in overweight or obese subjects with T2DM. This study will enroll subjects aged 18 to 74 years with a body mass index (BMI) ≥ 27 and ≤ 35 kg/m2. Subjects will have a diagnosis of T2DM and inadequate blood glucose control as defined by an HbA1c of 6.5% to 8.5%, and will be on metformin monotherapy. Subjects prescribed oral dual therapy with a dipeptidyl peptidase-4 inhibitor, sulphonylurea, glitinide, or a sodium-glucose co-transporter 2 inhibitor in addition to metformin at screening may be eligible to enter the study in Cohort 2 only following a 4-week washout period.

Twenty subjects will be enrolled to 2 cohorts: Cohort 1 (n = 8) and Cohort 2 (n = 12). For each cohort, subjects will be randomly assigned in a 3:1 ratio to receive MEDI0382 at doses titrated to a [redacted] or placebo. The study has a run-in period of 10 days and an up to 8-week up-titration treatment period (for the primary analysis) followed by a 3-week treatment extension period at the HCTD followed by a 28-day follow up period.

In Cohort 1, MEDI0382 or matched placebo will be administered daily starting at [redacted]

Subjects will be asked to provide informed consent before undergoing screening assessments to determine their eligibility to participate in the study. Consent may be collected at a visit prior to performing the assessments themselves. Screening will take place within 14 days of subjects starting a 10-day run-in period. The screening period may be extended to up to 42 days for those subjects who are undergoing wash-out from a second anti-hyperglycemic agent. During the run-in period, subjects will refrain from taking prohibited medications but will continue to take their prescribed stable dose of metformin as they will for the duration of their participation in the study. [redacted] may receive further training in self-injection technique if required, as determined at the screening visit. An ambulatory blood pressure monitoring (ABPM) device will be fitted and worn for 24 hours.

Following the run-in period, subjects will be admitted to the clinical unit on Day -2 and will undergo initial safety assessments and blood tests. At this time, an ABPM device will be fitted and worn for 24 hours; [redacted]. Subjects will be weighed on the morning of Day -1, and further blood tests and a series of ECGs will be conducted. Subjects will eat a standardized, breakfast, lunch, and evening meal at given times without consuming any other food until the following day. Eligibility criteria will also be reverified prior to dosing. Subjects will be randomized at any time from Day -1 to prior to receiving a MEDI0382 or placebo dose on Day 1.

Each dosing period consists of 7 days of dosing and will begin on Day 1. On Day 1, dosing will begin after predose safety assessments including vital signs, blood tests, and an ECG. [redacted] will require a dilution by site staff prior to administration, subjects will have the option to remain as inpatients or alternatively attend the clinical unit daily for dosing and other assessments as applicable during the first two weeks. During this time, subjects will undergo supervision to self-administer the investigational product. If the subject returns on a daily basis, the visits should be at approximately the same time each day. Investigational

product should be administered within 24 to 28 hours post the last dose. On the morning of Days 7 and 14, subjects not still residing in the clinical unit will be admitted to undergo blood samples for PK, and fitting of the ABPM device that is worn for 24 hours. On Days 8 and 15, safety assessments will be performed and an up-titration step made as per the randomization. Subjects who elect to remain as inpatients will be discharged home following completion of the Day 15 visit. Subjects will attend the clinical unit thereafter as indicated in the schedule of events.

On Day 35 subjects will be admitted to the clinic, for PK and safety assessments prior to up-titration [redacted] the following day, then remaining in-house for approximately 24 hours for safety and efficacy assessments. This inpatient period will be repeated on Days 42 and 49 and will include up-titration to [redacted]; subject to the findings of the DEC who will review 72 hours safety data at each of these dose levels. Subjects will return to the clinic following an overnight fast as an outpatient to undergo PK sampling and fitting of the ABPM device on Day 56, subject to continued dose escalation and will be discharged on the first day of the treatment extension period.

After the initial titration period to determine the HCTD, subjects will continue at the HCTD for a further 3 weeks, returning to the clinical unit at Days 7 (for an outpatient visit) and Days 20-21 (for an inpatient visit) of the treatment extension for safety and efficacy assessments and resupply of investigational product as required. A follow up visit will be performed for final safety assessments 28 days after the last dose of investigational product or as convenient in the event of discontinuation.

Subjects in Cohort 2 will follow the up-titration schedule defined by Cohort 1, with the 3-week treatment extension period being conducted at the HCTD; thus, the duration of Cohort 2 subjects' participation in the study will be determined by the results obtained from Cohort 1. Dosing in Cohort 2 will occur ≥ 7 days after initiation of Cohort 1.

TARGET SUBJECT POPULATION

Overweight or obese subjects with T2DM, aged ≥ 18 ≤ 74 years with a BMI ≥ 27 and ≤ 35 kg/m2. Subjects will have a diagnosis of T2DM and inadequate blood glucose control as defined by an HbA1c of 6.5% to 8.5%, and will be on metformin monotherapy.

TREATMENT GROUPS AND REGIMENS

MEDI0382 will be administered for up to 8 weeks during the up-titration period to determine the HCTD as follows:

STATISTICAL METHODS

Sample size: The total study sample size is 20 subjects, who will be randomized by 2 cohorts: 8 subjects in Cohort 1 and 12 subjects in Cohort 2. For each cohort, subjects will be randomized in a 3:1 ratio to the MEDI0382 arm or the placebo arm. The sample size for this study was empirically determined to obtain adequate safety and tolerability evaluation. [redacted]

Statistical analyses:

Two analyses are planned for this study as follows:

- A primary analysis after the up-titration period for Cohort 2, and
- A final analysis after the safety follow-up period for Cohort 2.

Analyses will be conducted for each cohort and for two cohorts combined. Formal statistical modeling analysis for certain efficacy endpoints will only be conducted for two-cohort combined analyses.

Pharmacokinetic analysis and immunogenicity:

PK parameters such as MEDI0382 C_{max}, T_{max}, and area under the concentration-time curve during the dosing interval ($AUC_{0\text{-}tau}$) will be evaluated from [redacted] Descriptive statistics including mean, standard deviations, median, minimum, and maximum will be generated for all PK parameters for MEDI0382 at each dose level separately, and for the $C_{troughs}$. Samples confirmed positive for ADA will be tested and analyzed for antibody titer and reported. ADA incidence rate and titer will be tabulated for each treatment.

[redacted]

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LIST OF ABBREVIATIONS

Abbreviation or Specialized Term	Definition
ABPM	ambulatory blood pressure monitoring
ADA	anti-drug antibody
AE	adverse event
AESI	adverse event of special interest
ALP	alkaline phosphatase
ALT	alanine transaminase
AST	aspartate transaminase
AUC	area under the concentration-time curve
AV	atrioventricular
BMI	body mass index
BP	blood pressure
[redacted]	[redacted]
CI	confidence interval
C_{max}	maximum observed concentration
C_{trough}	trough plasma concentration
CSR	Clinical Study Report
DEC	dose escalation committee
DILI	drug-induced liver injury
ECG	electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
E-R	exposure-response
GCP	Good Clinical Practice
GI	gastrointestinal
GFR	glomerular filtration rate
GLP-1	glucagon-like peptide 1
HbA1c	hemoglobin A1c
hCG	human chorionic gonadotropin
HCTD	highest clinically tolerated dose
HIV	human immunodeficiency virus
IB	Investigator's Brochure
ICH	International Council on Harmonisation

Abbreviation or Specialized Term	Definition
IEC	Independent Ethics Committee
LC-MS/MS	liquid chromatography-tandem mass spectrometry
MDRD	Modification of Diet in Renal Disease
MedDRA	Medical Dictionary for Regulatory Activities
MMTT	mixed meal tolerance test
NASH	non-alcoholic steatohepatitis
NOAEL	no-observed-adverse-effect-level
PK	pharmacokinetic(s)
PT	preferred term
SAE	serious adverse event
SC	subcutaneous
SID	subject identification
SOC	system organ class
T2DM	type 2 diabetes mellitus
TBL	total bilirubin
TEAE	treatment-emergent adverse event
T_{max}	time to maximum observed concentration
ULN	upper limit of normal
w/v	weight/volume

1 INTRODUCTION

1.1 Disease Background

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

1.2 MEDI0382 Background

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

MEDI0382, a synthetic oxyntomodulin-like peptide with targeted glucagon-like peptide 1 (GLP-1) and glucagon receptor activity, is under development for the treatment of T2DM, obesity, and non-alcoholic steatohepatitis (NASH). GLP-1 receptor agonists are established treatments for T2DM that improve glycemic control, delay gastric emptying, and depress appetite leading to modest, but often non-sustained weight loss (typically 3% versus baseline at one year). Glucagon has similar effects to GLP-1 on gastric emptying and appetite, and has also been shown to promote increased energy expenditure (Habegger et al, 2013; Lynch et al, 2014). Oxyntomodulin, a naturally occurring peptide with GLP-1 and glucagon receptor co-agonist activity, has been shown to promote weight loss through effects on appetite and energy expenditure (Wynne et al, 2006). Co-infusion of GLP-1 and glucagon has synergistic effects on reducing food intake and promoting weight loss in human subjects (Cegla et al, 2014). MEDI0382 has previously delivered significant metabolic benefit to overweight and obese patients with T2DM over a relatively short period of dosing in a Phase 1/2 clinical study (D5670C00002) (Ambery et al, 2018).

1.3 Summary of Nonclinical Experience

Consistent with GLP-1 receptor monoagonists, MEDI0382 exposure in both rats and cynomolgus monkeys resulted in the anticipated pharmacologic effects on body weight (reduced gain or loss), food consumption (sporadic reductions), water consumption (low throughout dosing periods), gastric emptying (delayed in rats), liver (changes indicative of an effect on energy homeostasis in both species), pancreas (hypercellularity of the pancreatic islets and acinar degranulation), adrenal glands (increased prominence of the zona glomerulosa), and lungs (increased macrophage in rats only). [redacted]

Refer to the current MEDI0382 IB for a complete summary of nonclinical information.

1.4 Summary of Clinical Experience

In a randomized Phase 1/2 study of MEDI0382 in overweight/obese subjects with T2DM (D5670C00002), treatment with MEDI0382 at doses ≤ 200 µg for 41 days, including two 4-day titration steps at 100 µg (starting dose) and 150 µg, was associated with a reduction in a mixed meal tolerance test (MMTT) glucose area under the concentration-time curve (AUC) from time zero to 4 hours ($AUC_{0\text{-}4h}$) of 32.78% (90% confidence interval [CI] 36.98, 28.57) versus 10.16% (90% CI 14.10, 6.21) in placebo ($p < 0.001$). A reduction in body weight of 4.12% (90% CI 4.48, 3.36) in MEDI0382-treated subjects versus 1.78% (90% CI 2.52, 1.03) in placebo ($p < 0.001$) was also observed at this dose level. The majority of subjects experienced at least 1 treatment-emergent adverse event (TEAE), and the most frequent TEAEs were gastrointestinal (GI)-related. The most frequently reported TEAEs (> 30%) in subjects receiving MEDI0382 were nausea (52%), vomiting (32%), and headache (36%). The majority of TEAEs were mild or moderate in severity.

Additional cohorts in the same study were treated with MEDI0382 at ≤ 300 µg for 7 days following either three (Cohort 5) or two (Cohort 6) 5-day titration steps from a starting dose of 100 µg. A reduction in MMTT glucose AUC of 41.7% and 36.7% was observed following treatment with MEDI0382 in Cohorts 5 and 6, respectively, whereas treatment with placebo yielded a decrease of 14.5% and 8.0%, respectively ($p \leq 0.0001$ for each). A decrease in body weight versus placebo was observed in Cohorts 5 and 6 with a least squares mean change from baseline of -3.4 kg (90% CI -4.4, -2.4) and -2.1 kg (90% CI -3.3, -0.9), respectively in MEDI0382-treated subjects versus -0.68 kg (90% CI -2.2, 0.9) and -0.86 (90% CI -2.7, 1.0), respectively, in placebo. The titration regimens of both cohort 5 and 6 were tolerated with 82% and 83% of subjects, respectively, reporting at least 1 treatment-related adverse event (AE); none of the treatment-related AEs were ≥ grade 3 or serious. In Cohort 5, 72.7% of subjects treated with MEDI0382 reported GI-related AEs, with 27.3% reporting at least 1 event of nausea and 27.3% at least 1 event of vomiting. In Cohort 6, 75% of subjects treated with MEDI0382 reported GI-related AEs, with 41.7% reporting at least 1 event of nausea and 8.3% at least 1 event of vomiting.

Refer to the current MEDI0382 IB for a complete summary of clinical information.

1.5 Rationale for Conducting the Study

Ongoing clinical Phase 2a and 2b studies (D5670C00011 and D5670C00004) are investigating MEDI0382 doses at ≤ 300 µg for up to 24 months in subjects with T2DM. This study will evaluate the safety and tolerability of higher doses of MEDI0382 [redacted] than previously studied, and the impact of starting at a lower dose [redacted] resulting in a slower titration regimen, on the tolerability profile.

Current experience with marketed GLP-1 receptor agonists (eg, liraglutide) (Habegger et al, 2013; Henderson et al, 2016) suggests that exposure to higher doses may be associated with greater extent and durability of weight loss (Astrup et al, 2009; Davies et al, 2015). This may be particularly true of GLP1/glucagon dual receptor agonists where the glucagon agonist component is likely to drive incremental weight loss over time (Habegger et al, 2013; Henderson et al, 2016). Thus, it is anticipated that higher doses of MEDI0382 will achieve greater weight loss over a given period with the potential to impact insulin resistance and further improve glucose control. This study will explore the safety and tolerability of higher doses of MEDI0382 (to determine the highest clinically tolerated dose (HCTD), which can then be studied in future long-term efficacy studies as a potential maintenance dose.

It is also known from currently available GLP-1 monoagonists that a controlled up-titration regime is associated with improved tolerability. This study will therefore also explore the effect of starting at a lower starting dose of MEDI0382 than has previously been studied, on tolerability, particularly in relation to GI side effects. This will allow the identification of the optimal titration regime for further exploration in future studies.

1.6 Benefit-Risk and Ethical Assessment

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

MEDI0382 is a GLP-1 receptor and glucagon receptor co-agonist that promotes glucose lowering and weight loss and is targeted at subjects with T2DM. MEDI0382 has the potential to deliver improvements in glycemic control and body weight, and is anticipated to be a useful therapy for T2DM. However, it should be noted that given the short treatment duration in this study little direct benefit to the subject's underlying T2DM should be expected.

Potential risks for MEDI0382 are based on available published data for GLP-1 receptor monoagonists and glucagon receptor monoagonists, as well as clinical and nonclinical data for MEDI0382. Identified risks for MEDI0382 are nausea and vomiting. According to the current IB, potential risks for MEDI0382 include tachycardia, alterations in blood pressure (BP), QT-interval prolongation, anaphylactic-type reactions, injection site reactions, skin rash, pancreatitis, pancreatic carcinoma, and thyroid cancer. The study design aims to minimize potential risks to subjects participating in this study based on the proposed inclusion/exclusion criteria, safety monitoring, and up-titration dosing schedule. Additionally, all subjects will be monitored throughout the study to ensure adequate glycemic control.

Since nausea and vomiting events have been observed in other clinical studies with MEDI0382 and are known class effects associated with marketed GLP-1 receptor agonists, the

study protocol includes strategies to manage GI AEs if they arise. These include reduction of meal sizes, maintaining adequate hydration, and treating the subjects with antiemetics if required. To further mitigate the GI AEs, subjects enrolled in this study will initiate treatment with MEDI0382 at a dose level of [redacted] thus introducing two additional titration steps not previously used.

The investigator will provide a summary of available, relevant, clinical safety data to the medical monitor/sponsor, which will form part of the package of information the Dose Escalation Committee (DEC) will review to make escalation decisions. More information on the DEC can be found in the DEC charter.

Refer to the current IB for further information on the potential benefits of MEDI0382 and an assessment of the potential and known risks.

1.7 Research Hypotheses

1.7.1 Primary Hypothesis

Daily SC administration of ascending doses MEDI0382, titrated weekly to the HCTD will result in an acceptable safety/tolerability profile in overweight/obese subjects with T2DM.

1.7.2 Secondary Hypotheses

- Once daily SC administration of MEDI0382, titrated weekly to the HCTD, will have a predictable pharmacokinetic (PK) and immunogenic profile in overweight/obese subjects with T2DM.

- Once daily SC administration of MEDI0382 titrated weekly to the HCTD, will result in clinically relevant improvement in blood glucose control versus placebo in overweight/obese subjects with T2DM.
- Once daily administration of MEDI0382 titrated weekly to the HCTD, will result in clinically relevant body weight loss versus placebo in overweight/obese subjects with T2DM.

2 OBJECTIVES AND ENDPOINTS

2.1 Primary Objective(s) and Associated Endpoints

Table 1 Primary Objective(s) and Associated Endpoints

Type	Objective	Endpoint
Safety	Assess the safety and tolerability of MEDI0382 titrated up to the highest clinically tolerated dose (HCTD)	• Incidence of treatment-emergent adverse events and treatment-emergent serious adverse events through the end of the up-titration period (up to 8 weeks) and through the end of the follow-up period • Clinically important changes in 12-lead electrocardiogram, vital signs (including heart rate and blood pressure), physical examination, and clinical laboratory evaluations through the end of up-titration period (up to 8 weeks) and through the end of the follow-up period

2.1.1 Secondary Objectives and Associated Endpoints

Table 2 Secondary Objective(s) and Associated Endpoints

Type	Objective	Endpoint
PK	To characterize the pharmacokinetic (PK) profile of MEDI0382 titrated up to the highest clinically tolerated dose (HCTD)	• AUC over a dosing duration (AUC_{tau}), maximum observed concentration (C_{max}), time to C_{max} (T_{max}), trough plasma concentration (C_{trough}), and accumulation ratio (C_{min} [R_0])
Immunogenicity	To characterize the immunogenicity of MEDI0382 titrated up to the HCTD	• Anti-drug antibodies (ADAs) to MEDI0382 at baseline through end of study

Table 2 Secondary Objective(s) and Associated Endpoints

Type	Objective	Endpoint
[redacted]	[redacted]	[redacted]
Efficacy	To assess the effects of MEDI0382, titrated up to the HCTD, on additional measures of glucose control	• Change in plasma fasting glucose from Day -1 versus each week of the up-titration period, the end of the up-titration period, and the end of the treatment extension period • Change in HbA1c from Day -1 to the end of the treatment extension period
Efficacy	To assess the effects of MEDI0382, titrated up to the HCTD, on body weight	• Percentage and absolute change in body weight from baseline to the end of the up-titration period and the end of the treatment extension • Percentage and absolute change in body weight from baseline to the end of each week of the up-titration period

Table 2 Secondary Objective(s) and Associated Endpoints

Type	Objective	Endpoint
		• Proportion of subjects achieving > 5% body weight loss from baseline to the end of the treatment extension period.

[redacted]

3 STUDY DESIGN

3.1 Description of the Study

3.1.1.1 Overview

This is a randomized, blinded, placebo-controlled study designed to evaluate the safety, tolerability, PK and efficacy of ascending doses of MEDI0382 in overweight or obese subjects with T2DM. This study will enroll subjects aged ≥ 18 and ≤ 74 years with a body mass index (BMI) ≥ 27 and ≤ 35 kg/m^2. Subjects will have a diagnosis of T2DM and inadequate blood glucose control as defined by a hemoglobin A1c (HbA1c) of 6.5% to 8.5%, and will be on metformin monotherapy. Subjects prescribed oral dual therapy with a dipeptidyl peptidase-4 inhibitor, sulphonylurea, glitinide, or a sodium-glucose co-transporter 2 inhibitor in addition to metformin at screening may be eligible to enter the study in Cohort 2 only following a 4-week washout period.

[redacted]

[redacted]

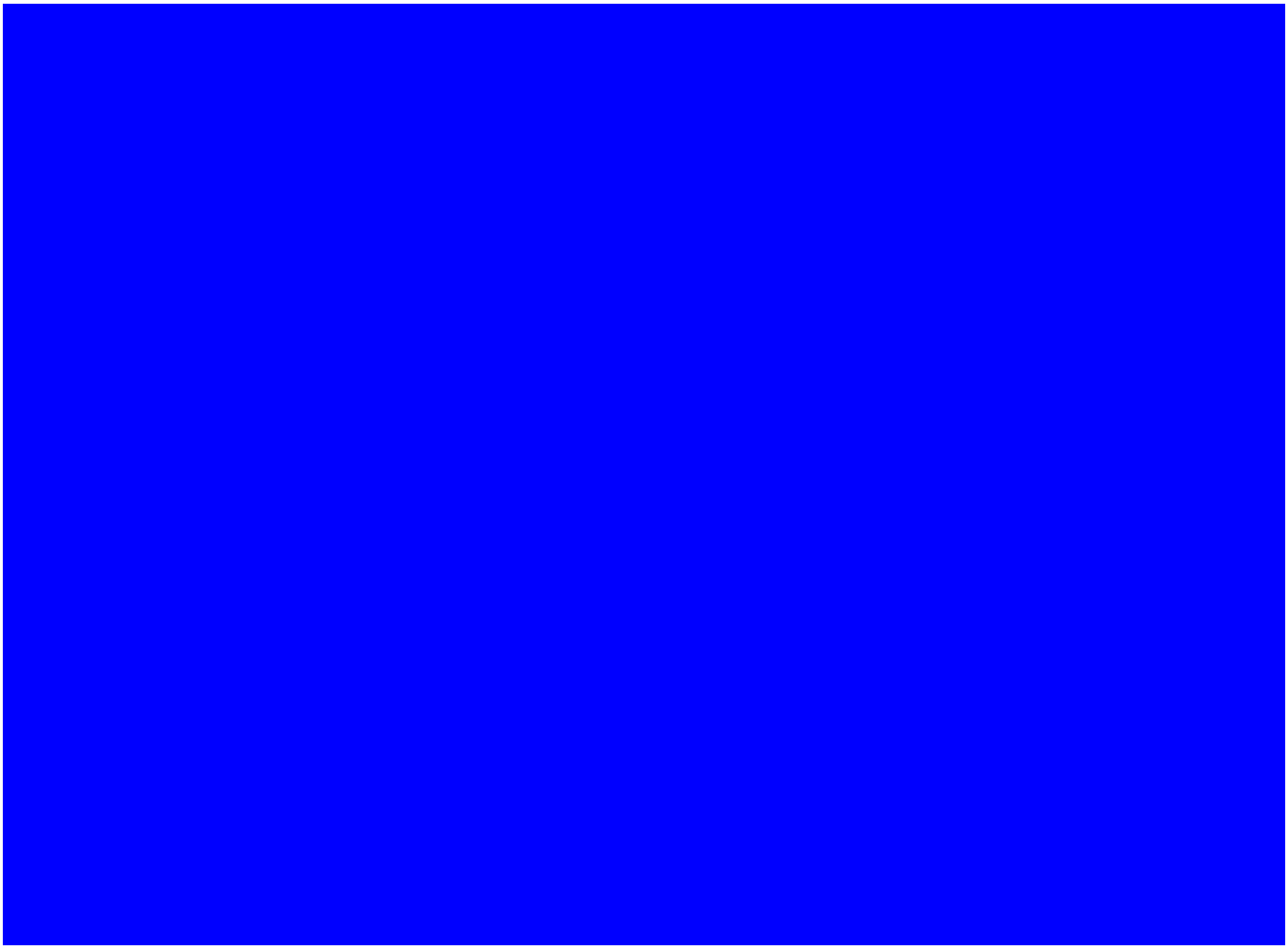
Subjects will be asked to provide informed consent before undergoing screening assessments to determine their eligibility to participate in the study. Screening will take place within 14 days of subjects starting a 10-day run-in period. The screening period may be extended to up to 42 days for those subjects who are undergoing wash-out from a second anti-hyperglycemic agent. During the run-in period, subjects will refrain from taking prohibited medications but will continue to take their prescribed stable dose of metformin as they will for the duration of their participation in the study. [redacted], and may receive further training in self injection technique if required, as determined at the screening visit. An ambulatory blood pressure monitoring (ABPM) device will be fitted and worn for 24 hours.

Following the run-in period, subjects will be admitted to the clinical unit on Day -2 and will undergo initial safety assessments and blood tests. At this time, an ABPM device will be fitted and worn for 24 hours; [redacted] Subjects will be expected to wear a sensor continuously until the end of the study, which will require periodic replacement. Following an overnight fast, subjects will be weighed on the morning of Day -1, and further blood tests and a series of electrocardiograms (ECGs) will be conducted. Subjects will eat a standardized, breakfast, lunch, and evening meal at given times without consuming any other food until the following day. Eligibility criteria will also be reverified prior to dosing. Subjects will be randomized at any time from Day -1 to prior to receiving a MEDI0382 or placebo dose on Day 1.

[redacted]

After the initial titration period to determine the HCTD, subjects will continue at the HCTD for a further 3 weeks, returning to the clinical unit at Day 7 (for an outpatient visit) and Days 20-21 (for an inpatient visit) of the treatment extension for safety and efficacy assessments and resupply of investigational product as required. A follow-up visit will be performed for final safety assessments 28 days after the last dose of investigational product or as convenient in the event of discontinuation.

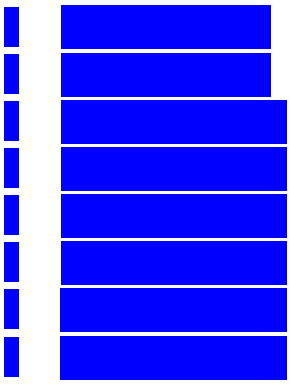
Subjects in Cohort 2 will follow the up-titration schedule defined by Cohort 1, with the 3-week treatment extension period being conducted at the HCTD; thus, the duration of Cohort 2 subjects' participation in the study will be determined by the results obtained from Cohort 1. Dosing in Cohort 2 will occur ≥ 7 days after initiation of Cohort 1.



3.1.2 Treatment Regimen

Following randomization, eligible subjects will receive either MEDI0382 or placebo (3:1 ratio) once daily in the morning via SC injection.

MEDI0382 will be administered for up to 8 weeks during the up-titration period to determine the HCTD as follows:



[redacted]

3.1.3 Dose Escalation

[redacted] If progression to the next dose level is not endorsed by the DEC, the prior dose level will be declared as the HCTD. Subjects will be down titrated to the HCTD on the next feasible dosing day and complete the 7-day dosing period at that level. The 3-week treatment extension will be triggered from the end of that 7-day dosing period.

More detailed information on dose escalation can be found in the DEC charter.

3.1.3.1 Dose Escalation Committee

A DEC will be formed for safety data review and monitoring. The DEC will also make decisions on progression to treatment at a higher dose or on meeting dose escalation stopping criteria as outlined in the DEC Charter.

Relevant available safety data will be reviewed at the DEC meeting for subjects at the current dose period as well as the cumulative safety data (including data that are not yet source document verified such as laboratory values, AEs, ECG, and vital signs) to date, to make an informed decision on whether to dose escalate or not.

After reviewing the data from a given dose period, the DEC will make one of the following decisions:

- Escalate to the next dose level
- Stop dose escalation and proceed to 3-week treatment extension at the HCTD.

- Request for review and decision by the MedImmune Safety Review Board on how to proceed, or whether to suspend or stop the study.

The rules for dose escalation are discussed in Section 3.1.3.2.

3.1.3.2 Dose Escalation Stopping Criteria

Dose escalation will be stopped if the DEC determines that any of the following criteria are met.

- More than 50% of subjects treated with MEDI0382 in a specific dose period experience grade 2 or higher AEs assessed as related to MEDI0382 and require discontinuation of MEDI0382
- One serious adverse event (SAE) occurs in a MEDI0382 subject that is assessed as related to MEDI0382
- Two or more subjects receiving MEDI0382 experiences any of the following:
  - An average absolute (regardless of baseline value) cardiac QTc interval corrected for heart rate by the formula of Fridericia (QTcF) > 500 msec, or an increase of QTcF > 60 msec above the baseline value, confirmed (persistent for ≥ 5 minutes) on a repeat 12-lead ECG
  - Tachycardia, defined as resting supine heart rate > 125 beats per minute persisting for at least 10 minutes (measured at 5 timepoints in the 10-minute period)
  - Symptomatic bradycardia, defined as resting supine heart rate < 40 beats per minute while awake, persisting for at least 10 minutes; or asymptomatic bradycardia defined as resting supine heart rate < 30 beats per minute while awake persisting for at least 10 minutes (measured at 5 timepoints in the 10-minute period)
  - Hypertension, defined as an increase from baseline in resting supine systolic blood pressure (BP) > 40 mmHg or above 180 mmHg and persisting for at least 10 minutes, or an increase from baseline in resting supine diastolic BP > 20 mmHg or above 100 mmHg and persisting for at least 10 minutes
- The above cardiac criteria do not apply if provoked by complicated venepuncture or other vagal provocation

If any of these criteria are met, then the DEC will either:

- Recommend that the study proceed to 3-week treatment extension at the HCTD, or
- Request for review and decision by the MedImmune Safety Review Board on how to proceed or whether to suspend or stop the study

3.1.4 Management of Study Medication Related Toxicities

GI Tolerability

In this study, dose escalation may be limited by GI tolerability, specifically with respect to nausea and vomiting

Prior to receiving investigational product, subjects will be advised that transient nausea and vomiting are possible and will receive counseling about meal size and eating habits. Specifically, subjects will be advised to avoid administering the medication close to a large or high-fat meal; to consume small, frequent meals 4 to 5 times a day that are low in fat and insoluble fibers; and to stop eating when they are feeling full. Subjects will also be advised to avoid carbonated beverages, alcohol, and smoking to help prevent the occurrence of nausea and vomiting. This advice should be reiterated should symptoms of nausea and vomiting occur once investigational product dosing has initiated. If symptoms do not improve despite a change of dietary habits, metformin may be withheld for 3 days, or alternatively, subjects should be offered antiemetic therapy in accordance with institutional and local practice guidelines. A centrally acting antiemetic such as a 5HT-3 antagonist (eg, ondansetron) or cyclizine is the preferred treatment in the first instance, rather than a prokinetic agent such as domperidone or metoclopramide.

Hyperglycemia

In the unlikely event of suspected persistent hyperglycemia in a subject based on either symptoms of hyperglycemia (eg, thirst, polyuria, blurred vision), capillary blood glucose readings (eg, 3 readings > 260 mg/dL [14.4 mmol/L] within one week), the investigator should perform additional fasting blood glucose levels as necessary to further investigate, and subjects should be asked to monitor capillary plasma glucose levels up to 5 times per day. If 2 or more laboratory plasma fasting glucose levels of > 260 mg/dL [14.4 mmol/L] taken at least 3 days apart are detected, the subject should be discontinued from the study (Section 4.1.6), and rescue therapy should be considered in line with current local guidelines.

Hypoglycemia

Any blood glucose level 54 mg/dL (< 3.0 mmol/L) with or without symptoms is considered as clinically significant hypoglycemia and should be reported by the Investigator as an AE. Spontaneous and clinically significant hypoglycemia has not been observed in prior studies with MEDI0382 up to a dose of 300 µg alongside metformin treatment. All subjects will be provided with a glucometer and will be advised to check their capillary blood glucose level if they have symptoms of hypoglycemia (hunger, dizziness, shaking, sweating, or irritability) or feel unwell. Any such subjects should be managed using local protocols for treatment and follow-up of any hypoglycemic episode. Pharmacological treatments administered for hypoglycemia, eg, dextrose/glucose tablets, glucose infusion, glucagon injection etc, should be recorded in the electronic case report form (eCRF) as concomitant medications.

3.2 Rationale for Dose, Population, and Endpoints

3.2.1 Dose Rationale

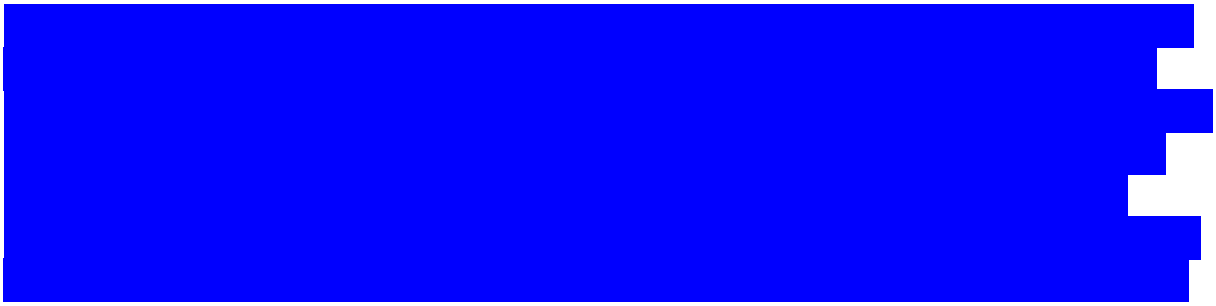
Based on PK/pharmacodynamic (PD) modeling conducted using available clinical literature data on GLP-1 and glucagon receptor modulators, the clinically efficacious dose of

MEDI0382 was predicted to be in the range of 300 to 2000 µg/day; however, clinical data from Study D5670C00001 identified dose-limiting tolerability issues (multiple episodes of vomiting) at the 300 µg dose administered as a single dose without initial up-titration. The principle of dose up-titration to achieve greater tolerability at higher than initial doses was well established with daily GLP-1 agents (Victoza, 2016). Studies of other GLP-1 receptor agonists suggest that the maximal dose response with respect to weight loss may be seen at higher doses in comparison to those at which maximal reduction in blood glucose is achieved (Davies et al, 2015; Nauck and Marre, 2009). This is particularly true of GLP-1/glucagon dual agonists where the glucagon agonist component is likely to drive incremental weight loss over time, and confer accompanying improvements in glycemic control (Henderson et al, 2016).

This study is designed to explore both the appropriate dose titration schedule for repeated doses of MEDI0382 and the highest clinically tolerated repeat-dose in subjects with T2DM. Therefore, the proposed dose range allows characterization of the safety/tolerability profile of MEDI0382 at a relevant pharmacological range and facilitates design of future studies.

The no-observed-adverse-effect-level (NOAEL) of 90 µg/kg/day was based on findings in the 9-month, daily repeat dose SC toxicology study in the cynomolgus monkey. These were considered to be consistent with pharmacology-mediated induction of weight loss/lower weight gain, reversible changes in the pancreas (acinar degranulation and hypercellularity of the pancreatic islets), and changes in energy utilization and associated metabolic stress (minor changes in blood chemistry parameters, lower thymus weights). Treatment was also associated with changes in the skin (dermal irritation, acanthosis and hyperkeratosis) in 3 of 4 female cynomolgus monkeys dosed.

While the NOAEL determined in the rat 6-month, daily repeat dose SC toxicology study (ie, 7.5 µg/kg/day) was lower than that in the cynomolgus monkey, this was driven primarily by the findings in the thyroid gland (C-cell hyperplasia, adenoma, and carcinoma) that were considered, in this species, to be adverse. This is a known class effect with GLP-1 receptor agonists that is considered rodent specific and of unknown relevance to humans (Center for Drug Evaluation and Research, 2005). Therefore cynomolgus monkey, and the toxicity profile of MEDI0382 generated in that species, are considered to be the most appropriate non-clinical species to use for clinical risk assessment and the setting of safety margins.



[redacted]

3.2.2 Rationale for Study Population

MEDI0382 is a synthetic oxyntomodulin-like peptide with targeted GLP-1 and glucagon receptor activity, which relies upon glucose-dependent insulin release (the incretin effect) for glucose lowering efficacy, and is therefore targeted at subjects with T2DM.

Adult subjects with T2DM who are overweight or obese are likely to benefit most from losing weight. While subjects with a BMI > 40 kg/m^2, or > 35 kg/m^2 with 1 or more obesity-related comorbidity may be offered bariatric surgery, those with a BMI in the range of 27-35 kg/m^2 rely upon conservative or medical management for weight reduction. The entry criteria with respect to T2DM and BMI of 27-35 kg/m^2 creates a more homogeneous population than has been studied previously, limiting the potential effect of exposure on tolerability, while generating safety, and tolerability data in the likely intended clinical population.

3.2.3 Rationale for Endpoint(s)

3.2.3.1 Primary Endpoint

In a previous study (D5670C00002), repeat doses of MEDI0382 ≤ [redacted] have been shown to have an acceptable tolerability and safety profile. However, this study is the first to explore higher doses of MEDI0382 [redacted] in the T2DM population. Therefore, it is appropriate that safety and tolerability represent the primary endpoint. Safety and tolerability will be measured with safety laboratory tests, physical examination, ABPM recording of heart rate and BP, ECG and other vital signs, and recording of AEs.

3.2.3.2 Secondary Endpoints

Pharmacokinetic and Immunogenicity Profile

Plasma concentrations of MEDI0382 will be used to evaluate the PK profile (C_{max}, time to maximum observed concentration [T_{max}], AUC_{tau}). In addition, trough plasma concentrations (C_{trough}) will be evaluated to establish accumulation ratio and explore PK linearity.

Anti-drug antibody (ADA) incidence rate and titer will be tabulated for each treatment to monitor immunogenicity. Samples confirmed positive for ADA will be tested and analyzed for antibody titer and reported.

[redacted]

Body Weight

Prior experience with MEDI0382 has demonstrated a weight-lowering effect at doses ≤ 300 µg (Ambery et al, 2018). Therefore, percentage and absolute change in weight and the proportion of subjects achieving clinically significant weight loss (> 5% of body weight) will be recorded to document the effect of MEDI0382 on body weight at higher doses than previously studied [redacted]

[redacted]

[redacted]

4 MATERIALS AND METHODS

4.1 Subjects

4.1.1 Number of Subjects

Up to 20 subjects will be randomized in 2 cohorts: 8 subjects in Cohort 1 and 12 subjects in Cohort 2.

4.1.2 Inclusion Criteria

Subjects must meet all of the following criteria:

1 Subjects aged 18 to 74 years (inclusive) at screening
2 Provision of signed and dated written informed consent (with the exception of consent for genetic and non-genetic research) prior to any study specific procedures
3 BMI between 27 and 35 kg/m^2 (inclusive) at screening
4 HbA1c range of 6.5% to 8.5% (inclusive) at screening (Note: Subjects may be re-tested for the HbA1c entry criterion only once.)
5 Willing and able to self-inject investigational product for the duration of the study
6 Diagnosed with T2DM with glucose control managed with metformin monotherapy where no significant dose change (increase or decrease ≥ 500 mg/day) has occurred in the three months prior to screening. For inclusion into Cohort 2 only, subjects prescribed oral dual therapy with a dipeptidyl peptidase-4 inhibitor, sulphonylurea, glitinide, or a sodium-glucose co-transporter 2 inhibitor in addition to metformin at screening may be eligible to enter the study following a 4-week washout period. Following wash-out, the subject must re-attend for fasting plasma glucose and HbA1c measurement to confirm eligibility prior to run-in. At this visit, an HbA1c of between 6.5% to 8.5%, inclusive **and** fasting plasma glucose level < 225 mg/dL (< 13.0 mmol/L) is acceptable. If the subject fails to meet these criteria, one repeat measurement is allowed on a different day prior to Day -10.
7 Female subjects must have a negative pregnancy test at screening and randomization, and must not be lactating.
8 Female subjects of childbearing potential who are sexually active with a male partner must be using at least one highly effective method of contraception (see Appendix A for definition of females of childbearing potential and for a description of highly effective methods of contraception) from screening and up to 4 weeks after the last dose of

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

4.1.3 Exclusion Criteria

1 History of, or any existing condition that, in the opinion of the investigator, would interfere with evaluation of the investigational product, put the subject at risk, influence the subject's ability to participate or affect the interpretation of the results of the study and/or any subject unable or unwilling to follow study procedures during the run-in period

2 Any subject who has received another investigational product as part of a clinical study or a GLP-1 analogue containing preparation within the last 30 days or 5 half-lives of the drug (whichever is longer) at the time of screening

3 Concurrent participation in another study of any kind and repeat randomization in this study is prohibited

4 Any subject who has received any of the following medications within the specified timeframe prior to the start of the study (see Section 4.7.2 for further details)

- Herbal preparations within one week prior to the start of dosing or drugs licensed for control of body weight or appetite (eg, orlistat, bupropion-naltrexone, phentermine-topiramate, phentermine, lorcaserin) within 30 days (or 5 half-lives of the drug) prior to the start of dosing
- Opiates, domperidone, metoclopramide, or other drugs known to alter gastric emptying and within 2 weeks prior to the start of dosing
- Antimicrobials within the quinolone (eg, ciprofloxacin), macrolide (eg, clarithromycin) or azole class (eg, ketoconazole) within 2 weeks prior to the start of dosing
- Any change in antihypertensive medication within 3 months prior to screening
- Aspirin (acetylsalicylic acid) at a dose greater than 150 mg once daily
- Paracetamol (acetaminophen) or paracetamol-containing preparations at a total daily dose of greater than 3000 mg
- Ascorbic acid (vitamin C) supplements at a total daily dose of greater than 1000 mg

5 Severe allergy/hypersensitivity to any of the proposed study treatments, standardized meals, or excipients

6 Symptoms of acutely decompensated blood glucose control (eg, thirst, polyuria, weight loss), a history of type 1 diabetes mellitus or diabetic ketoacidosis, or if the subject has been treated with daily SC insulin within 90 days prior to screening

7 Acute pancreatitis, pancreatic amylase, and/or pancreatic lipase > 3 × ULN; history of chronic pancreatitis; or serum triglyceride levels > 11 mmol/L (1000 mg/dL) at screening

8 Significant inflammatory bowel disease, gastroparesis or other severe disease or surgery affecting the upper GI tract (including weight-reducing surgery and procedures), which

may affect gastric emptying or could affect the interpretation of safety and tolerability data

9 Significant hepatic disease (except for NASH or non-alcoholic fatty liver disease without portal hypertension or cirrhosis) and/or subjects with any of the following results at screening:
   - Aspartate transaminase (AST) ≥ 3 × upper limit of normal (ULN)
   - Alanine transaminase (ALT) ≥ 3 × ULN
   - Total bilirubin (TBL) ≥ 2 × ULN

10 Impaired renal function defined as estimated glomerular filtration rate (GFR) < 60 mL/minute/1.73m^2 at screening (GFR estimated according to Modification of Diet in Renal Disease (MDRD) using MDRD Study Equation IDMS-traceable [SI units]).

11 Poorly controlled hypertension defined as:
   - Systolic BP > 160 mmHg
   - Diastolic BP or ≥ 90 mmHg

   After 10 minutes of supine rest and confirmed by repeated measurement at screening. Subjects who fail BP screening criteria may be considered for 24-hour ABPM at the discretion of the investigator. Subjects who maintain a mean 24-hour BP < 160/100 mmHg with a preserved nocturnal dip of > 15% will be considered eligible.

12 Any clinically important abnormalities in rhythm, conduction, or morphology of the resting 12-lead ECG or any abnormalities that may interfere with the interpretation of serial ECG changes, including corrected QT (QTc) interval changes at screening, as judged by the investigator

13 Prolonged QT intervals corrected for heart rate using Fridericia's formula (QTcF) > 450 ms, or family history of long QT-segment at screening

14 PR (PQ) interval prolongation (> 220 msec), intermittent second (Wenckebach block while asleep is not exclusive), or third-degree atrioventricular (AV) block, or AV dissociation

15 Persistent or intermittent complete bundle branch block. Subjects with QRS > 110 msec but < 115 msec are acceptable if there is no evidence of ventricular hypertrophy or pre-excitation

16 Unstable angina pectoris, myocardial infarction, transient ischemic attack, or stroke within 3 months prior to screening, or subjects who have undergone percutaneous coronary intervention or a coronary artery bypass graft within the past 6 months or who are due to undergo these procedures at the time of screening

17 Severe congestive heart failure (New York Heart Association Class III or IV)

18 Basal calcitonin level > 50 ng/L at screening or history/family history of medullary thyroid carcinoma or multiple endocrine neoplasia

19 Hemoglobinopathy, hemolytic anemia or chronic anemia (hemoglobin, <11.5 g/dL [115 g/L]) for males, < 10.5 g/dL (105 g/L) for females) at screening or any other condition known to interfere with the interpretation of HbA1c measurement

20 History of neoplastic disease within 5 years prior to screening, except for adequately treated basal cell, squamous cell skin cancer, or in situ cervical cancer

21 Any positive results for serum hepatitis B surface antigen, hepatitis C antibody, and human immunodeficiency virus (HIV) antibody
22 History of substance dependence, alcohol abuse, or excessive alcohol intake (defined as an average daily intake of > 24 g for men or > 12 g women) within 3 years prior to screening and/or a positive screen for drugs of abuse or alcohol at screening or on admission to the study unit. Subjects who use benzodiazepines for chronic anxiety or sleep disorders may be permitted to enter the study.
23 Symptoms of depression or any other psychiatric disorder requiring treatment with medication (eg, anti-depressants, anti-psychotics) at screening. However, subjects who use benzodiazepines for chronic anxiety or sleep disorders may be permitted to enter the study.
24 History of severe allergy/hypersensitivity, including to any component of the investigational product formulation or other biological agent, or ongoing clinically important allergy/hypersensitivity as judged by the investigator
25 Blood/plasma donation within 1 month of screening
26 Involvement of any AstraZeneca, MedImmune, the contract research organization, or the virtual study site employee or their close relatives

Subjects may be rescreened once if in the opinion of the investigator there is a reason to believe they may be eligible.

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 MedImmune subject identification (SID) number will be assigned by the investigational site comprised of the 7-digit site number plus a progressive 4-digit number before screening evaluations may begin to assess study eligibility (inclusion/exclusion) criteria. The MedImmune SID number will be used to identify the subject during the screening process and throughout study participation, if applicable.

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

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.

4.1.5 Withdrawal from the Study

Subjects are free to withdraw their consent to participate in the study (investigational product and protocol-defined assessments) at any time, without prejudice to further treatment. Subjects who withdraw consent will be asked about the reason(s) and the presence of any AEs. If the

subject is willing, the subject will be seen and assessed by the investigator (early discontinuation visit). AEs will be followed up, and all study medications should be returned by the subject. 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

2 Lost to follow-up

3 An AE that, in the opinion of the investigator or the sponsor, warrants discontinuation of further dosing

4 Pregnancy in a female subject (see Section 5.6.2 for additional details regarding pregnancy)

5 Signs or symptoms of severe hepatic impairment including abnormal laboratory values according to below:

   (a) ALT and/or AST are > 3 × ULN and TBL > 2 × ULN

   (b) ALT and/or AST are > 5 × ULN for ≥ 14 consecutive days, at any time after initial confirmatory results

   (c) ALT and/or AST are > 8 × ULN

6 Average absolute (regardless of baseline value) cardiac QTc interval corrected for heart rate by QTcF > 500 msec, or an increase of QTcF > 60 msec above the baseline value, confirmed (persistent for ≥ 5 minutes) on a repeat 12-lead ECG

7 Any one of the following:

   (a) **Tachycardia**, defined as resting supine pulse rate > 125 beats per minute persisting for at least 10 minutes

   (b) **Symptomatic bradycardia,** defined as resting supine pulse rate < 40 beats per minute while awake, persisting for at least 10 minutes

   (c) **Asymptomatic bradycardia**, defined as resting supine pulse rate < 30 beats per minute while awake persisting for at least 10 minutes

   (d) **Hypertension,** defined as an increase from baseline in resting supine systolic > 40 mmHg or above 180 mmHg and persisting for at least 10 minutes and/or increase from baseline in resting supine diastolic BP > 20 mmHg or above 100 mmHg and persisting for at least 10 minutes

8 Persistent hyperglycemia detected as 2 or more laboratory plasma fasting glucose levels of > 260 mg/dL (14.4 mmol/L) taken at least 3 days apart are detected

Subjects who are permanently discontinued from receiving investigational product will be followed for protocol-specified assessments including the 28-day post-last-dose safety follow-up visit and continued follow-up of any AEs unless consent is withdrawn from further study participation, the subject is lost to follow-up, the subject starts alternative treatment, or the subject is enrolled in another clinical study.

4.1.7 Replacement of Subjects

Subjects will not be replaced.

For Cohort 1, up to 3 additional subjects may be screened and enter the run-in period to ensure that a sufficient number of subjects are randomized. If these subjects are not required for Cohort 1, they are available to be randomized into Cohort 2.

If the screening visit for these subjects is outside the allowed time window, they will undergo a second screening and run in period in order to be eligible for Cohort 2. When these subjects are randomized, the data from the second screening/run in (if needed) will be used for reporting.

4.1.8 Withdrawal of Informed Consent for Data and Biological Samples

If a subject withdraws consent to the use of mandatory biological samples, the samples will be disposed of/destroyed, and the action documented. If samples are already analyzed, MedImmune is not obliged to destroy the results of this research. As collection of the biological samples is an integral part of the study, then the subject is withdrawn from further study participation.

The principal investigator:

- Ensures subjects' withdrawal of informed consent to the use of donated samples is notified immediately to MedImmune.
- Ensures that biological samples from that subject, if stored at the study site, are immediately identified, disposed of/destroyed, and the action documented.
- Ensures the organization(s) holding the samples is/are informed about the withdrawn consent immediately and that samples are disposed of/destroyed, the action documented and the signed document returned to the study site.
- Ensures that the subject and MedImmune are informed about the sample disposal.

MedImmune ensures the organizations holding the samples is/are informed about the withdrawn consent immediately and that samples are disposed of/destroyed and the action documented and returned to the study site.

4.2 Schedule of Study Procedures

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

4.2.1 Enrollment/Screening Period

Table 5 shows all procedures to be conducted at the screening visit. Assessments should, where practically possible, be performed in the order shown in the table.

Table 5 Schedule of Screening and Run-in Procedures

Study Period	Screening [a]	Run-in
Visit Number	**V1**	**V2**
Procedure / Study Day	**Day -25 to -12**	**Day -11 to -3 [l]**
Written 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	
Medical history, including smoking and alcohol history	X	
Physical examination (full) [b]	X	
Verify eligibility criteria	X	
Weight [c], height, and BMI calculation	X	
Demographics	X	
12-lead ECG [d]	X	
Vital signs (BP, pulse, body temperature, RR) [e]	X	
Collect blood for:		
Serum chemistry	X	
Coagulation panel	X	
Hematology	X	
HbA1c [f]	X	
Plasma glucose [g]	X	
Calcitonin	X	
HIV-1 and -2 antibodies; hepatitis B and C serology	X	
Triglycerides	X	
Pancreatic amylase, lipase	X	
Serum b-HCG (pregnancy test, females only)	X	
FSH (postmenopausal females only) [m]	X	
Collect urine for:		
Urinalysis	X	
Urine drug and alcohol screen [h]	X	
[redacted]	[redacted]	

Table 5 Schedule of Screening and Run-in Procedures

Study Period	Screening [a]	Run-in
Visit Number	**V1**	**V2**
Procedure / Study Day	**Day -25 to -12**	**Day -11 to -3 [l]**
SC injection training/demonstration [j]	X	X
[redacted]		[redacted]
ABPM [k]		X
Glucometer and diary dispensed		X

ABPM = ambulatory blood pressure monitoring; BMI = body mass index; BP = blood pressure; [redacted] ECG = electrocardiogram; FSH = follicle-stimulating hormone; HbA1c = hemoglobin A1c; HIV = human immunodeficiency virus; SC = subcutaneous; SID = subject identification; V = visit

[a] Screening period may be extended to Day -42 in Cohort 2 if washout of oral anti-diabetic therapy (other than metformin) is required

[b] Only the screening physical examination will be a full examination. For all time points thereafter, only a targeted physical examination is required.

[c] Body weight should be measured in the morning while the subject is fasted and prior to breakfast, after the subject has toileted and removed bulky clothing, including shoes. Calibrated scales should be used.

[d] A single digital ECG recording should be performed after the subject has rested for 10 minutes.

[e] BP and heart rate should be measured once at heart level in the non-dominant arm where possible, with the subject supine for 10 minutes prior to the measurement (rest period for ECG will suffice).

[f] HbA1C to be re-checked prior to the start of the run-in period only for those subjects washing out from a second anti-hyperglycemic agent

[g] **Fasting** plasma glucose to be checked prior to the start of the run-in period for those subjects washing out from a second anti-hyperglycemic agent

[h] An alcohol breath test is an acceptable alternative to an alcohol urine test.

[i] Subjects should be shown the device and given an explanation as to how it is worn.

[j] Subject's ability to administer a SC injection will be verified by undergoing a single SC injection using normal saline provided by the site. Willingness to perform this for the duration of the study should be discussed with the subject. Further training may be given during the run-in period as required.

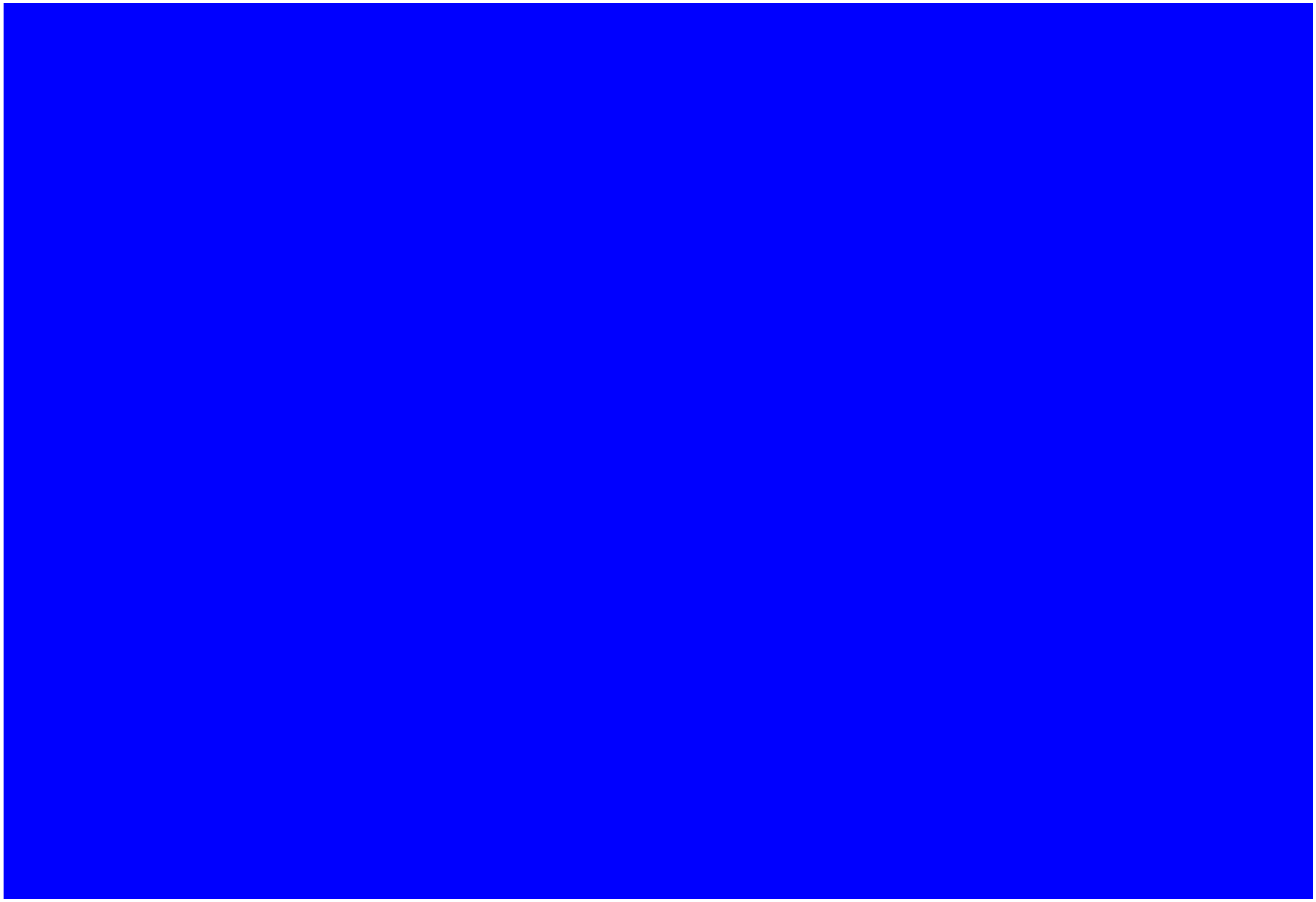
[k] Subjects will be fitted with the ABPM device while at the clinical unit, which may involve practice inflations. The subject will then wear the monitor/cuff for approximately 24 hours (including overnight at home) and will remove the device at home at the end of the 24-hour period.

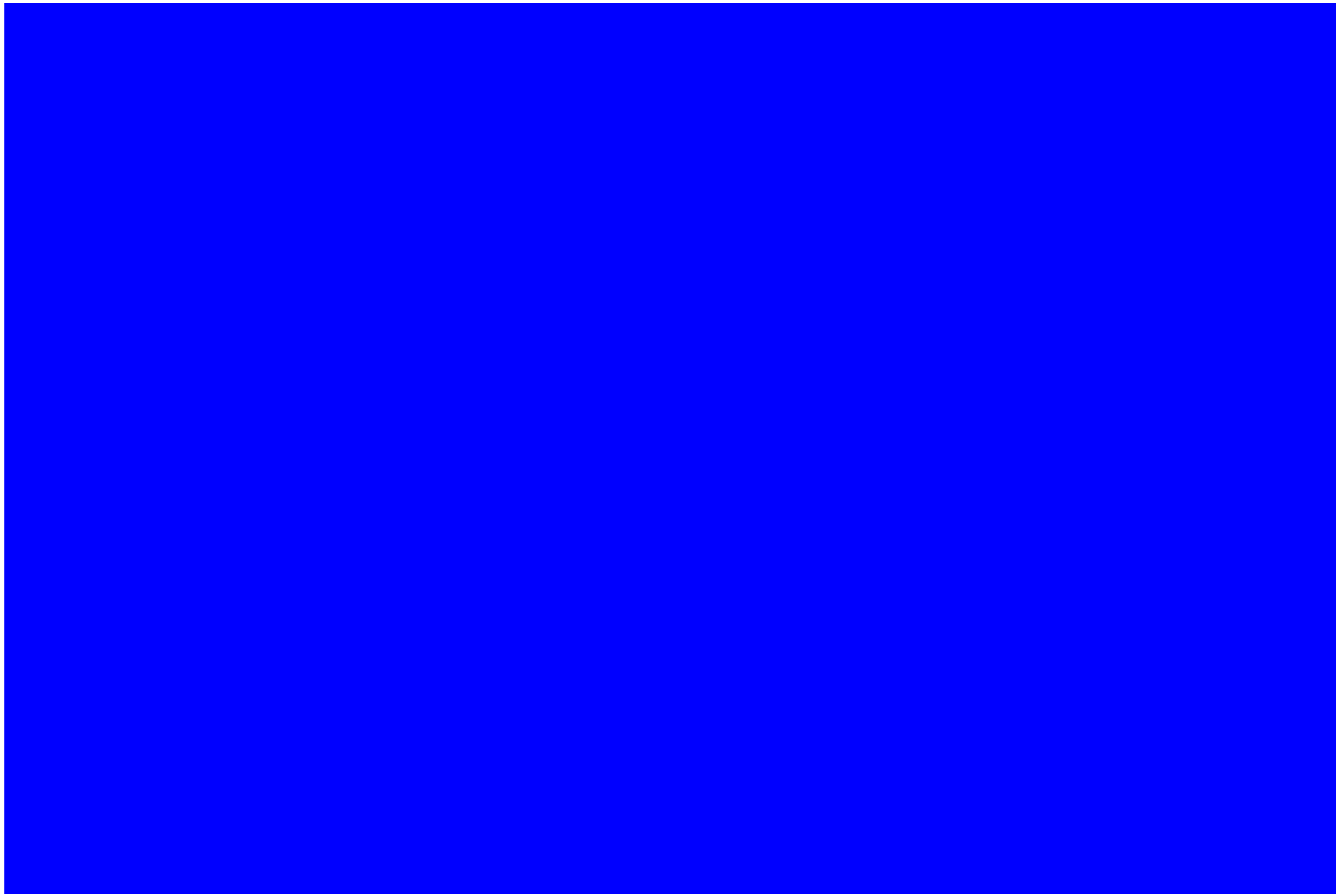
[l] [redacted]

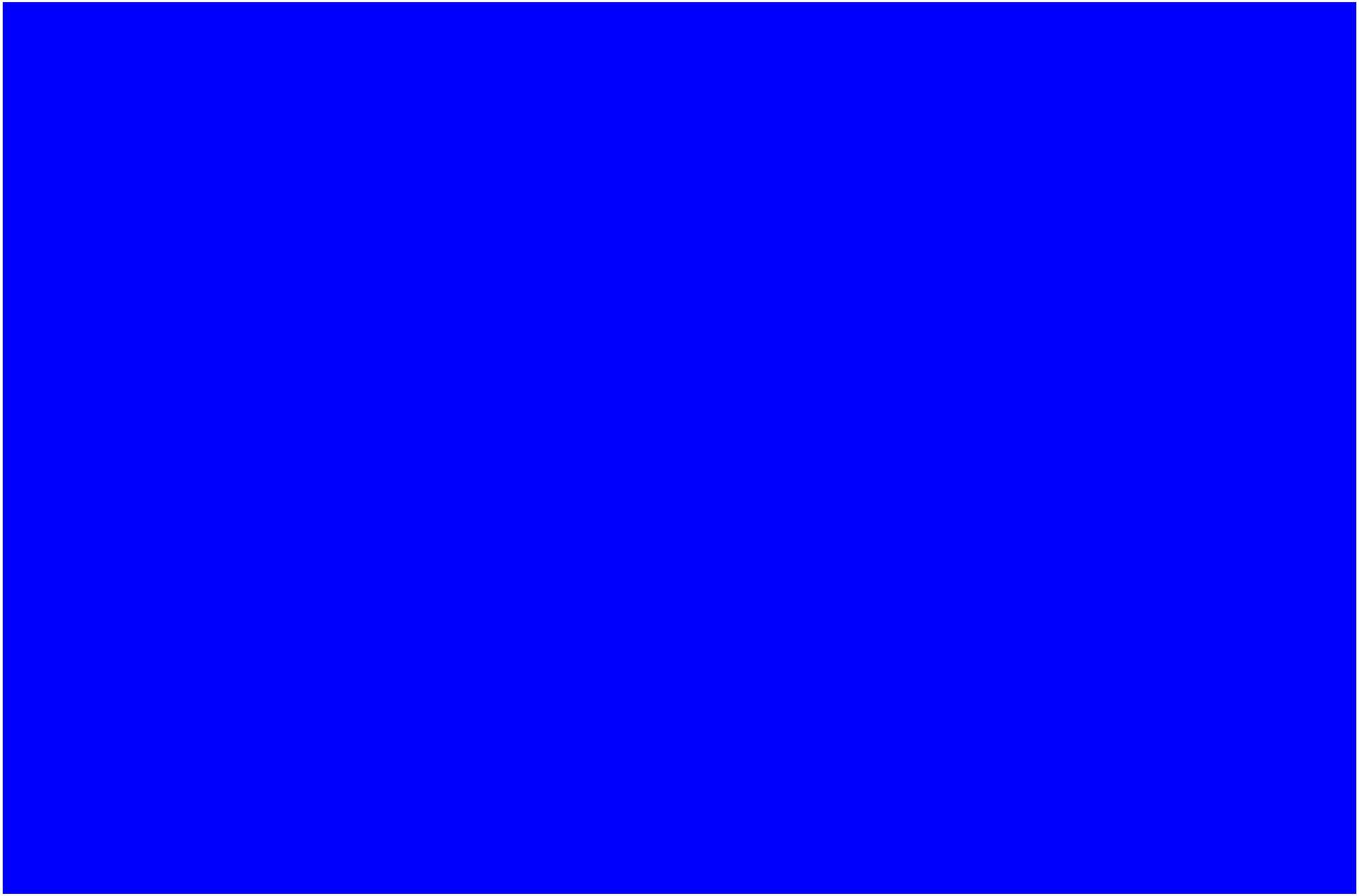
[m] FSH should only be checked in female subjects who are post-menopausal and have no previous confirmatory laboratory FSH result available.

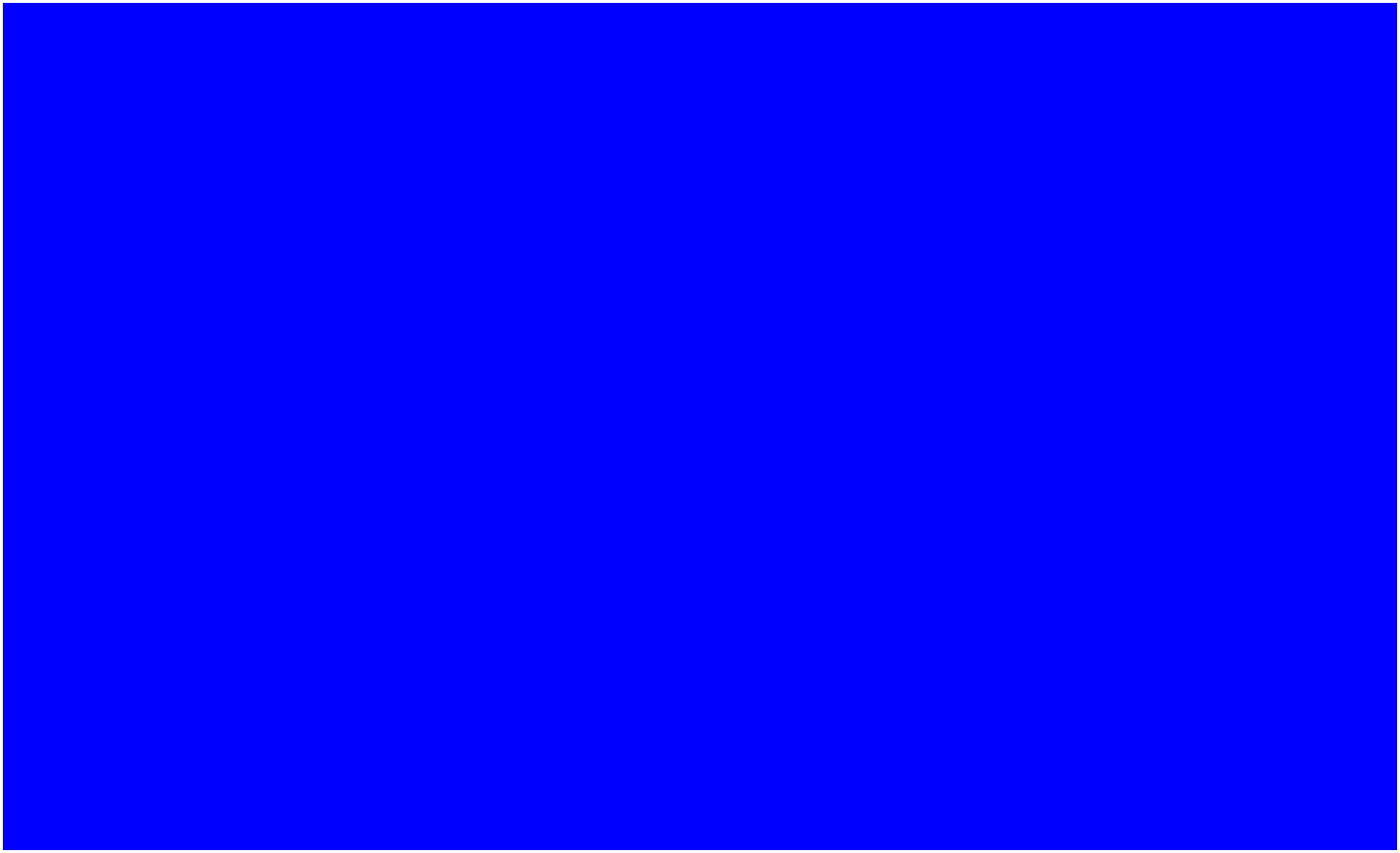
[#] Collection of Informed consent may occur prior to the other screening assessments, on a separate visit if required

[redacted]









4.2.3 Treatment Extension at HCTD and Follow-up Period

Table 7 shows all procedures to be conducted during the treatment extension and follow-up period.

Table 7 Schedule of Procedures for Treatment Extension at HCTD and Follow-up Periods

Study Period	**Treatment Extension at HCTD**				**Follow-up**			
Timepoint	**Day 1 of TE**	**Day 7 of TE**	**Day 20 of TE**	**Day 21 of TE**	**Day 1 post last dose**	**Day 2 post last dose**	**Day 3 post last dose**	**28 days post last dose/EDV (± 3 days)**
Procedure/Visit Number	**V11**	**V12**	**V13**			**V14**	**V15**	**V16**
Outpatient clinic visit		X			X [a]	X [a]	X [a]	X
Inpatient clinic visit	X		X	X				
Day of discharge from clinical unit on completion of assessments	X				X			
Fasting for minimum of 10 hours prior to the morning of the study day				X				
Standardized meal day [b]				X				
Targeted physical examination			X					X
Vital signs (BP, pulse, body temperature) [c]		X	X	X				X
ABPM [d]				X				
ECG [e]	X	X		X	X	X	X	X
Body weight [f]		X		X				X
Investigational product administration	Subject will self-administer investigational product daily via SC injection							
Blood tests								

Table 7 Schedule of Procedures for Treatment Extension at HCTD and Follow-up Periods

Study Period	Treatment Extension at HCTD				Follow-up			
Timepoint	**Day 1 of TE**	**Day 7 of TE**	**Day 20 of TE**	**Day 21 of TE**	**Day 1 post last dose**	**Day 2 post last dose**	**Day 3 post last dose**	**28 days post last dose/EDV (± 3 days)**
Procedure/Visit Number	**V11**	**V12**	**V13**			**V14**	**V15**	**V16**
Hematology panel				X				X
Serum Chemistry panel				X				X
Fasting plasma glucose				X				
Fasting lipase and amylase				X				
Calcitonin								X
Fasting lipid panel				X				X
HbA1c				X				X
PK for MEDI0382[g]	X	X		X	X	X	X	
PK for metformin [h]	X	X		X	X	X	X	
ADA				X				X
Blood sample for optional future non-genetic research				X				
Urine collection for:								
Urinalysis (dipstick; predose as applicable)		X	X					X
Pregnancy test (if applicable)			X					X
[redacted]								

Table 7 Schedule of Procedures for Treatment Extension at HCTD and Follow-up Periods

Study Period	Treatment Extension at HCTD				Follow-up			
Timepoint	**Day 1 of TE**	**Day 7 of TE**	**Day 20 of TE**	**Day 21 of TE**	**Day 1 post last dose**	**Day 2 post last dose**	**Day 3 post last dose**	**28 days post last dose/EDV (± 3 days)**
Procedure/Visit Number	**V11**	**V12**	**V13**			**V14**	**V15**	**V16**
[redacted]								
AEs/SAEs	Throughout study							
Concomitant medications	Throughout study							

ADA = anti-drug antibody; AE = adverse event; ABPM = ambulatory blood pressure monitoring; BP = blood pressure; [redacted] ECG = electrocardiogram; EDV = early discontinuation visit; HbA1c = hemoglobin A1c; PK = pharmacokinetics; SAE = serious adverse event; SC = subcutaneous; TE = treatment extension

[a] Subjects may choose to remain in the clinical unit as an inpatient if it is more convenient.

[b] Subjects will eat a standardized breakfast, lunch and evening meal at approximately 9 am, 1 pm and, 6 pm. No further food should be consumed until any fasted assessments have been carried out the following morning. Water is permitted ad libitum.

[c] Vital Signs Schedule (BP, pulse, and temperature): on days where ABPM is due to be checked a predose set of vital signs should be performed prior to application of the ABPM cuff. Blood pressure should be measured once at heart level in the nondominant arm where possible, [redacted] with the subject supine for 10 minutes prior to the measurement. 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. Vital signs should be measured predose (where applicable) on a given day.

[d] ABPM device will be worn for 24 hours while in the clinical unit

[e] A triplicate ECG recording will be collected on Days 1 and 7 of TE, predose; Day 21 of TE; predose, 1, 2 (± 15 minutes); 4, 6, 8, and 12 and 24, 48, and 72 (± 30 minutes) hours postdose. The ECG triplicate recording should be done prior to the PK samples being taken.

[f] Body weight should be measured in the morning while the subject is fasted and prior to breakfast, after the subject has toileted and removed bulky clothing including shoes. Calibrated scales should be used.

[g] PK Sampling Schedule for MEDI0382: Days 1 and 7 of TE, predose; Day 21 of TE; predose, 1, 2 (± 15 minutes); 4, 6, 8, and 12 and 24, 48, and 72 (± 30 minutes) hours postdose.

[h] PK Sampling Schedule for Metformin: Days 1 and 7 of TE, predose; Day 21 of TE; predose, 1, 2 (± 15 minutes); 4, 6, 8, and 12 hours post dose. Further predose samples should be taken on Days 1, 2 and 3 post last MEDI0382 dose. On days where metformin PK samples are collected, the dose, time and date of the last metformin dose should be recorded relative to the samples taken

[i] [redacted]

4.3 Description of Study Procedures

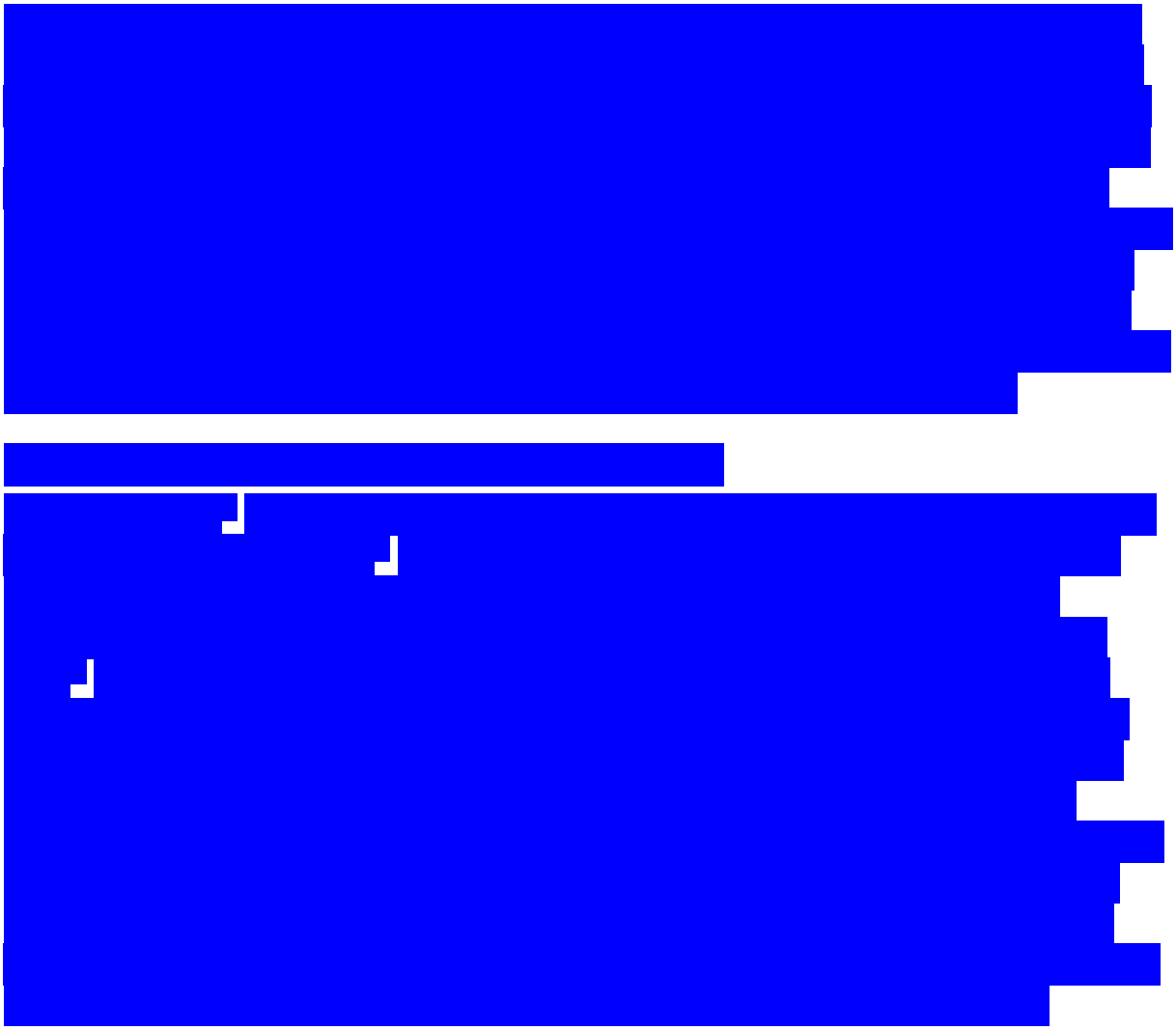
4.3.1 Efficacy

The following efficacy assessments will be performed and/or measured at the time points specified in the schedules of study procedures (Table 5, Table 6, and Table 7).

4.3.1.1 Glucose measurements

All subjects will be provided with a glucometer and a diary during the run-in period, and site staff will explain how the glucometer works and allow the subject to demonstrate proper use under supervision before being discharged from the clinic.

Subjects will be advised to use the glucometer to check their capillary blood glucose level as per their usual schedule and if they have symptoms of hypoglycemia (hunger, dizziness, shaking, sweating, or irritability) or feel unwell and will be expected to record the level and symptoms in their diary.



4.3.1.2 Standardized Meals

On standardized meal days, subjects should only consume what is provided to them to eat by staff. Subjects will receive the same nutritionally balanced breakfast, lunch, and evening meal at approximately 9 am, 1 pm, and 6 pm respectively, ensuring there is at least 4 hours between the start of each meal on any given day. The clinical site may determine appropriate meals to serve, however subjects must be served the same meals on each day the assessment is specified. Water may be given ad libitum but subjects should refrain from any other beverages until 7 am the following morning when the fast may be broken. Subjects will be required to fast for at least 10 hours prior to breakfast on the standardized meal day.

4.3.1.3 Body Weight

Body weight will be measured according to the schedule presented in Table 5, Table 6, and Table 7. Body weight should be measured in the morning while the subject is fasted and prior to breakfast. Weight will be measured at the time points specified in the schedules of procedures, after the subject has toileted and removed bulky clothing including shoes. Whenever possible after screening, at the site the same (properly calibrated) scale should be used for each measurement for any given subject. The subject's body weight will be recorded in kg to 1 decimal place at minimum.

4.3.2 Safety

4.3.2.1 Medical History and Physical Examination

Complete medical history will include history (including smoking and alcohol history) and current medical conditions, past or present cardiovascular disorders, respiratory, GI, renal, hepatic, neurologic, endocrine, lymphatic, hematologic, immunologic, dermatologic, psychiatric, genitourinary, drug and surgical history, or any other diseases or disorders.

Physical examinations will be performed by a physician or qualified designee and full examinations include the following body systems: immunologic/allergy; head, ears, eyes, nose, and throat; respiratory; cardiovascular; GI; musculoskeletal; neurological 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); dermatologic; hematologic/lymphatic; and, endocrine. In addition, the injection site will be assessed.

Clinically significant abnormal findings will be recorded. A complete physical examination will be performed according to the schedule presented in Table 5, Table 6, and Table 7.

Targeted examinations (evaluation of selective body systems at the judgment of the physician or qualified designee based on subject presentation) are sufficient for the remaining time points.

4.3.2.2 Body Mass Index

BMI will be calculated as BMI = weight / (height)^2], where weight is measured in kg, and height in meters. The height measurement recorded at screening will be used for each BMI calculation for a given subject.

BMI will be measured according to the schedules presented in Table 5, Table 6, and Table 7.

4.3.2.3 Electrocardiograms

Subjects should rest in the supine position at least 10 minutes before ECG recordings are conducted. ECGs may be repeated per site's local procedure. Further ECGs will be performed in accordance with the schedule provided in Table 5 and Table 7 (screening and treatment extension).

The ECGs will be interpreted by a qualified physician (the investigator or qualified designee) at the clinical study site. The investigator should date and sign the ECG tracing and record the clinical significance of any abnormal result on the tracing. ECG data and evaluation will be recorded in the eCRF.

Paper copies of ECGs will be stored at the study center and digital copies transmitted to a central archive. Digital copies may be interpreted where required by other qualified physicians outside the study site.

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

Telemetry

Telemetry will be used to continuously monitor heart rate 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 performed for a minimum of 8-hours post dosing during inpatients visits and on Day -1 as specified in the schedule of events. 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 ECG.

4.3.2.4 Vital signs

Vital sign measurements (BP, heart rate, respiration rate, and body temperature) are to be obtained in accordance with the schedule provided in Table 5, Table 6, and Table 7. Vital signs are to be taken prior to investigational product administration, and, if possible, before drawing blood.

On days where ABPM is due to be checked, a predose set of vital signs should be performed prior to application of the ABPM cuff. Blood pressure should be measured once with the arm at heart level and measurements performed using an adequate arm cuff size. The nondominant arm should be used where possible, [redacted] with the subject supine for 10 minutes prior to the measurement. 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. The pulse rate should be measured for 30 seconds to determine the rate. If a specific post dose reading falls on a given day, only those reading need be taken.

Further vital signs measurements will be recorded in accordance with the schedule provided in Table 5 and Table 7 (screening and treatment extension).

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 BP cuff will be selected and the device will be fitted to the nondominant 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 mmHg, 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, heart rate pressure, heart rate, and mean arterial pressure readings will be recorded over a period of 24 hours.

4.3.3 Clinical Laboratory Tests

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

Clinical laboratory safety tests including serum pregnancy tests will be performed in a licensed local clinical laboratory. Urine tests may be performed at the site using a licensed test (dipstick). Abnormal clinically significant laboratory results should be repeated as soon as possible (preferably within 24 to 48 hours).

The following clinical laboratory tests will be performed. See Table 5, Table 6, and Table 7 for the schedule of tests.

4.3.3.1 Serum Chemistry

- blood urea nitrogen
- creatinine
- total protein
- albumin
- TBL
- alkaline phosphatase
- ALT
- AST
- calcium
- glucose (fasting where required)
- sodium
- potassium
- chloride
- bicarbonate
- phosphorus
- gamma glutamyl transferase

Tests for AST, ALT, ALP, and TBL must be conducted concurrently and assessed concurrently.

4.3.3.2 Hematology

- red blood cell count
- hemoglobin
- hematocrit
- absolute white blood cell count
- white blood cell count with percent differential
- platelet count
- mean cell volume
- mean corpuscular hemoglobin concentration
- mean corpuscular hemoglobin

4.3.3.3 Coagulation Panel (Screening Only)

- prothrombin time
- activated partial thromboplastin time
- thrombin time
- international normalized ratio

4.3.3.4 Urinalysis

- pH
- specific gravity
- glucose
- blood (urine hemoglobin/erythrocytes/blood)
- color
- appearance
- ketones
- protein
- microscopic analysis (if positive for blood, nitrates, or protein) by local laboratory
- bilirubin
- leukocytes
- urobilinogen

Urinalysis for pH, specific gravity, protein, glucose, ketones, bilirubin, blood, leukocytes, urobilinogen and nitrate may be performed at the site using a licensed test (dipstick).

4.3.3.5 Drug/Alcohol Screen

- Site standard urine drug screen will be used.
- Breathalyzer or urine alcohol screening is acceptable.

4.3.3.6 Other Tests

- Urine human chorionic gonadotropin (hCG) (All Females)
- Follicle-stimulating hormone (postmenopausal women only)
- Serum beta-hCG (at screening only) (All Females)
- Serum HIV-1
- Serum HIV-2 antibodies
- Serum hepatitis B surface antigen
- Serum hepatitis C antibody
- Calcitonin
- Pancreatic amylase, lipase
- Fasting lipid panel (Total cholesterol, high-density lipoprotein, low-density lipoprotein, triglycerides)
- HbA1c

4.3.4 Pharmacokinetic Evaluation and Methods

Blood will be collected predose and at specific post dose times to evaluate PK of MEDI0382 in plasma (see Table 6 and Table 7 for collection time points). The PK of MEDI0382 in plasma will be measured utilizing a validated liquid [redacted]

Blood will be collected predose and at specific post dose times to evaluate PK of metformin in plasma (see Table 6 and Table 7 for collection time points). The PK of metformin in plasma will be measured utilizing a validated LC-MS/MS method.

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

4.3.5 Immunogenicity Evaluation and Methods

Blood samples will be collected to evaluate ADA responses to MEDI0382 (see Table 6 and Table 7 for collection time points). Evaluations will be performed using validated immunoassays. Tiered analyses will be performed to include screening, confirmatory, and titer assay components, and the positive-negative cut points will be statistically determined from drug-naive validation samples. Cross-reactivity to GLP-1 and glucagon may be assessed on samples confirmed positive for MEDI0382 specific ADA. Samples may be utilized for further characterization of the ADA response, including possible assessment of neutralizing antibody.

Instructions for immunogenicity (ADA) sample collection, processing, storage, and shipment can be found in the Laboratory Manual. Serum samples for analysis of ADA will be collected according to the schedule presented in Table 6 and Table 7.

At the end of study visit, if a subject's sample is ADA positive, the subject will be asked to return to provide another sample in 3 months to evaluate whether or not ADAs persist. If the sample taken in 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). If the sample is ADA positive at 6 months, the investigator and the medical monitor will discuss what further action will be taken.

4.3.6 Genetic Evaluations and Methods

The subject's consent to participate in the genetic research components of the study is optional. See Appendix E for further information.

4.3.7 Storage, Re-use and Destruction of Biological Samples

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

4.3.8 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 approximately 589 mL.

4.4 Study or Study Component Suspension or Termination

MedImmune reserves the right to temporarily suspend or permanently terminate this study or component of the study at any time. The reasons for temporarily suspending or permanently 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
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 of the investigational product for this indication
5 Sponsor decision to terminate the study based on a planned futility analysis

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

4.5 Investigational Products

4.5.1 Identity of Investigational Product(s)

The sponsor will provide the investigator(s) with investigational product (Table 8) using designated distribution centers.

4.5.1.1 Investigational Product Handling and Inspection

Investigational Product Inspection

Each vial selected for dose preparation should be inspected prior to use. The MEDI0382 or placebo solution in vials should not be cloudy, discolored, or contain any visible particles. 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 (Section 4.5.1.5) for further instructions.

In-clinic Investigational Product Handling

Investigational product should be stored at 2°C to 8°C in the original container, and should be protected from heat and light.

Investigational products are supplied in single-use vials and do not contain preservatives, so after dose preparation any unused portion must be discarded. Preparation of syringes for dose administration is to be performed using aseptic techniques. 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. 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. Subjects should be asked to ensure they have a normal domestic refrigerator at home, which should be between 2°C and 8°C. Investigational product should be protected from heat and light.

Subjects should be instructed not to store the investigational product directly adjacent to the refrigerator cooling element. Investigational product should not be used if it has been frozen.

The subject should be instructed to remove from the refrigerator only the 1-vial kit required for their daily dose. All other kits are to be kept in the original carton in the refrigerator until required. Prior to administration, the single vial of investigational product to be used for injection should be removed from the refrigerator and kept at room temperature for approximately 15 minutes for temperature equilibration. The subject is not to administer investigational product if the time outside of the refrigerator exceeds 4 hours; if storage time exceeds this limit, a new dose must be prepared from a new vial.

Vials are single-use only, and the subject should be instructed not to re-use the vial after administration of a single dose. After administration, the used vial, syringe and needle should be directly discarded into the provided sharps bin.

4.5.1.2 Dose Preparation

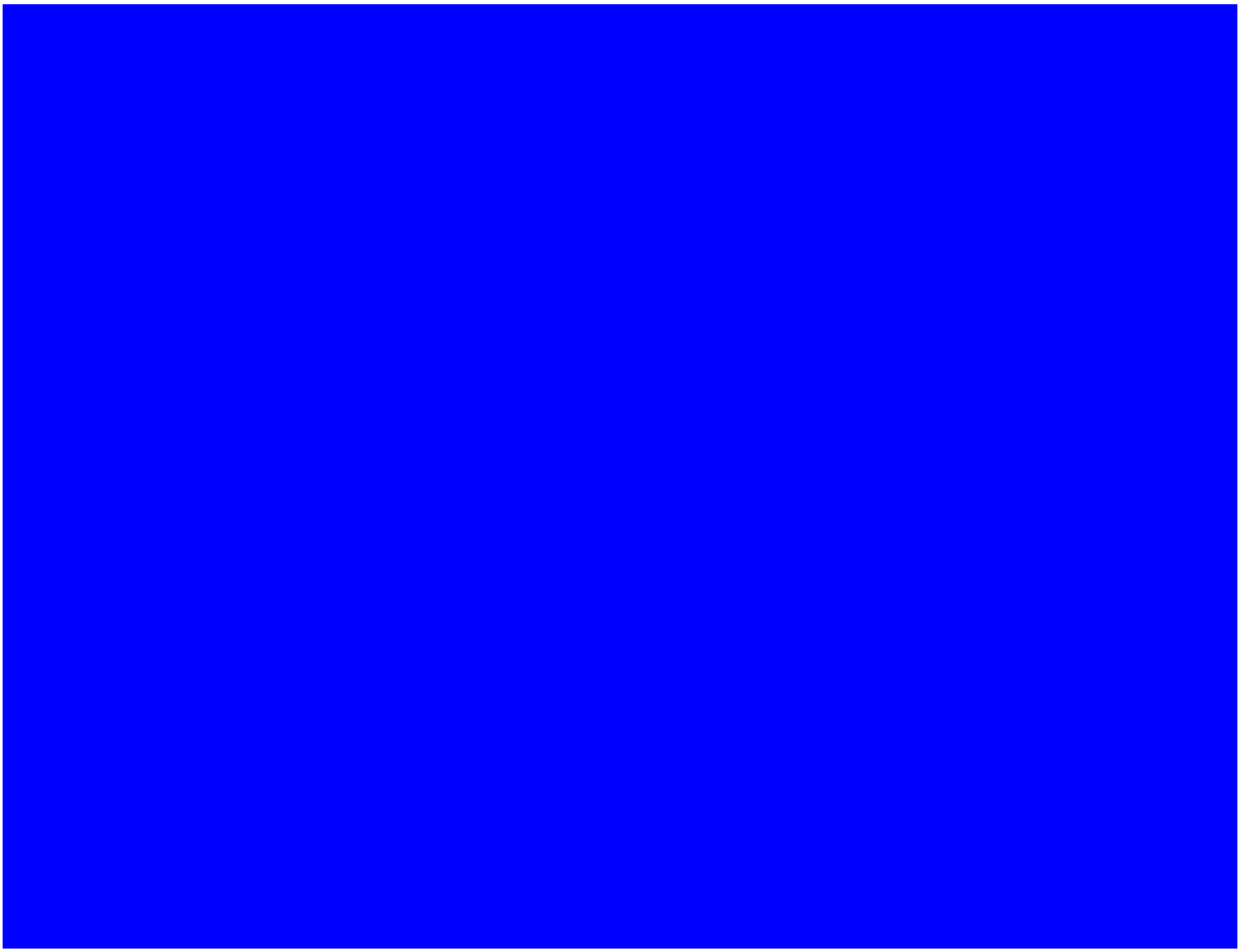
[redacted] Only the supplied diluent may be used for this dilution step.

If diluent is required, investigational product should be removed from the refrigerator and kept at room temperature for at least 30 minutes and a maximum of 4 hours for temperature equilibration. If no dilution is required, 15 minutes is recommended for temperature equilibration.

To make a 10-fold dilution of MEDI0382 or placebo, it is recommended to withdraw 0.1 mL of the supplied investigational product using a 1 mL syringe and 27G needle, and add it into a sterile empty vial. Using a new 1 mL syringe and 27G needle, add 0.9 mL of diluent into the same vial. The needle specified for dilution may be substituted for either a 20 or 30G needle

as feasibility dictates. The vial should be mixed by swirling gently to make a homogenous final admixture. Do not shake. The diluted dose should be administered using a 1.0 mL syringe (Table 9). Dilution and preparation of doses for administration is to be performed using aseptic techniques.

Doses of 100 µg or greater do not require a dilution step and should be administered directly using a 0.3 mL insulin syringe.



4.5.1.3 Treatment Administration

In-clinic Treatment Administration

The first day of dosing is considered Day 1. On the day of each dose, investigational product will be administered according to the schedule of procedures, as soon as practical upon waking each morning prior to breakfast, ideally at the same time each day. Investigational product will be administered by the subject under supervision as an SC injection in the lower

abdomen using [redacted]

At-home Treatment Administration

[redacted] as soon as practical upon waking each morning prior to breakfast, ideally at the same time each day. Subjects should be instructed to rotate the injection site around the abdomen.

After administration, the used vial, needle and syringe should all be directly discarded in the provided sharps bin. Further details are provided in the home dosing instructions.

If a dose of investigational product is missed, subjects should contact the site for further instructions.

Subjects must return any unused investigational product, and the sharps bin, at their next visit to the clinical site. All items can be returned at room temperature.

4.5.1.4 Monitoring of Dose Administration

Monitoring of In-clinic Dose Administration

As with any exogenous peptide delivered SC, 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 post-dosing period, vital signs will be periodically assessed (see Section 4.3.2.4). Injection sites should be routinely examined at each study site visit. If any injection-site reaction meets the criteria for an AE (see Section 5), the event is to be reported on the AE eCRF, with the reaction described as specifically as possible.

Recording of Missed Doses During At-home Dose Administration

Subjects will be instructed on how and what to record daily for missed doses in the Daily Diary.

4.5.1.5 Reporting Product Complaints

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

MedImmune contact information for reporting product complaints:

Email: productcomplaints@medimmune.com

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

Fax: +1-301-398-8800

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

4.5.2 Additional Study Medications

No other study medications are specified for use in this clinical protocol.

4.5.3 Labeling

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

4.5.4 Storage

All investigational product should be kept in a secure place under appropriate storage conditions. Investigational product should be stored at 2°C to 8°C (36°F to 46°F) in the original container while in the clinic. Separate instructions for at-home dosing and storage will be provided.

4.5.5 Treatment Compliance

Investigational product will be administered by subjects while being observed by study site personnel, who will monitor compliance during the inpatient period. Compliance during the at-home dosing period will be monitored via returned vials.

4.5.6 Accountability

4.5.6.1 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.

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

Subjects will be instructed to return any unused vials, and the sharps bin, to the site when they return for their next clinic visits.

4.6 Treatment Assignment and Blinding

4.6.1 Methods for Assigning Treatment Groups

Subjects will be randomized using a 3:1 ratio to receive either MEDI0382 or placebo. A manual randomization schedule will be used assign a unique randomization code and investigational product kit(s) for the subject at each randomization.

Investigational product (MEDI0382 or placebo) must be administered within 24 hours after the treatment group is assigned. If there is a delay in the administration of investigational product such that it will not be administered within the specified timeframe, the medical monitor must be notified immediately.

4.6.2 Methods to Ensure Blinding

This is a blinded study in which the subjects and investigator are blinded to investigational product, and MedImmune staff involved in the study are unblinded. Investigational product and placebo are indistinguishable in appearance, identically labelled, and supplied as fully blinded kits.

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 using emergency unblinding envelopes which will be held securely at the study site. In general, unblinding should only occur if management of the medical emergency would be different based on the subject having received investigational product. In most cases, the management of a medical emergency would be the same whether or not investigational product was received by the subject. If this was the case, the investigational product allocation should not be unblinded.

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

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

4.6.3.2 Unblinding for Planned Analysis Purposes

Planned analyses are described in Section 4.8.1. Since MedImmune staff are unblinded to investigational product treatment per the study design, no additional procedures related to unblinding are required for analysis purposes.

4.7 Restrictions During the Study and Concomitant Treatment(s)

The investigator must be informed as soon as possible about any medication taken from the time of screening until the 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 identified as "excluded" as listed in Section 4.7.2. Specifically, subjects should receive full supportive care during the study, including transfusions of blood and blood products, and treatment with antibiotics (except those listed in section 4.7.2), anti-emetics, anti-diarrheal, and analgesics, and other care as deemed appropriate, and in accordance with their institutional guidelines.

Concomitant medications being taken for stable concurrent conditions not felt to impact study integrity may be acceptable upon approval of the investigator and sponsor (or designee). A stable regimen of antihypertensive agents for a minimum of 3 months prior to screening is permitted. Similarly, a stable treatment regimen of thyroid replacement therapy for a minimum of 2 months prior to screening is permitted.

4.7.2 Prohibited Concomitant Medications

Other than the medications described above, use of the following medications, including over the counter medications, herbal supplements, vitamins etc. at the times specified in the list below is not permitted, generally speaking from the time specified in the entry criteria until after the 28-day post-last-dose safety follow-up visit

Subjects should not be initiated on any new medications to control blood glucose levels during the dosing and follow up period unless it is deemed necessary by the Investigator for safety and following discussion with the Medical Monitor.

- Concurrent or previous use of a GLP-1 analogue containing preparation within the last 30 days or 5 half-lives of the drug, whichever is longest, prior to the start of screening (Visit 1)
- Concurrent or prior use of any herbal preparations or dietary supplements marketed for control of body weight or appetite within 1 week prior to the start of screening

- Concurrent or previous use of drugs approved for weight loss (eg, orlistat, bupropion-naltrexone, phentermine-topiramate, phentermine, lorcaserin) within the last 30 days or 5 half-lives of the drug, whichever is longest, prior to the start of screening
- Antidepressant (eg, escitalopram) or anti-psychotic agents (eg, chlorpromazine) must not be started during the course of the study.
- Systemic corticosteroids by oral, intravenous, intra-articular, or intramuscular route are prohibited within 3 months prior to screening and during the study unless prescribed for a very brief period of less than 7 days.
- Concurrent use of aspirin (acetylsalicylic acid) at a dose greater than 150 mg once daily and within the last 72 hours prior to the start of the study (Visit 2)
- Concurrent use of paracetamol (acetaminophen) at a total daily dose greater than 3000 mg once daily and within the last 72 hours prior to the start of the study (Visit 2)
- Concurrent use of ascorbic acid (vitamin C) at a total daily dose of > 1000 mg and within the last 72 hours prior to the start of the study (Visit 2)
- Concurrent use of medications (other than metformin) for control of blood glucose within 4 weeks prior to the start of the study (Visit 2) unless it is deemed necessary by the investigator for safety reasons.
- Antimicrobials within the quinolone (eg, ciprofloxacin), macrolide (eg, clarithromycin) or azole class (eg, ketoconazole)
- Metoclopramide or domperidone for the treatment of emesis should only be considered if the subject is unable to tolerate a 5HT3 antagonists (eg, ondansetron)

This is not a comprehensive listing. If the exclusion status of any concomitant medication is in question, the study physician should be contacted for discussion. The sponsor or designee should be contacted if the investigator is informed of any restriction violations. The sponsor will decide whether a subject with restriction violations will be allowed to continue study participation.

4.8 Statistical Evaluation

4.8.1 General Considerations

Tabular summaries will be presented by treatment group. Categorical data will be summarized by the number and percentage of subjects in each category. Continuous variables will be summarized by descriptive statistics. Additional details of statistical analyses will be described in the statistical analysis plan.

The as-treated population is defined as all subjects who are randomized and receive any investigational product analyzed according to treatment received. All analyses will be based on the as-treated population.

Two analyses are planned for this study as follows:

1 A primary analysis after the up-titration period for Cohort 2, and
2 A final analysis after the safety follow-up period for Cohort 2.

Analyses will be conducted for each cohort and for two cohorts combined. Formal statistical modeling analysis for certain efficacy endpoints will only be conducted for two-cohort combined analyses.

4.8.2 Sample Size

The total study sample size is 20 subjects, who will be randomized by 2 cohorts: 8 subjects in Cohort 1 and 12 subjects in Cohort 2. For each cohort, subjects will be randomized in a 3:1 ratio to the MEDI0382 arm or the placebo arm. The sample size for this study was empirically determined to obtain adequate safety and tolerability evaluation. [redacted]

4.8.3 Efficacy

4.8.3.1 Primary Efficacy Analysis

There are no primary efficacy objectives or analyses planned for this study.

4.8.3.2 Secondary Efficacy Analyses

The continuous secondary efficacy endpoints for two cohorts combined analysis will be compared between the MEDI0382 and placebo arms using an analysis of covariance model adjusting for baseline value and treatment arm. For the secondary proportion-related efficacy endpoints, a logistic regression model will be used with baseline value and treatment arm.

Same endpoints for each cohort analysis will only be summarized without formal statistical comparisons.

4.8.3.3 Exploratory Analyses

Exploratory efficacy endpoints will be summarized without formal statistical comparisons and testing.

4.8.4 Safety

4.8.4.1 Analysis of Adverse Events

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) by system organ class (SOC) and preferred term (PT). Specific AEs will be counted once for each subject for calculating rates, but will be presented in total in subject listings. In addition, if the same AE occurs multiple times within a particular subject, the

highest severity and level of causality will be reported. If any associations of interest between AEs and baseline characteristics are observed, additional stratified results may be presented. All treatment-emergent AEs will be summarized overall and by MedDRA SOC and PT, by severity and relationship to investigational product. In addition, summaries of deaths, SAEs and treatment discontinuations due to AEs will be provided.

Additionally, the incidence and event rate of nausea and vomiting will be summarized weekly during the treatment period.

4.8.4.2 Analysis of Clinical Laboratory Parameters

Laboratory parameters will be assessed at baseline as well as throughout the study. Frequencies of abnormal laboratory measurements will be presented for each laboratory parameter. Also, laboratory parameters will be assessed by presenting tables containing information related to laboratory shifts from baseline relative to the normal range, as well as descriptively over time.

Other safety data such as vital signs, ECG and physical examination findings will be descriptively summarized at each time point by treatment. Mean ambulatory BP and heart rate measurements recorded over 24 hours at different time points will be analyzed using an analysis of covariance model, adjusting for treatment and measurement at baseline.

[redacted]

4.8.5 Analysis of MEDI0382 Immunogenicity/Pharmacokinetics

PK parameters such as MEDI0382 C_{max}, T_{max}, and AUC_{tau} will be estimated (if data allow) from plasma concentration time data for MEDI0382 at each dose level separately except for the [redacted] evels by cohort. Additional PK parameters such as AUC_{inf} and terminal half-life may be derived if data allow, at the HCTD from samples collected at the end of extension period

Descriptive statistics including mean, standard deviations, median, minimum, and maximum will be generated for all PK parameters for MEDI0382 at each dose level separately, and for the C_{trough}. Subjects who have at least one measurable concentration time point of investigational product will be used for this analysis.

Individual C_{trough} will be listed by cohort, treatment and day and will be summarized as maximum, minimum, arithmetic mean, and geometric mean.

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 dose level. Data on titers and cross-reactivity to GLP-1 and glucagon (where applicable) will be listed. If warranted by the data, the association of ADA positive with observed PK data may be explored.

5 ASSESSMENT OF SAFETY

5.1 Definition of Adverse Events

An AE is the development of any untoward medical occurrence in a subject or clinical study subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (eg, an abnormal laboratory finding), symptom (eg, nausea, chest pain), or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

The term AE is used to include both serious and non-serious AEs and can include a deterioration of a pre-existing medical occurrence. An AE may occur at any time, including run-in or washout periods, even if no study treatment has been administered.

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

5.2 Definition of Serious Adverse Events

An SAE is any AE that:

- Results in death
- Is immediately life-threatening
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity

- Is a congenital anomaly/birth defect in offspring of the subject
- Is an important medical event that may jeopardize the subject or may require medical intervention to prevent one of the outcomes listed above

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

5.3 Definition of Adverse Events of Special Interest

An adverse event of special interest (AESI) is one of scientific and medical interest specific to understanding of the investigational product and may require close monitoring and rapid communication by the investigator to MedImmune. 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.

There are no AESIs defined for this study.

5.4 Recording of Adverse Events

AEs will be recorded on the eCRF using a recognized medical term or diagnosis that accurately reflects the event. AEs will be assessed by the investigator for severity, relationship to the investigational product, possible etiologies, and whether the event meets criteria of an SAE and therefore requires immediate notification to MedImmune (see Section 5.5). See Section 5.2 for the definition of SAEs and Section Appendix B for guidelines for assessment of severity 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.

5.4.1 Time Period for Collection of Adverse Events

All AEs regardless of severity will be collected from randomization throughout the treatment period and including the follow-up period. All SAEs and any AEs related to study procedures will be recorded from the time of informed consent.

5.4.2 Follow-up of Unresolved Adverse Events

Any AEs that are unresolved at the subject's last AE assessment 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.

5.4.3 Adverse Events Based on Signs and Symptoms

All AEs spontaneously reported by the subject or reported in response to the open question from the study site staff: *'Have you had any health problems since the previous visit/you were last asked?'*, or revealed by observation will be collected and recorded in the eCRF. When collecting AEs, the recording of diagnoses is preferred (when possible) to recording a list of signs and symptoms. However, if a diagnosis is known and there are other signs or symptoms that are not generally part of the diagnosis, the diagnosis and each sign or symptom will be recorded separately.

5.4.4 Adverse Events Based on Examination and Tests

The results from the protocol-mandated laboratory tests and vital signs will be summarized in the CSR. 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 increased)

If deterioration in a laboratory value/vital sign is associated with clinical signs and symptoms, the sign or symptom will be reported as an AE and the associated laboratory result/vital sign will be considered as additional information. Wherever possible the reporting investigator uses the clinical, rather than the laboratory term (eg, anemia versus low hemoglobin value). In the absence of clinical signs or symptoms, clinically relevant deteriorations in non-mandated parameters should be reported as AE(s).

Any new or aggravated clinically relevant abnormal medical finding at a physical examination as compared with the baseline assessment will be reported as an AE

5.4.5 Hy's Law

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

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 in the course of the study, then investigators or other site personnel must inform the appropriate sponsor representative(s) within 1 day, ie, immediately but no later than 24 hours after becoming aware of the event.

The designated study representative works with the investigator to ensure that all the necessary information is provided to the sponsor's patient safety data entry site within 1 calendar day of initial receipt for fatal and life-threatening events and within 5 calendar days of initial receipt for all other SAEs.

For fatal or life-threatening AEs where important or relevant information is missing, active follow-up is undertaken immediately. Investigators or other site personnel 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 after becoming aware of the event.

Once the investigators 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 an SAE to the appropriate sponsor representative by telephone. The sponsor representative will advise the investigator/study site personnel how to proceed.

The reference document for definition of expectedness/listedness is the IB.

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 IB, 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 on a MedImmune investigational product occurs during the course of the study, then the investigator or other site personnel should inform appropriate sponsor representatives immediately, but no later than 24 hours after becoming aware of the event.

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 (ie, those not associated with an AE or SAE), reporting must occur within 30 days.

5.6.2 Pregnancy

All pregnancies and outcomes of pregnancy should be reported to the sponsor except for:

- If the pregnancy is discovered before the study subject has received any investigational product.
- Pregnancies in the partner of male subjects

5.6.2.1 Maternal Exposure

If a subject becomes pregnant during the course of the study investigational product should be discontinued immediately.

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

If any pregnancy occurs during the course of the study, then the investigator or other site personnel will inform the appropriate sponsor representatives within 1 day, ie, immediately but **no later than 24 hours** after becoming aware of the event.

The designated study 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 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.

5.6.3 Medication Error

For the purposes of this clinical study a medication error is an unintended failure or mistake in the treatment process for a MedImmune study drug that either causes harm to the subject or has the potential to cause harm to the subject.

A medication error is not lack of efficacy of the drug, but rather a human- or process-related failure while the drug is in control of the study site staff or subject.

Medication error includes situations where an error:

- Occurred

- Was identified and intercepted before the subject received the drug
- Did not occur, but circumstances were recognized that could have led to an error

Examples of events to be reported in clinical studies as medication errors:

- Drug name confusion (ie, instead of receiving the investigational product, the subject received a drug that has a similar-sounding name)
- Dispensing error, eg, medication prepared incorrectly, even if it was not actually given to the subject
- Drug not administered as indicated, for example, wrong route or wrong site of administration
- Drug not taken as indicated, eg, tablet dissolved in water when it should be taken as a solid tablet
- Drug not stored as instructed, eg, kept in the refrigerator when it should be at room temperature
- Wrong subject received the medication
- Wrong drug administered to subject

Examples of events that **do not** require reporting as medication errors in clinical studies:

- Subject accidentally missed drug dose(s), eg, forgot to take medication
- Accidental overdose (will be captured as an overdose)
- Subject failed to return unused medication or empty packaging
- Errors related to background and rescue medication, or standard of care medication in open label studies, even if an AZ or MedImmune product

Medication errors are not regarded as AEs but AEs may occur as a consequence of the medication error.

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

The designated MedImmune representative works with the investigator to ensure that all relevant information is completed within 1 or 5 calendar days if there is an SAE associated with the medication error (see Section 5.5) and within 30 days for all other medication errors. Medication errors should be reported using a Medication Error Report Form.

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 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 protocol and the Clinical Study Agreement, the terms of the protocol shall prevail with respect to the conduct of the study and the treatment of subjects; in all other respects not relating to study conduct or the 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 their last protocol-specified visit/assessment (including telephone contact) regardless of the number of doses of investigational product that was received.

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

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

6.4 Data Management

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

An electronic data capture system will be used for data collection and query handling. The investigator will ensure that data are recorded in the eCRFs as specified in the study protocol and in accordance with the eCRF 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 Subject Data Protection

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

Extra precautions will be taken to preserve confidentiality and prevent genetic data being linked to the identity of the subject. 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**.**

7.2 Ethics and Regulatory Review

The IEC responsible for each site must review and approve the final study protocol, including the final version of the informed consent form and any other written information and/or materials to be provided to the subjects. The IEC must also approve all advertising used to recruit subjects for the study. The investigator is responsible for submitting these documents to the applicable IEC, and distributing them to the study site staff.

The opinion of the IEC must be given in writing. The investigator must provide a copy of the written approval to MedImmune before enrollment of any subject into the study.

MedImmune should approve any substantive modifications to the informed consent form that are needed to meet local requirements.

If required by local regulations, the protocol must be re-approved by the IEC annually.

Before the study is initiated, MedImmune will ensure that the national regulatory authority in each country has been notified and their approval has been obtained, as required. MedImmune will provide safety updates/reports according to local requirements, including suspected unexpected serious adverse reactions where relevant, to regulatory authorities, IEC, and principal investigators.

7.3 Informed Consent

Informed consent of each subject will be obtained through a written and verbal explanation process that addresses all elements required by ICH/GCP. MedImmune will develop a core informed consent form for use by all investigators in the clinical study. MedImmune must approve any modifications to the informed consent form that are needed to meet local requirements.

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 informed consent form is given to the subject
- Ensure that any incentives for subjects who participate in the study as well as any provisions for subjects harmed as a consequence of study participation are described in the informed consent form that is approved by an IEC

7.4 Changes to the Protocol and Informed Consent Form

Study procedures will not be changed without the mutual agreement of the Principal Investigator and MedImmune. Any changes must be documented in a study protocol amendment.

For a substantial change to the protocol, MedImmune will distribute amended versions of the protocol to the principle investigator(s). Before implementation, amended protocols must be approved by relevant IEC (see Section 7.2) and reviewed as per local regulatory authority requirements. The IEC must also approve revisions to the informed consent form, advertising, and any other written information and/or materials resulting from the change to the protocol.

Any non-substantial changes will be communicated to or approved by each IEC.

7.5 Audits and Inspections

Authorized representatives of MedImmune, a regulatory authority, or an IEC may perform audits or inspections at the center, including source data verification. The purpose of an audit or inspection is to systematically and independently examine all study-related activities and

documents, to determine whether these activities were conducted, and data were recorded, analyzed, and accurately reported according to the protocol, GCP, ICH guidelines , 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

9.1 Protocol Amendment 3, 16Apr2019

The administrative change described below has been incorporated into the current version of the protocol. Table numbering in the appendices was also corrected, and the Table of Contents was reformatted and updated.

Summary of Revision to the Protocol (Amendment 3)

Key Detail of the Amendment	Reason for Amendment
Amendment 3 (16Apr2019)	
Title Page	The medical monitor has changed for the study, and new contact information has been provided.
Appendix A	The numbering of the table in this section was corrected.

9.2 Protocol Amendment 2, 17Dec2018

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

Summary of Revisions to the Protocol (Amendment 2)

Key Details of the Amendment	Reason for Amendment
Amendment 2 (17Dec2018)	
Section 4.1.2 (Inclusion Criteria)	Typos (µg to mg and blood to plasma) were corrected. Added the need for female subjects of childbearing potential to have a negative pregnancy test at screening and randomization
Section 4.1.3 (Exclusion Criteria)	The definition of excessive alcohol intake was revised.
Table 5 (Schedule of Screening and Run-in Procedures)	Fasting was removed from plasma glucose as subjects cannot be fasting prior to consent. Footnote added to clarify when follicle-stimulating hormone should be collected.
Table 6 (Schedule of Treatment/Up-titration Period Study Procedures)	Text was added to correct the footnotes to the table. The optional inpatient or daily visit was corrected for dose period 20-50 µg to state “from Day 2”.
Table 7 (Schedule of Procedures for Treatment Extension at HCTD and Follow-up Periods)	Added clarification of the metformin PK sample collection timepoints to footnote
[redacted]	[redacted]
Section 4.3.1.2 (Standardized Meals)	Instructions on when meals should be given were clarified.
Section 4.3.2.4 (Vital Signs)	Incorrect text was removed

Summary of Revisions to the Protocol (Amendment 2)

Key Details of the Amendment	Reason for Amendment
Amendment 2 (17Dec2018)	
Section 4.5.1.2 (Dose Preparation)	Text was added to clarify that substitution of other specific needle gauges was allowed.
Appendix D (Actions Required in Cases of Increases in Liver Biochemistry and Evaluation of Hy's Law)	Updated in response to Sponsor's new process

9.3 Protocol Amendment 1, 31October2018

All changes described below have been incorporated into the current version of the protocol. [redacted] Other minor corrections (typos, grammatical revisions) were made.

Summary of Revisions to the Protocol (Amendment 1)

Key Details of the Amendment	Reason for Amendment
Amendment 1 (31Oct2018)	
Section 3.1.3.2 (Dose Escalation Stopping Criteria)	Text was revised to clarify actions the DEC will take if any of the dose escalation stopping criteria are met (ie, recommending that the study proceed to 3-week treatment extension at the HCTD or requesting for review and decision by the MedImmune Safety Review Board on how to proceed or whether to suspend or stop the study).
Section 4.1.3 (Exclusion Criteria)	Criterion 7 amended to reduce the acceptable upper limit of pancreatic amylase and lipase to 3 × ULN.
Section 4.1.5 (Withdrawal from the Study) and Table 7 (Schedule of Procedures for Treatment Extension at HCTD and Follow-up Periods)	Text was added specifying that subjects who withdraw their consent to participate in the study, if willing, will be seen and assessed by the investigator at an early discontinuation visit.
Table 7 (Schedule of Procedures for Treatment Extension at HCTD and Follow-up Periods)	The table was revised for accuracy, including correcting visit numbers, deletion of medical and disease history, and correcting visits for ABPM and ECG procedures.

Appendix A Contraception Guidance

For females of childbearing potential:

- Females of childbearing potential are defined as those who are not surgically sterile (ie, surgical sterilization includes bilateral tubal ligation, bilateral oophorectomy, or hysterectomy) or those who are not postmenopausal (defined as 12 months with no menses) without an alternative medical cause and have follicle-stimulating hormone levels in the normal range for postmenopausal phase (25.8-134.8 IU/L) in previous laboratory results.
- A highly effective method of contraception is defined as one that results in a low failure rate (ie, less than 1% per year) when used consistently and correctly. The acceptable methods of contraception are described in Table 10.
- Female subjects must refrain from egg cell donation and breastfeeding while on study and for 28 days after the final dose of investigational product.

Table 10 Highly Effective Methods of Contraception

• Tubal occlusion
• Copper T intrauterine device
• Levonorgestrel-releasing intrauterine system or implant; eg, Mirena®) [a]
• Medroxyprogesterone injections (eg, Depo-Provera®)
• Etonogestrel implants (eg, Implanon®, Norplan®)
• Norelgestromin/ethinyl estradiol transdermal system
• Intravaginal device (eg, NuvaRing®)

[a] This is also considered a hormonal method.

Appendix B Additional Safety Guidance

Further Guidance on the Definition of a Serious Adverse Event (SAE)

Life threatening

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

Hospitalization

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

Important Medical Event or Medical Intervention

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

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

Examples of such events are:

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

Assessment of Severity

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

Grade 1	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 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

A guide to Interpreting the Causality Question

The investigator is required to provide an assessment of relationship of AEs and SAEs to the investigational product. The following factors should be considered when deciding if there is a "reasonable possibility" that an AE may have been caused by the investigational product.

- Time Course. Exposure to suspect investigational product. Has the subject actually received the suspect investigational product? Did the AE occur in a reasonable temporal relationship to the administration of the suspect investigational product?
- Consistency with known investigational product profile. Was the AE consistent with the previous knowledge of the suspect investigational product (pharmacology and toxicology) or products of the same pharmacological class? OR could the AE be anticipated from its pharmacological properties?
- De-challenge experience. Did the AE resolve or improve on stopping or reducing the dose of the suspect investigational product?

- No alternative cause. The AE cannot be reasonably explained by another aetiology such as the underlying disease, other drugs, or other host or environmental factors.
- Re-challenge experience. Did the AE reoccur if the suspected investigational product was reintroduced after having been stopped? MedImmune would not normally recommend or support a re-challenge.
- Laboratory tests. A specific laboratory investigation (if performed) has confirmed the relationship?

In difficult cases, other factors could be considered such as:

- Is this a recognized feature of overdose of the investigational product?
- Is there a known mechanism?

Causality of 'related' is made if following a review of the relevant data, there is evidence for a 'reasonable possibility' of a causal relationship for the individual case. The expression 'reasonable possibility' of a causal relationship is meant to convey, in general, that there are facts (evidence) or arguments to suggest a causal relationship.

The causality assessment is performed based on the available data including enough information to make an informed judgment. With limited or insufficient information in the case, it is likely that the event(s) will be assessed as 'not related'.

Causal relationship in cases where the disease under study has deteriorated due to lack of effect should be classified as no reasonable possibility.

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 aetiology other than the procedure/ intervention that was described in the protocol (the alternative aetiology must be documented in the study subject's medical record).

Appendix C National Institute of Allergy and Infectious Disease 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 Disease/Food Allergy and Anaphylaxis Network symposium. J Allergy Clin Immunol. 2006;117:391-7.

National Institute of Allergy and Infectious Disease (NAID) and Food Allergy and Anaphylaxis Network (FAAN) 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
   (a) Respiratory compromise (eg, dyspnoea, wheeze-bronchospasm, stridor, reduced peak expiratory flow (PEF), hypoxemia)
   (b) Reduced blood pressure (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 subject (minutes to several hours):
   (a) Involvement of the skin-mucosal tissue (eg, generalized hives, itch-flush, swollen lips-tongue-uvula)
   (b) Respiratory compromise (eg, dyspnoea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)
   (c) Reduced BP or associated symptoms (eg, hypotonia [collapse], syncope, incontinence)
   (d) Persistent gastrointestinal symptoms (eg, crampy abdominal pain, vomiting)
3 Reduced BP after exposure to known allergen for that subject (minutes to several hours):
   (a) Infants and children: low systolic BP (age specific) or greater than 30% decrease in systolic BP
   (b) Adults: systolic BP of less than 90 mmHg or greater than 30% decrease from that person’s baseline

Appendix D Actions Required in Cases of Increases in Liver Biochemistry and Evaluation of Hy's Law

D 1 Introduction

This appendix describes the process to be followed to identify and appropriately report Potential Hy's Law (PHL) cases and of Hy's Law (HL) cases. 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 PHL criteria at any point during the study.

All sources of laboratory data are appropriate for the determination of PHL and HL events; this includes samples taken at scheduled study visits and other visits including central and all local laboratory evaluations even if collected outside of the study visits; for example, PHL criteria could be met by an elevated alanine aminotransferase (ALT) from a central laboratory **and/or** elevated total bilirubin (TBL) from a local laboratory.

The investigator will also review adverse event (AE) data (for example, for AEs that may indicate elevations in liver biochemistry for possible PHL events.

The investigator participates, together with MedImmune clinical project representatives, in review and assessment of cases meeting PHL criteria to agree whether HL criteria are met. Hy's Law criteria are met if there is no alternative explanation for the elevations in liver biochemistry other than drug-induced liver injury (DILI) caused by the investigational product.

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

D 2 Definitions

D 2.1 Potential Hy's Law

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

D 2.2 Hy's Law

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

For potential Hy's Law and Hy's Law, 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.

D 3 Identification of Potential Hy's Law Cases

In order to identify cases of potential Hy's Law, 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 potential Hy's Law criteria (see Section D 2) by reviewing laboratory reports from all previous visits
- Promptly enter the laboratory data into the laboratory eCRF

D 4 Follow-up

D 4.1 Potential Hy's Law Criteria Not Met

If the subject does not meet potential Hy's Law criteria the investigator will:

- Inform the study representative that the subject has not met potential Hy's Law criteria.
- Perform follow-up on subsequent laboratory results according to the guidance provided in the study protocol.

D 4.2 Potential Hy's Law Criteria Met

If the subject does meet potential Hy's Law criteria the investigator will:

- Notify the sponsor study representative who will then inform the study team
- Within 1 day of PHL criteria being met, the investigator will report report the case as an SAE of Potential Hy's Law; serious criteria 'Important medical event' and causality assessment 'yes/related' according to the Clinical Study Protocol process for SAE reporting.

- For subjects that met PHL criteria prior to starting investigational product, the investigator is not required to submit a PHL SAE unless there is a significant change in the subject's condition.

The medical monitor 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 medical monitor.
- If at any time (in consultation with the medical monitor) the potential Hy's Law case meets serious criteria, report it as an SAE using standard reporting procedures

D 5 Review and Assessment of Potential Hy's Law Cases

The instructions in this section should be followed for all cases where potential Hy's Law 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 potential Hy's Law criteria other than DILI caused by the investigational product, to ensure timely analysis and reporting to health authorities within 15 calendar days from date PHL criteria were met. The 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: update the previously submitted PHL SAE and AE CRFs accordingly with the new information (reassessing event term; causality and seriousness criteria) following the sponsor's 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:

- Send updated 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 15 calendar days in obtaining the information necessary to assess whether or not the case meets the criteria for Hy's Law, then it is assumed that there is no alternative explanation until such time as an informed decision can be made:

- Provide any further update to the previously submitted SAE of PHL (report term now 'Hy's Law case') ensuring causality assessment is related to investigational product and seriousness criteria is medically important, according to clinical study protocol (CSP) process for SAE reporting
- 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 still met. Update the previously submitted PHL SAE report following CSP process for SAE reporting, according to the outcome of the review and amending the reported term if an alternative explanation for the liver biochemistry elevations is determined.

D 6 Laboratory Tests

The list below represents the standard, comprehensive list of follow-up tests which are recommended when using a central laboratory. For individual studies, the list may be reduced to a subset of tests after consultation with the Hepatic Safety Knowledge Group.

Some of the tests may also be considered for use with local laboratories that have respective testing capabilities. Any test results need to be recorded in the CRF.

Hy's Law Lab Kit for Central Laboratories

Additional standard chemistry and coagulation tests	GGT LDH Prothrombin time INR
Viral hepatitis	IgM anti-HAV IgM and IgG anti-HBc HBsAg HBV DNA IgM and IgG anti-HCV HCV RNA

	IgM anti-HEV HEV RNA
Other viral infections	IgM & IgG anti-CMV IgM & IgG anti-HSV IgM & IgG anti-EBV
Alcoholic hepatitis	Carbohydrate deficient transferrin (CD-transferrin)
Autoimmune hepatitis	Antinuclear antibody (ANA) Anti-Liver/Kidney Microsomal Ab (Anti-LKM) Anti-Smooth Muscle Ab (ASMA)
Metabolic diseases	alpha-1-antitrypsin Ceruloplasmin Iron Ferritin Transferrin Transferrin saturation

References

Aithal et al 2011, Clinical Pharmacology and Therapeutics 89(6):806-815.

Food and Drug Administration (FDA) Guidance for Industry (issued July 2009) 'Drug-induced liver injury: Premarketing clinical evaluation':

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

Appendix E Genetic Research

Rationale and Objectives

MedImmune intends to collect and store DNA for genetic research to explore how genetic variations may affect clinical parameters, risk and prognosis of diseases, and the response to medications. Genetic research may lead to better understanding of diseases, better diagnosis of diseases or other improvements in health care and to the discovery of new diagnostics, treatments or medications.

In addition, collection of DNA samples from populations with well described clinical characteristics may lead to improvements in the design and interpretation of clinical trials and, possibly, to genetically guided treatment strategies.

Genetic Research Plan and Procedures

Selection of genetic research population

Study selection record

All subjects will be asked to participate in this genetic research. Participation is voluntary and if a subject declines to participate there will be no penalty or loss of benefit. The subject will not be excluded from any aspect of the main study.

Inclusion criteria

For inclusion in this genetic research, subjects must fulfill all inclusion criteria described in the main body of the Clinical Study Protocol **and**:

- Provide informed consent for the genetic sampling and analyses.

Exclusion criteria

Exclusion from this genetic research may be for any of the exclusion criteria specified in the main study

Discontinuation of subjects from this genetic research

Specific reasons for discontinuing a subject from this genetic research are:

Withdrawal of consent for genetic research: Subjects may withdraw from this genetic research at any time, independent of any decision concerning participation in other aspects of the main study. Voluntary discontinuation will not prejudice further treatment. Procedures for discontinuation are outlined in Section 4.1.8 of the protocol.

Collection of samples for genetic research

The blood sample for genetic research will be obtained from the subjects at Day -2. Although DNA is stable, early sample collection is preferred to avoid introducing bias through

excluding subjects who may withdraw due to an AE, such subjects would be important to include in any genetic analysis. If for any reason the sample is not drawn at Day -2, it may be taken at any visit until the last study visit. Only one sample should be collected per subject for genetics during the study. Samples will be collected, labelled, stored and shipped as detailed in the Laboratory Manual.

Coding and storage of DNA samples

The processes adopted for the coding and storage of samples for genetic analysis are important to maintain subject confidentiality. Samples will be stored for a maximum of 15 years, from the date of last subject last visit, after which they will be destroyed. DNA is a finite resource that is used up during analyses. Samples will be stored and used until no further analyses are possible or the maximum storage time has been reached.

An additional second code will be assigned to the blood either before or at the time of DNA extraction replacing the information on the sample tube. Thereafter, the sample will be identifiable by the second, unique number only. This number is used to identify the sample and corresponding data at the MedImmune genetics laboratories, or at the designated organization. No personal details identifying the individual will be available to any person (MedImmune employee or designated organizations working with the DNA).

The link between the subject enrollment/randomization code and the second number will be maintained and stored in a secure environment, with restricted access at MedImmune or designated organizations. The link will be used to identify the relevant DNA samples for analysis, facilitate correlation of genotypic results with clinical data, allow regulatory audit and to trace samples for destruction in the case of withdrawal of consent.

Ethical and Regulatory Requirements

The principles for ethical and regulatory requirements for the study, including this genetics research component, are outlined in Section 7 of the protocol.

Informed consent

The genetic component of this study is optional and the subject may participate in other components of the main study without participating in the genetic component. To participate in the genetic component of the study the subject must sign and date both the consent form for the main study and the genetic component of the study. Copies of both signed and dated consent forms must be given to the subject and the original filed at the study center. The principal investigator(s) is responsible for ensuring that consent is given freely and that the subject understands that they may freely discontinue from the genetic aspect of the study at any time.

Subject data protection

MedImmune will not provide individual genotype results to subjects, any insurance company, any employer, their family members, general physician 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 physician 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.

Data management

Any genotype data generated in this study will be stored at a secure system at MedImmune and/or designated organizations to analyze the samples.

The results from this genetic research may be reported in a separate report from the CSR or published in scientific journals.

MedImmune and its designated organizations may share summary results (such as genetic differences from groups of individuals with a disease) from this genetic research with other researchers, such as Hospitals, Academic Organization or Health Insurance Companies. This can be done by placing the results in scientific databases, where they can be combined with the results of similar studies to learn even more about health and disease. The researchers can only use this information for health-related research purposes. Researchers may see summary results but they will not be able to see individual subject data or any personal identifiers.

Some or all of the clinical datasets from the main study may be merged with the genetic data in a suitable secure environment separate from the clinical database.

Statistical Methods and Determination of Sample Size

The number of subjects that will agree to participate in the genetic research is unknown. It is therefore not possible to establish whether sufficient data will be collected to allow a formal statistical evaluation or whether only descriptive statistics will be generated. A Statistical Analysis Plan will be prepared where appropriate.

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