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A Phase 2a, Randomised, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy, Safety, and Pharmacokinetics of MEDI0382 in Subjects with Type 2 Diabetes Mellitus and Renal Impairment

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Contract Research Organization: Covance, Inc.

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PROTOCOL SYNOPSIS

TITLE

A Phase 2a, Randomised, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy, Safety, and Pharmacokinetics of MEDI0382 in Subjects with Type 2 Diabetes Mellitus and Renal Impairment

HYPOTHESES

Primary Hypothesis:

Administration of MEDI0382 once daily titrated up to a dose level of [redacted] will result in superior blood glucose control versus placebo after 32 days of treatment in subjects with type 2 diabetes mellitus (T2DM) and renal impairment.

Secondary Hypotheses:

- Administration of MEDI0382 once daily titrated up to a dose level of [redacted] across 32 days will be well tolerated in subjects with T2DM and renal impairment
- Administration of MEDI0382 once daily titrated up to a dose level of [redacted] will result in superior weight loss versus placebo after 32 days of treatment in subjects with T2DM and renal impairment
- Administration of MEDI0382 once daily titrated up to a dose level of [redacted] will have a predictable pharmacokinetic (PK) profile in subjects with T2DM and renal impairment

OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary	
To assess the effect of MEDI0382 titrated up to a dose level of [redacted] on glucose control versus placebo after 32 days of treatment	• Percentage change in glucose area under the curve (AUC) as measured by a standardised mixed-meal tolerance test (MMTT) from baseline (Day -5) to the end of 32 days of treatment (Day 32)
Secondary	
To characterise the safety profile and tolerability of MEDI0382 titrated up to a dose level of [redacted] during dosing and follow-up in subjects with T2DM and renal impairment	• Measures of safety and tolerability (adverse events/serious adverse events [AEs/SAEs], vital signs, postural blood pressure [BP] changes, electrocardiogram [ECG], laboratory test results) • Change in mean 24-hour pulse rate, systolic and diastolic blood pressure from baseline (Day -5) to the end of dosing at each dose level (Days 4, 11, 18 and 32)
To assess the effects of MEDI0382 titrated up to a dose level of [redacted] on additional measures of glycaemic control versus placebo after 32 days of treatment	• Change in haemoglobin A1c (HbA1c) from baseline (Day 1) to the end of 32 days of treatment (Day 32) • Change in fasting glucose from baseline (Day 1) to the end of 32 days of treatment (Day 32) • Change in percentage of time spent within a target glucose range of 70 mg/dL (3.9 mmol/L) to 180 mg/dL (10 mmol/L) over a 7-day period at baseline (Days -8 to - 2) to the final week of treatment (Days 26-32)
To assess the effects of MEDI0382 titrated up to a dose level of [redacted] on weight versus placebo after 32 days of treatment	• Percentage and absolute change in body weight from baseline (Day 1) to the end of 32 days of treatment (Day 33)

To characterise the PK profile and immunogenicity of MEDI0382	• PK endpoints: AUC over a dosing duration, maximum observed concentration (C_{max}), time to C_{max} (T_{max}), trough plasma concentration (C_{trough}) • Development of anti-drug antibodies (ADA) and titre (if confirmed positive)
Exploratory	
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

[redacted]	[redacted]
[redacted]	[redacted]

STUDY DESIGN

This is a randomised, double-blind, placebo-controlled study to evaluate the safety, tolerability, efficacy, and PK profile of MEDI0382 titrated from [redacted] up to [redacted] and administered once daily by subcutaneous (SC) injection over 32 days in subjects with T2DM and renal impairment (eGFR ≥ 30 and < 60 mL/min/1.73 m^2). The study has a 14-day run-in period of diet and exercise and continuous glucose monitoring (CGM), a 32-day treatment period, and a 28-day follow-up period. Diet and exercise guidance will be according to local practices. It is planned to randomise approximately 40 subjects across multiple study sites. Subjects will be consented, screened for suitability, and randomised within 40 days of screening, if eligible.

Throughout the study, subjects will have the choice to either travel to the clinic for visits or stay overnight locally whenever consecutive daily visits are required. Subjects will be expected to fast for at least 8 hours overnight prior to Visit 3 (Day -5), Visit 4 (Day 1), Visit 9 (Day 32), and Visit 12 (Day 60). [redacted]

On Visit 2 (Day -14) subjects will attend the clinical unit for a short visit. At this visit they will be given advice on diet and exercise (in accordance with local practices) and training in SC injection administration, and fitted with a CGM sensor that the subject will be expected to wear continuously for the duration of the study until the second follow-up visit (Visit 11). [redacted] On Visit 3 (Day -5), subjects will attend the clinical unit for a long visit and will undergo safety assessments and a mixed-meal tolerance test (MMTT). At this time, an ambulatory blood pressure monitoring (ABPM) device will be fitted on the contralateral arm to the CGM sensor and will be worn for 24 hours. [redacted] Subjects will be randomised on Visit 4 (Day 1) to receive either MEDI0382 or placebo and dosing will commence following predose baseline vital signs, blood tests (including HbA1c), an ECG, body weight measurement, [redacted]. Subjects will then return for daily dosing or remain overnight locally until Day 5, and thereafter will have visits at weekly intervals until a maintenance dose of [redacted] is established. At Visits 6, 7, and 8, ABPM recordings [redacted] will be performed. On the last day of dosing (Visit 9; Day 32), subjects will attend for a long day visit and undergo a repeat MMTT, HbA1c, ABPM, [redacted] and serial PK sampling alongside safety assessments. On the following day (first follow-up visit, Visit 10; Day 33) subjects will return to the clinic for a blood draw, urine collection, weight measurement, [redacted]. Two additional follow-up visits (Visit 11; Day 40±5 and Visit 12; Day 60±5) will be performed after the last dose for safety assessments.

TARGET SUBJECT POPULATION

Male and female subjects ≥ 18 and < 85 years of age with renal impairment (eGFR ≥ 30 and < 60 mL/min/1.73 m^2) and T2DM, and who may be on insulin and/or combination oral therapies.

TREATMENT GROUPS AND REGIMENS MEDI0382 or placebo will be administered once daily in the morning via SC injection:

- MEDI0382 [redacted] once daily for 4 days, followed by [redacted] daily for 7 days, [redacted] daily for 7 days, and [redacted] daily for 14 days (n = 20)
- Placebo once daily for 32 days (n = 20)

STATISTICAL METHODS

Sample size: Forty subjects (20 completers in the MEDI0382 group and 20 completers in placebo group) will provide > 85% power to detect 18.1% difference between the two treatment groups in percentage change in the MMTT glucose AUC from baseline (Day -5) to the end of 32 days of treatment (Day 32), with a two-sided significance level of 0.1 and assuming the standard deviation of 20%.

Statistical analyses: The primary efficacy analysis will be performed using the intent-to-treat (ITT) population. The primary efficacy endpoint, percentage change in MMTT glucose AUC from baseline (Day -5) to the end of 32 days of treatment will be analysed using an analysis of covariance (ANCOVA) model. The model will include fixed effect of treatment and baseline AUC as a covariate. The difference of the percent change in glucose AUC between the two treatment arms will be compared with a two-sided significance level of 0.10. Secondary efficacy analyses will be performed using the ITT population. All secondary efficacy endpoints will be summarised by visit and by treatment group. The change in percentage of time spent within a target glucose range of 70 mg/dL (3.9 mmol/L) to 180 mg/dL (10 mmol/L) over a 7-day period at baseline to the final week of treatment will be analysed using a Wilcoxon rank-sum test. All other continuous endpoints will be analysed using a similar ANCOVA model as that for the primary analysis.

Safety analyses will be performed using the as-treated population. AEs and SAEs will be coded by the most updated version of Medical Dictionary for Regulatory Activities (MedDRA), and the type, incidence, severity, and relationship to study investigational product will be summarised by MedDRA System Organ Class and Preferred Term and by treatment. AEs leading to discontinuation, AEs leading to death, and deaths will also be summarised. Specific AEs will be counted once for each subject for calculating percentages. In addition, if the same AE occurs multiple times within a particular subject, the highest severity and level of relationship observed will be reported. Subject-level data listings of all AEs will be presented. Other safety data, such as vital signs, clinical laboratory data, ECG, and physical examination findings will be descriptively summarised at each time point by treatment. Mean ambulatory blood pressure and pulse rate measurements recorded over 24 hours at different time-points will be analysed using an ANCOVA model, adjusting for treatment and measurement at baseline.

Pharmacokinetic analyses: Pharmacokinetic parameters such as maximum concentration (C_{max}), time to maximum observed concentration (T_{max}), and AUC_{tau}, will be estimated from plasma concentration-time data for MEDI0382 at the [redacted] dose level. Descriptive statistics will be generated for PK parameters for the MEDI0382 group at [redacted] and for C_{trough} at each dose level.

Immunogenicity analyses: 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 treatment.

Interim analysis: No interim analysis is planned for this study.

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LIST OF ABBREVIATIONS

Abbreviation or Specialized Term	Definition
ABPM	ambulatory blood pressure monitoring
ACR	albumin creatinine ratio
ADA	anti-drug antibody(ies)
AE	adverse event
AESI	adverse event of special interest
ALP	alkaline phosphatase
ALT	alanine transaminase
ANCOVA	analysis of covariance
AST	aspartate transaminase
AUC	area under the curve
$AUC_{MMT.4h}$	area under the curve for glucose measured over 4 hours by the mixed meal tolerance test
AUC_{tau}	area under the curve during the dosing interval
[redacted]	[redacted]
BMI	body mass index
BP	blood pressure
CGM	continuous glucose monitoring
CI	confidence interval
C_{max}	maximum observed concentration
CRF	case report form
CSR	clinical study report
C_{trough}	trough plasma concentration
DILI	drug-induced liver injury
DPPIV	dipeptidyl peptidase-4
ECG	electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
eGFR	estimated glomerular filtration rate
GCP	Good Clinical Practice
GI	gastrointestinal
GLP-1	glucagon-like peptide-1
HbA1c	haemoglobin A1c
hCG	human chorionic gonadotropin
HIV	human immunodeficiency virus

Abbreviation or Specialized Term	Definition
IB	Investigator's Brochure
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IFU	instructions for use
IP	investigational product
IRB	Institutional Review Board
ITT	intent-to-treat
IXRS	interactive voice/web response system
LC/MS-MS	liquid chromatography-tandem mass spectrometry
MedDRA	Medical Dictionary for Regulatory Activities
MHRA	Medicines & Healthcare products Regulatory Agency
MMTT	mixed-meal tolerance test
MTD	maximum tolerated dose
NOAEL	no-observed-adverse-effect level
PFS	prefilled syringe
PK	pharmacokinetic(s)
PT	preferred term
RBC	red blood cell
SAE	serious adverse event
SAP	statistical analysis plan
SC	subcutaneous
SGLT2	sodium-glucose co-transporter 2
SID	subject identification
SOC	system organ class
T2DM	type 2 diabetes mellitus
TEAE	treatment emergent adverse event
T_{max}	time to maximum concentration
ULN	upper limit of normal
WBC	white blood cell
w/v	weight per 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 glycaemic control, cardiovascular risk, and mortality rates, and may even slow or reverse disease progression (Petersen et al, 2005). Many existing therapies for T2DM focus upon lowering blood glucose; however, there is a major unmet need for treatments that both improve glycaemic control and achieve disease-modifying weight loss.

Renal impairment attributed to chronic hyperglycaemia and hypertension is common in patients with longstanding T2DM, and is often exacerbated by obesity. Patients with significant renal impairment and T2DM therefore stand to benefit from medications that can deliver both improvements in glycaemic control and weight loss.

1.2 MEDI0382 Background

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

MEDI0382 is a synthetic peptide with both glucagon-like peptide-1 (GLP-1) and glucagon receptor co-agonist activity, which is under development for the treatment of T2DM and obesity. GLP-1 receptor agonists are established treatments for T2DM that improve glycaemic 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 (Lynch et al, 2014; Habegger et al, 2013). 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) and co-infusion of GLP-1 and glucagon has synergistic effects on reducing food intake and promoting weight loss in human subjects (Bagger et al, 2015).

1.3 Summary of Nonclinical Experience

[redacted]

[redacted]

1.4 Summary of Clinical Experience

[redacted]

[redacted]

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

1.5 Rationale for Conducting the Study

[redacted]

[redacted]

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 ICH/GCP, and applicable regulatory requirements.

MEDI0382 is a synthetic peptide with both GLP-1 and glucagon receptor co-agonist activity that promote glucose lowering and weight loss and is targeted at subjects with T2DM. MEDI0382 has the potential to deliver improvements in glycaemic control and lipid homeostasis, and is predicted to be a useful therapy for T2DM.

The study design aims to minimise potential risks to subjects participating in this study based on the proposed inclusion/exclusion criteria, safety monitoring, and up-titration dosing schedule. All subjects will be monitored throughout the study to ensure adequate glycaemic control. Subjects will be given appropriate training in subcutaneous (SC) injection administration as well as use of any devices.

Refer to the current IB for 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

- Administration of MEDI0382 once daily titrated up to a dose level of [redacted] will result in superior blood glucose control versus placebo after 32 days of treatment in subjects with T2DM and renal impairment.

1.7.2 Secondary Hypotheses

- Administration of MEDI0382 once daily titrated up to a dose level of [redacted] across 32 days will be well tolerated in subjects with T2DM and renal impairment
- Administration of MEDI0382 once daily titrated up to a dose level of [redacted] will result in superior weight loss versus placebo after 32 days of treatment in subjects with T2DM and renal impairment
- Administration of MEDI0382 once daily titrated up to a dose level of [redacted] will have a predictable pharmacokinetic (PK) profile in subjects with T2DM and renal impairment

2 OBJECTIVES AND ENDPOINTS

2.1 Primary Objective and Associated Endpoint

Table 1 Primary Objective and Associated Endpoint

Type	Objective	Endpoint
Efficacy	To assess the effect of MEDI0382 titrated up to a dose level of [redacted] on glucose control versus placebo after 32 days of treatment	• Percentage change in glucose area under the curve (AUC) as measured by a standardised mixed-meal tolerance test (MMTT) from baseline (Day -5) to the end of 32 days of treatment (Day 32)

2.2 Secondary Objectives and Associated Endpoints

Table 2 Secondary Objectives and Associated Endpoints

Type	Objective	Endpoints
Safety	To characterise the safety profile and tolerability of MEDI0382 titrated up to a dose level of [redacted] during dosing and follow-up in subjects with T2DM and renal impairment	• Measures of safety and tolerability (adverse events/serious adverse events [AEs/SAEs], vital signs, postural blood pressure [BP] changes, electrocardiogram [ECG], laboratory test results) • Change in mean 24-hour pulse rate, systolic and diastolic blood pressure from baseline (Day -5) to the end of dosing at each dose level (Days 4, 11, 18, and 32)
Efficacy	To assess the effects of MEDI0382 titrated up to a dose level of [redacted] on additional measures of glycaemic control versus placebo after 32 days of treatment	• Change in haemoglobin A1c (HbA1c) from baseline (Day 1) to the end of 32 days of treatment (Day 32) • Change in fasting glucose from baseline (Day 1) to the end of 32 days of treatment (Day 32) • Change in percentage of time spent within a target glucose range of 70 mg/dL (3.9 mmol/L) to 180 mg/dL (10 mmol/L) over a 7-day period at baseline (Days -8 to - 2) to the final week of treatment (Days 26-32)
Efficacy	To assess the effects of MEDI0382 titrated up to a dose level of [redacted] on weight versus placebo after 32 days of treatment	• Percentage and absolute change in body weight from baseline (Day 1) to the end of 32 days of treatment (Day 33)

Table 2 Secondary Objectives and Associated Endpoints

Type	Objective	Endpoints
PK/Immunogenicity	To characterise the PK profile and immunogenicity of MEDI0382	• PK endpoints: AUC over a dosing duration, maximum observed concentration (C_{max}), time to C_{max} (T_{max}), trough plasma concentration (C_{trough}) • Development of anti-drug antibodies (ADA) and titre (if confirmed positive)

2.3 Exploratory Objectives and Endpoints

[redacted]

Type	Objective	Endpoints
[redacted]	[redacted]	[redacted]

Table 3 Exploratory Objectives and Endpoints

Type	Objective	Endpoints
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

3 STUDY DESIGN

3.1 Description of the Study

3.1.1 Overview

This is a randomised, double-blind, placebo-controlled study to evaluate the safety, tolerability, efficacy, and PK profile of MEDI0382 titrated from [redacted] up to [redacted] and administered once daily by subcutaneous (SC) injection over 32 days in subjects with T2DM and renal impairment (eGFR ≥ 30 and < 60 mL/min/1.73 m^2). The study has a 14-day run-in period of diet and exercise and continuous glucose monitoring (CGM), a 32-day treatment period, and a 28-day follow-up. Diet and exercise guidance will be according to local practices. It is planned to randomise approximately 40 subjects across multiple study sites. Subjects will be consented, screened for suitability, and randomised within 40 days of screening, if eligible.

Throughout the study, subjects will have the choice to either travel to the clinic for visits or stay overnight locally whenever consecutive daily visits are required. Subjects will be expected to fast for at least 8 hours overnight prior to Visit 3 (Day -5), Visit 4 (Day 1), Visit 9 (Day 32), and Visit 12 (Day 60). [redacted]

On Visit 2 (Day -14) subjects will attend the clinical unit for a short visit. At this visit they will be given advice on diet and exercise (in accordance with local practices) and training in SC injection administration, and fitted with a CGM sensor that the subject will be expected to wear continuously for the duration of the study until the second follow-up visit (Visit 11). [redacted]. [redacted] On Visit 3 (Day -5), subjects will attend the clinical unit for a long visit and will undergo safety assessments and a mixed-meal tolerance test (MMTT). At this time, an ambulatory blood pressure monitoring (ABPM) device will be fitted on the contralateral arm to the CGM sensor and will be worn for 24 hours. [redacted] Subjects will be randomised on Visit 4 (Day 1) to receive either MEDI0382 or placebo and dosing will commence following predose baseline vital signs, blood tests (including HbA1c), an ECG, body weight measurement, [redacted]. Subjects will then return for daily dosing or remain overnight locally until Day 5, and thereafter will have visits at weekly intervals until a maintenance dose of [redacted] is established. At Visits 6, 7, and 8, ABPM recordings [redacted]. On the last day of dosing (Visit 9; Day 32), subjects will attend for a long day visit and undergo a repeat MMTT, HbA1c, ABPM, [redacted] and serial PK

sampling, alongside safety assessments. On the following day (first follow-up visit, Visit 10; Day 33) subjects will return to the clinic for a blood draw, urine collection, weight measurement, [redacted].
Two additional follow-up visits (Visit 11; Day 40±5 and Visit 12; Day 60±5) will be performed after the last dose for safety assessments.

[redacted]

[redacted]

[redacted]

3.1.2 Treatment Regimen

MEDI0382 or placebo will be administered once daily in the morning via SC injection:

- [redacted]
- [redacted]

[redacted]

3.1.4 Management of Study Medication Related Toxicities and Dose Modification

Nausea and Vomiting

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

[redacted]

[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

[redacted]

[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

[redacted]

[redacted]

[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

Management of Hyperglycaemia and Rescue Therapy

In subjects who have sustained hyperglycaemia [redacted] additional open-label rescue therapy should be considered by the investigator and should be documented in the relevant section of the CRF. For subjects where hyperglycaemia

is suspected, additional venous fasting plasma glucose measurements may be performed if necessary to investigate further.

Rescue therapy should be considered by the investigator following discussion with the medical monitor if any of the following apply:

- Fasting plasma glucose >200 mg/dL (11.1 mmol/L) on two occasions less than 8 days apart
- Three capillary plasma glucose levels > 250 mg/dL (13.9 mmol/L) in one week
- More than 30% of readings in hyperglycaemic range on CGM defined as > 250 mg/dL (13.9 mmol/L) in one week

[redacted] If rescue medication is required, subjects should continue to participate in the study and receive their study medication. An interim prescription of the rescue medication will be provided by the study site if necessary, but continued prescription of rescue therapy will remain the responsibility of the primary care physician or usual diabetes physician. Rescue medication will not be provided by the Sponsor for this study.

Investigators should consider discontinuing the investigational product in subjects with persistent fasting venous plasma glucose level of > 260 mg/dL (14.4 mmol/L), despite a maximum tolerated dose (MTD) of rescue therapy to enable optimization of the subject's glycaemic control. The subject should however remain in the study for all other study procedures and continued follow-up until their scheduled end of study date.

[redacted]

[redacted]

Management of Hypoglycaemia

A hypoglycaemic event is considered severe if associated with severe cognitive impairment requiring external assistance for recovery, as defined by the American Diabetes Association; clinically significant hypoglycaemia is defined as a capillary or venous plasma glucose reading of < 3.0 mmol/L (54 mg/dL). Spontaneous and clinically significant hypoglycaemia has not been experienced in prior studies with MEDI0382 up to a dose of [redacted] alongside metformin treatment.

All subjects will be provided with a diary and a glucose meter and will be advised to check their capillary plasma glucose level if they have symptoms of hypoglycaemia (hunger, dizziness, shaking, sweating, or irritability) or feel unwell and will be expected to record the level in their diary. Local protocols for treatment and follow-up of any hypoglycaemic episode should be followed. Any clinically significant hypoglycaemia should be reported by investigators as an AE regardless of whether or not the subject is experiencing symptoms or not. Pharmacological treatments administered for hypoglycaemia, eg, dextrose/glucose tablets, glucagon etc should be recorded in the electronic case report form (eCRF) as concomitant medications.

For subjects who experience a severe hypoglycaemic episode or a clinically significant episode of hypoglycaemia (defined as a capillary or venous plasma glucose reading of < 54 mg/dL (3.0 mmol/L) or an interstitial glucose reading < 54 mg/dL (3.0 mmol/L) recorded on CGM on two occasions across 15 minutes) a reduction in total daily dose of insulin of 20% should be made from the time of awareness of the event. If the subject is not using insulin during the study, a 50% dose reduction in oral medication should be made in the following order of preference: sulfonylureas, glitinide, pioglitazone, metformin, DPPIV inhibitors. Dose reduction should also be considered at the discretion of the investigator and following discussion with the medical monitor if > 2% of interstitial glucose readings on CGM are < 70 mg/dL (3.9 mmol/L).

Decline in Renal Function

For subjects who have a eGFR of 30-44 mL/min/1.73 m^2 (inclusive) at screening and are taking an existing dose of metformin that is higher than the recommended dose for that degree

of renal impairment, the dose of metformin should be reduced or discontinued at Visit 2 in accordance with local guidelines on metformin prescription in renal impairment, or to 500 mg once daily if no guidance is in place. Similarly, any subject experiencing a decline in eGFR during the study to 30-44 mL/min/1.73 m^2 (inclusive) should have their dose of metformin reduced or discontinued as described above.

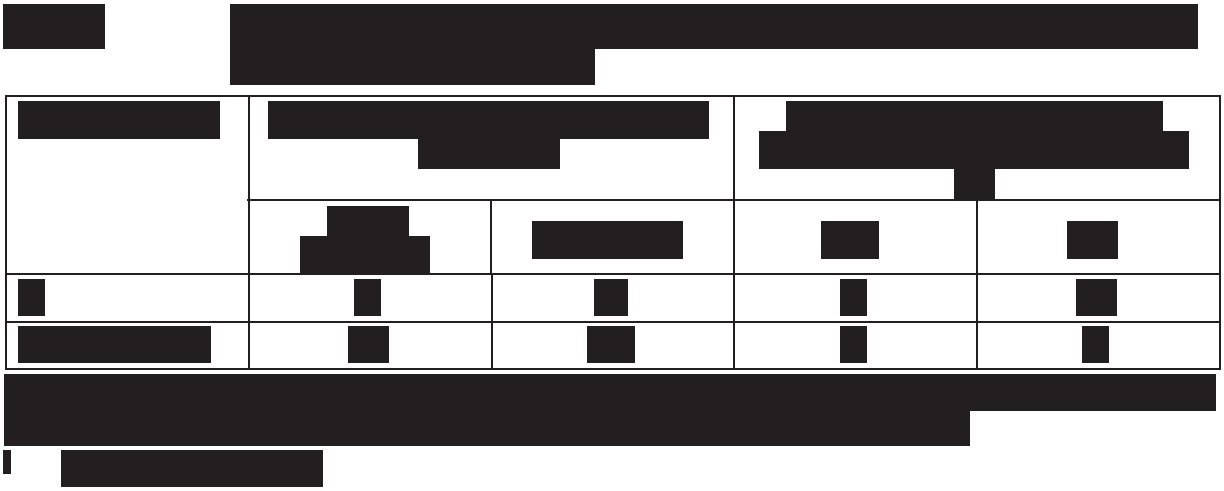
For subjects who are found to have a decline in renal function to eGFR < 30 mL/min/1.73 m^2 during the study, the subject should also be advised to stop metformin therapy and any other medications that are contraindicated for this degree of renal impairment.

For subjects who are eligible to take part in the study and are taking other medications for diabetes that are prescribed at a higher dose than recommended for their degree of renal insufficiency, dose reduction should be performed at Visit 2 in accordance with local treatment guidelines or the drug labelling.

For subjects who are found to have a decline in renal function to eGFR ≤ 25 mL/min/1.73 m^2 during the study, the subject should undergo a repeat eGFR level one week later, and if the eGFR remains ≤ 25 mL/min/1.73 m^2 on a second consecutive test, the investigational product (IP) should be discontinued, and the subject should also be advised to stop metformin therapy (if they have not already done so) and any other medications that are contraindicated for this degree of renal impairment. However, the subject should remain in the study for all other study procedures until their scheduled end of study.

3.2 Rationale for Dose, Population, and Endpoints

3.2.1 Dose Rationale



3.2.2 Rationale for Study Population

MEDI0382 is a GLP-1 and glucagon receptor co-agonist that promotes glucose lowering and weight loss and is targeted at subjects with T2DM. Renal impairment attributed to diabetic kidney disease is common in patients with longstanding T2DM. The entry criteria with respect to T2DM and eGFR of ≥ 30 and < 60 mL/min/1.73 m^2 both maximise recruitment potential and provide efficacy, safety, and tolerability data in the intended clinical population who concurrently have moderate renal impairment. The eligibility criteria also permit inclusion of subjects with an HbA1c of 6.5-10.5% and those who are treated with any combination of oral therapy and/or insulin, which reflects the natural history of late stage T2DM and concurrent chronic kidney disease (CKD). There is no requirement for a given number of subjects in each gender to be enrolled. It is intended that at least 50% (n=20) of subjects enrolled in the study will be taking insulin at a dose of ≥ 20 units/day to enable any effect of MEDI0382 on insulin dose adjustment to be observed. In addition, it is intended that approximately 40% (n=16) of subjects enrolled in the study will have an eGFR of ≥ 30 and < 45 mL/min/1.73 m^2 and at least 40% (n=16) of subjects enrolled in the study will have an eGFR of ≥ 45 and < 60 mL/min/1.73 m^2. This is to ensure subjects at both ends of the moderate renal impairment spectrum are adequately represented.

3.2.3 Rationale for Endpoints

Primary Endpoint

The primary endpoint of glucose AUC as measured by MMTT is required to evaluate the efficacy of the [redacted] dose of MEDI0382 in this population of subjects with T2DM and renal impairment.

Secondary Endpoints

Safety and Tolerability

[redacted]

Additional Measures of Glucose Lowering and Weight Loss

To better characterise the glucose-lowering efficacy of MEDI0382 across 32 days of dosing in renally impaired subjects, additional markers of glucose control including HbA1c and fasting glucose level will be measured, alongside measures of the percentage of time spent within a target glucose range measured by CGM. [redacted]

Pharmacokinetic Profile and Immunogenicity

Plasma concentrations of MEDI0382 at the [redacted] dose level will be used to evaluate the PK profile (C_{max}, time to maximum concentration [T_{max}], AUC_{tau}) in this specific population. In addition, C_{trough} at each dose level will be evaluated to ensure exposure to the drug.

Prior studies of MEDI0382 and metformin co-therapy have shown no signs of a PK interaction between MEDI0382 and metformin. Plasma samples predose (C_{trough}) will be collected and stored for analysis of metformin levels in case that renal function data warrant such analyses.

Anti-drug antibodies (ADA) incidence rate and titre will be tabulated for each treatment to monitor immunogenicity. Tiered analyses will be performed to include screening, confirmatory and titre assay components; samples confirmed positive for ADA will be tested

and analysed for antibody titre and reported, and may be utilised for further characterisation of the ADA response.

4 MATERIALS AND METHODS

4.1 Subjects

4.1.1 Number of Subjects

It is planned to randomise approximately 40 subjects across multiple study sites.

4.1.2 Inclusion Criteria

Subjects must meet all of the following criteria:

1 Age ≥ 18 and < 85 years at screening.

2 Signed and dated written informed consent (with the exception of consent for genetic and nongenetic research) prior to performing any protocol-related procedures, including screening evaluations.

3 Diagnosed with T2DM with glucose control managed with any insulin*[1] and/or oral therapy combination where no significant dose changes of oral therapy of more than 50% have occurred in the 3 months prior to screening

4 Body mass index (BMI) between 25 and 45 kg/m^2 (inclusive) at screening

5 HbA1c range of 6.5 % to 10.5% (inclusive) at screening

6 Renal impairment with eGFR ≥ 30 and < 60 mL/min/1.73 m^2 at screening. Approximately 16 subjects (40%) are required to have a screening eGFR ≥ 30 and < 45 mL/min/1.73 m^2 and at least 16 subjects (40%) are required to have screening eGFR ≥ 45 and < 60 mL/min/1.73 m^2. eGFR will be determined by the chronic kidney disease-epidemiology collaboration (CKD-EPI) equation. In instances where the eGFR estimated during the screening period is outside the range expected from the subject's medical history, the subject may be re-tested once.

7 Females of childbearing potential must have a negative pregnancy test at screening and randomisation, and must not be lactating. Women of childbearing potential who are sexually active with a nonsterilized male partner must be using at least one highly effective method of contraception (see Section 10.2 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.

*[1] At least 50% of subjects (n=20) enrolled in the study should be taking insulin at a total daily dose of ≥ 20 units.

4.1.3 Exclusion Criteria

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

1 History or presence of significant medical or psychological conditions, including substance dependence/abuse, or significant abnormalities in laboratory parameters or vital signs including ECG, which in the opinion of the investigator, would compromise the subject's safety or successful participation in the study. As an example, severe anaemia (haemoglobin < 7.0 g/dL) could be exclusionary due to blood sampling required by the protocol, at the discretion of investigator.

2 Concurrent participation in another interventional study of any kind and repeat randomisation in this study is prohibited

3 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 (if known; whichever is longer) at the time of Visit 2

4 Any subject who has received any of the following medications within the specified timeframe prior to the start of the study (Visit 2) (see Section 4.7.2 for further details)

- Herbal preparations within 1 week prior to the start of dosing (Visit 4) 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 (Visit 4)
- Aspirin (acetylsalicylic acid) at a dose greater than 150 mg once daily and within the last 3 days prior to the start of the run-in period (Visit 2)
- Paracetamol (acetaminophen) or paracetamol-containing preparations at a total daily dose of greater than 3000 mg and within the last 3 days prior to the start of the run-in period (Visit 2)
- Ascorbic acid (vitamin C) supplements at a total daily dose of greater than 1000 mg and within the last 3 days prior to the start of the run-in period (Visit 2)
- Opiates, domperidone, metoclopramide, or other drugs known to alter gastric emptying and within 2 weeks prior to the start of dosing (Visit 4)

5 Severe allergy/hypersensitivity to any of the proposed study treatments 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

7 Subjects who have undergone a renal transplant

8 Subjects with suspicion of acute or subacute renal function deterioration (eg, subjects with large fluctuations of creatinine values documented within the 6 months prior to screening)

9 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

10 History of acute or chronic pancreatitis

11 Significant hepatic disease (except for non-alcoholic steatohepatitis or nonalcoholic fatty liver disease without portal hypertension or cirrhosis) and/or subjects with any of the following results:

- Aspartate transaminase (AST) ≥ 3 × upper limit of normal (ULN)
- Alanine transaminase (ALT) ≥ 3 × ULN
- Total bilirubin ≥ 2 × ULN

12 Poorly controlled hypertension defined as:

- Systolic BP > 180 mm Hg
- Diastolic BP ≥ 100 mm Hg

after 10 minutes of seated 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 systolic BP ≤ 180 or diastolic BP < 100 mm Hg with a preserved nocturnal dip of > 15% will be considered eligible

13 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

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

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

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

17 Any positive results for serum hepatitis B surface antigen (HBsAg), hepatitis C antibody, and human immunodeficiency virus (HIV) antibody

18 Nephrotic range proteinuria defined as spot urine ACR > 250 mg/mmol at screening

19 History of substance dependence, alcohol abuse, or excessive alcohol intake (defined as an average weekly intake of > 21 alcoholic drinks for men or > 10 alcoholic drinks for women) within 3 years prior to screening, and/or a positive screen for drugs of abuse or alcohol at screening or on Day -5. Subjects who use tricyclic antidepressants or

benzodiazepines for an established clinical indication may be permitted to enter the study based upon the judgement of the investigator.

20 Involvement of any AstraZeneca, MedImmune, contract research organization, or study site employee or their close relatives

4.1.4 Subject Enrollment and Randomisation

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

Approximately 40% of subjects (n = 16) enrolled in the study will have an eGFR of ≥ 30 and < 45 mL/min/1.73 m^2 and at least 40% (n = 16) will have an eGFR of ≥ 45 and < 60 mL/min/1.73 m^2. In addition, at least 50% of subjects (n=20) enrolled in the study should be taking insulin at a total daily dose of ≥ 20 units.

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 randomised), including the reason(s) for screening failure.

Subjects who fail to meet the inclusion/exclusion criteria (ie, screening failures) should not, under any circumstances, be randomised or receive investigational product. There can be no exceptions to this rule. Subjects who are enrolled, but subsequently found not to meet all the eligibility criteria, should not be randomised or initiated on treatment. If randomisation and treatment initiation occur for a subject found not to meet any eligibility criterion, withdrawal of the subject from the study will be the decision of the medical monitor.

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

4.1.5 Withdrawal from the Study

Subjects are free to withdraw their consent to participate in the study (investigational product and 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 adverse events (AEs) and will be encouraged to remain in study for the remainder of the scheduled follow-ups. Adverse events will be followed up; diary cards 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; specific examples include:

- Dose-limiting symptoms with respect to GI tolerability and in particular if a subject requires intravenous fluids to treat volume depletion secondary to nausea and vomiting, even after measures are taken to reduce the risk of vomiting, after discussion with the medical monitor
- eGFR $\leq$ 25 mL/min/1.73 m^2 on two consecutive blood tests
- Acute kidney injury (AKI) in a subject as defined by:
    - An increase in serum creatinine by 0.3 mg/dL (26.5 µmol/L) within 48 hours in at least 2 readings
    - An increase in serum creatinine to 1.5 times baseline in at least 2 readings, which is known or presumed to have occurred within the prior 7 days
- Subject noncompliance that, in the opinion of the investigator or sponsor, warrants withdrawal (eg, refusal to adhere to scheduled visits).
- Pregnancy in a female subject
- Subjects with persistent fasting glucose level of > 260 mg/dL (14.4 mmol/L) despite a MTD of rescue therapy to enable optimisation of the subject's glycaemic control
- Any subject where Hy's Law criteria on liver function tests is met: AST or ALT $\geq$ 3 × ULN **together with** Total bilirubin $\geq$ 2 × ULN
- Any subject who develops a life-threatening arrhythmia including sustained ventricular tachycardia, ventricular fibrillation or new ECG changes of second or third-degree heart block

Subjects who are permanently discontinued from receiving investigational product will be followed for protocol-specified assessments including follow-up of any AEs unless consent is withdrawn from further study participation (Section 4.1.5), the subject is lost to follow-up, the subject starts alternative treatment, or the subject is enrolled in another interventional clinical study.

4.1.7 Replacement of Subjects

Subjects who withdraw from the study will be replaced where possible. A maximum number of three subjects may be replaced during the study.

4.1.8 Withdrawal of Informed Consent for Data and Biological Samples

Biological Samples Obtained for the Main Study

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

4.2 Schedule of Study Procedures

Whenever vital signs, 12-lead ECGs, and blood draws are scheduled for the same nominal time, blood draws should occur last. The timing of the first two 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 9 shows all procedures to be conducted at the screening visit and run-in procedures.

Table 9 Screening and Run-in Procedures

Study Period	**Screening**	**Run-in**		
Visit Number	**V1**	**V2**	**V3** [a]	**Remote contact**
Procedure / Study Day	**D-40 to D-15**	**D-14**	**D-5**	**D-1**
Written informed consent/ assignment of SID number	X			
[redacted]	[redacted]			
[redacted]	[redacted]			
[redacted]	[redacted]			
Outpatient visit to clinic [c]	X	X	X	
Medical history	X			
Physical examination (full)	X			
Weight, height and BMI calculation	X			
ECG	X			
Vital signs [d, e]	X		X[e]	
Collect blood for				
Serum chemistry (including eGFR calculation)			X	
LFTs, Cr, and eGFR calculation	X			
Haematology (FBC)	X		X	
HbA1c	X			
Calcitonin	X			
HIV-1 and -2 antibodies; hepatitis B and C serology	X			

Table 9 Screening and Run-in Procedures

Study Period	**Screening**	**Run-in**		
Visit Number	**V1**	**V2**	**V3** [a]	**Remote contact**
Procedure / Study Day	**D-40 to D-15**	**D-14**	**D-5**	**D-1**
MMTT (collect samples for glucose at all time points) [f]			X	
Fasting blood sample for active GLP-1			X	
Collect urine for				
Urinalysis (dipstick)	X		X	
Urine albumin/creatinine ratio [g]	X	X	X	
Pregnancy test (women of childbearing potential only) [h]	X		X	
Drug and alcohol screen	X		X	
[redacted]			[redacted]	
CGM device demonstration	X	X		
CGM sensor application		X		
CGM [i]		←	———	→
ABPM [j]			X	
Diet and exercise advice		X		
[redacted]		[redacted]		
SC injection self-administration training [l]	X	X	X	
Concomitant medications	X	X [m]	X	
Verify eligibility criteria	X	X		X
Assessment of AEs / SAEs	X	X	X	X
Glucose meter and diary provision [n]			X	
[redacted]				[redacted]

AEs = adverse events; ABPM = ambulatory blood pressure monitoring; BMI = body mass index; BP = blood pressure; CGM = continuous glucose monitoring; CR = creatinine; D = Day; ECG = electrocardiogram; eGFR = estimated glomerular filtration rate; FBC = full blood count; GLP-1 = glucagon-like peptide-1; HbA1c = glycated haemoglobin; HIV = human immunodeficiency virus; IFU = instructions for use; LFT = liver function tests (albumin; alanine transaminase [ALT], aspartate transaminase [AST], alkaline phosphatase [ALP], and total bilirubin); MMTT = mixed meal tolerance test; PK = pharmacokinetic; SAE = serious adverse events; SC = subcutaneous; SID = subject identification; V = visit

[a] Subjects are required to fast for at least 8 hours overnight prior to the visit. Subjects are permitted to drink water during this period of fasting. For days where subjects are required to fast the investigator/study team may need to consider dose [redacted]

[c] The diet of subjects should not be restricted in any way during the study (unless fasting or a standardised liquid meal is specified).

[d] Blood pressure should be measured at heart level and opposite to the arm where the CGM device is applied, with the subject supine and rested for 10 minutes prior to the measurement. * Day-5: vital signs to be taken prior to fitting the ABPM device

[e] Vital Signs Schedule (blood pressures, pulse rate, respiratory rate, and temperature): on days where ABPM is due to be checked a set of vital signs should be performed prior to application of the ABPM cuff. Blood pressure should be measured at heart level and opposite to the arm where the CGM device is applied, with the subject supine and rested 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.

[f] Following a minimum 8-hour fast overnight, a blood sample for glucose will be taken immediately (within 15 minutes) prior to the subject drinking one entire can of Ensure Plus as a standardised meal (ie, '0 minutes'). Blood samples for glucose will additionally be drawn at 15, 30, 45, 60, 90, 120, 180 and 240 minutes (± 5 minutes) after consumption of the standardised meal.

[g] Urine sample for urine albumin/creatinine ratio at Visit 1 screening may be taken at any time and does not need to be a first void specimen. At Visit 2 (Day-14) and Visit 3 (Day -5) urine sample for urine albumin / creatinine ratio should be taken as an early morning specimen during the first void of the day.

[h] Pregnancy tests do not need to be conducted in women who are surgically sterile (ie, bilateral tubal ligation, bilateral oophorectomy, or complete hysterectomy) or are post-menopausal (defined as at least 1 year since last menses and/or having an elevated follicle stimulating hormone laboratory value which is in the post-menopausal range in previous laboratory test results).

[i] CGM device should be worn continuously throughout the study until V11 and the sensor should be applied to the arm, taking into account subject preference and which side the ABPM device will be used. The sensor applied to the skin is single use and may not be re-attached once removed.

[j] Subjects will be fitted with the ABPM device whilst at the clinical unit, which may involve practice inflations. The ABPM device should be applied on the arm contralateral to the arm where the CGM device is applied. The subject will then wear the monitor / cuff for approximately 24 hours and will remove at the end of the 24-hour period whilst at home and will return the monitor at their next visit.

[k] [redacted]

[l] Subject's ability to self-administer investigational product will be verified using normal saline subcutaneous injections as required by the subjects until they feel confident in self-injection. Training will be given to familiarise subject with Instructions for Use (IFU) booklet and to assess suitability for self-injection using the prefilled syringe (PFS).

[m] [redacted]

[n] A glucose meter, test strips and diary should be provided to the subject. The subject should be trained in its use and advised to test their capillary plasma glucose at any time the subject feels unwell or has symptoms of hypoglycaemia (hunger, dizziness, shaking, sweating or irritability).

[o] [redacted]

4.2.2 Randomised Treatment Period

Table 10 shows all procedures to be conducted during the treatment period.

Table 10 Treatment Period Study Procedures

Visit Number	**V4** [a]	**V5**	**V6**	**V7**	**V8**	**V9** [a]
Procedure / Study Day	**D1**	**D2, D3, D4**	**D5**	**D12**	**D19**	**D32**
Daily visits for dosing [b]		X				
Outpatient visit to clinic [c]	X		X	X	X	X
Concomitant medications	X	X	X	X	X	X
Physical examination (abbreviated)	X		X	X	X	X
Vital signs [d]	X		X	X	X	X
ABPM [e]			X	X	X	X
ECG [f]	X		X	X	X	X
Body weight [g]	X		X	X	X	X
[redacted]	[redacted]		[redacted]	[redacted]	[redacted]	[redacted]
Randomisation	X					
IP administration [i] **(SC)**	**X**	**X**	**X**	**X**	**X**	**X**
Dispense IP	X	X	X	X	X	.X
Up-titration [j]			X	X	X	
Collect blood for						
Haematology panel (predose as applicable)	X		X	X	X	X
Serum chemistry (including eGFR calculation; predose as applicable)	X		X	X	X	X

Table 10 Treatment Period Study Procedures

Visit Number	V4 [a]	V5	V6	V7	V8	V9 [a]
Procedure / Study Day	**D1**	**D2, D3, D4**	**D5**	**D12**	**D19**	**D32**
Lipase and amylase	X		X	X	X	X
Calcitonin	X					X
Lactate	X					X
Fasting lipid profile	X					X
Fasting glucose	X					X
HbA1c	X					X
PK for MEDI0382 [k]	X		X	X	X	X
Samples for potential future metformin PK analysis (predose)[l]	X		X	X	X	X
ADA [m]	X			X		X
[redacted]	[redacted]					
[redacted]	[redacted]					[redacted]
MMTT (collect samples for glucose only at all time points) [o]						X
Collect urine for						
Pregnancy test (women of childbearing potential only)[p]					X	
Urinalysis (dipstick; predose as applicable)	X		X	X	X	X
Urine albumin/creatinine ratio [q]	X		X	X	X	X

Table 10 Treatment Period Study Procedures

Visit Number	V4 [a]	V5	V6	V7	V8	V9 [a]
Procedure / Study Day	**D1**	**D2, D3, D4**	**D5**	**D12**	**D19**	**D32**
[redacted]	[redacted]		[redacted]	[redacted]	[redacted]	[redacted]
CGM [r]	←	—	—	—	—	→
CGM sensor application/change [s]	X			X	X	X
Check CGM readings [redacted]			X	X	X	X
Glucose meter and diary provision [t]	←	—	—	—	—	→
Assessments of AEs / SAEs	X	X	X	X	X	X

ABPM = ambulatory blood pressure monitoring; ADA = anti-drug antibody; AE = adverse event; BP = blood pressure; CGM = continuous glucose monitoring; D = Day; ECG = electrocardiogram; eGFR = estimated glomerular filtration rate;; HbA1c = glycated haemoglobin; IP = investigational product; MMTT = mixed meal tolerance test; PFS = prefilled syringe; PK = pharmacokinetic; SAE = serious adverse event; SC = subcutaneous; ULN = upper limit of normal; V = visit

[a] Subjects are required to fast for at least 8 hours overnight prior to the visit. Subjects are permitted to drink water during this period of fasting. For days where subjects are required to fast the investigator/study team may need to consider dose [redacted].

[b] Subjects are required to receive their doses at the clinic on Days 1 – 4, as preparation of the [redacted] dose necessitates dilution and must be performed by site staff. Subjects are also required to dose at the clinic on study day visits when predose assessments are required. Subjects may travel to the site for daily visits during this time, or alternatively should be given the option to stay overnight locally if this is more convenient.

[c] The diet of subjects should not be restricted in any way during the study (unless fasting or a standardised liquid meal is specified).

[d] Vital Signs Schedule (blood pressures (postural at Day 1 predose and Day 32), heart rate, respiratory rate, 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 whilst supine at heart level in the nondominant arm where possible, opposite to the arm where the CGM device is applied, with the subject supine and rested 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.

- Day 1; vital signs to be taken; predose (-15 min), 15, 30, and 60 minutes (± 5 min) and 2 hours (± 10 min) postdose

- Day 1 predose and Day 32; postural blood pressure supine and then standing should be performed
- Days 5, 12, 19, 32; vital signs to be taken prior to fitting ABPM device

[e] Subjects will be fitted with the ABPM device while at the clinical unit, which may involve practice inflations. The ABPM device should be applied on the opposite arm to the arm where the CGM device is applied. The subject will then wear the monitor/cuff for approximately 24 hours and will remove at the end of the 24-hour period whilst at home and will return the ABPM device at their next visit.

[f] A digital ECG recording should be performed predose and 2 hours post-dose after the subject has rested for 10 minutes in the supine position on Days 1 and 32. No specific time point is required for other visits.

[g] Body weight should be measured in the morning prior to breakfast (predose on Day 1); refer to Section 4.3.1.3 for details.

[h] [redacted]

[i] Dosing will occur daily from Day 1 to Day 32 inclusive. Subjects are required to be dosed at the clinic for the [redacted] dose and on study day visits when predose procedures are required (Days 5, 12, 19, and 32). See Section 4.3 for further information. Ideally subjects should self-administer doses under supervision and study site staff should ensure that the subject self-administers the first dose of IP delivered via PFS on Day 5 to ensure that they are confident in self-injecting via PFS at home.

[j] Up-titration steps will be performed on Day 5 (dose will increase from [redacted]), Day 12 (dose will increase from [redacted]) and Day 19 (dose will increase from [redacted])

[k] PK Sampling Schedule for MEDI0382:

- Day 1: Predose
- Day 5: Predose
- Day 12: Predose
- Day 19: Predose
- Day 32: Predose and at 0.5, 1, and 2 hours (± 15 min); 4, 6 and 8, (± 30 min) postdose
- Day 33: 24 hours (± 15 min) postdose

[l] Samples will be collected for potential future metformin PK analysis only in subjects who are taking metformin (metformin PK samples are to be taken prior to metformin dose administration and therefore subjects should be advised to delay their morning metformin dose until after this blood test on these study visits.)

[m] ADA sampling schedule: Day 1 predose; Day 12 predose; Day 32 predose

[n] During the informed consent process subjects will be asked to provide consent for the main study [redacted] Only sample(s) for which the subject has consented will be taken.

[o] MMTT schedule: Following a minimum 8-hour fast overnight and where relevant, 2.5 hours after taking the IP, a blood sample for glucose will be taken immediately prior (within 15 minutes) to the subject drinking one entire can of Ensure Plus as a standardised meal (ie, "0 minutes"). Blood samples for glucose will additionally be drawn at 15, 30, 45, 60, 90, 120, 180, and 240 minutes (± 5 min) after consumption of the standardised meal. [redacted]

[p] A urine pregnancy test should be conducted on any female subject of childbearing potential as detailed in the schedule. Pregnancy tests do not need to be conducted in women who are surgically sterile (ie, bilateral tubal ligation, bilateral oophorectomy, or complete hysterectomy) or are postmenopausal (defined as at least 1 year since last menses and/or having an elevated follicle stimulating hormone laboratory value which is in the postmenopausal range in previous laboratory test results).

[q] Urine sample for urine albumin / creatinine ratio should be taken as an early morning specimen during the first void of the day and predose where relevant.

[r] CGM device should be worn continuously throughout the study until the second follow-up visit (V11) and the sensor should be applied to the arm, taking into account subject preference and which side the ABPM device will be used on. The sensor applied to the skin is single-use and may not be re-attached once removed.

[s] CGM sensor application should occur at least 2 hours predose+/- 15 minutes on Day 1; thereafter, existing CGM sensors should be removed and a new sensor applied at 0800 hours ± 120 minutes on Day 12 and at any time on Day 19. On Day 32, a new sensor will be applied and worn until the second follow-up visit (V11). Whenever a new CGM sensor is applied, at least 1 hour afterwards, the site staff should ensure the sensor is activated.

[t] A glucose meter, test strips, and a diary should be provided to the subject. The subject should be trained in its use and advised to test their capillary plasma glucose at any time the subject feels unwell or has symptoms of hypoglycaemia (hunger, dizziness, shaking, sweating, or irritability).

4.2.3 Follow-up Period

Table 11 shows all procedures to be conducted during the follow-up period.

Table 11 Schedule of Follow-up Procedures

Study Period	**Follow-up Period**		
Visit Number	**V10**	**V11**	**V12 (EoS) [a]**
Procedure / Study Day	**D33**	**D40 ± 5**	**D60 ± 5**
Outpatient visit to the clinic	X	X	X
Physical examination (abbreviated)		X	X
Weight	X [b]	X	X
ECG		X	X
Vital signs		X	X
Collect blood for			
Serum chemistry (including eGFR calculation)	X	X	X
Fasting glucose			X
Calcitonin [c]			X [b]
Haematology		X	X
ADA[d]			X [c]
HbA1c			X
PK for MEDI0382[e]	X		
Collect urine for			
Urinalysis (dipstick)		X	X
Urine albumin / creatinine ratio [f]	X	X	X
Pregnancy test (women of childbearing potential only)[g]	X		X
Check CGM readings [redacted]	X	X	
Removal of CGM sensor		X	
Glucose meter and diary provision	X	X	
Assessment of AEs / SAEs	X	X	X
Concomitant medications		X	X

AE = adverse event; ADA = anti-drug antibody; BMI = body mass index; CGM = continuous glucose monitoring; ECG = electrocardiogram; eGFR = estimated creatinine clearance; EoS = End of study; HbA1c = glycated haemoglobin; SAE = serious adverse event.

[a] Subjects are required to fast for at least 8 hours overnight prior to the visit. [redacted]

[b] D33 body weight should be measured in the morning prior to breakfast. Refer to Section 4.3.1.3 for details.

[c] Calcitonin need only be re-measured in subjects who had a level > upper limit of normal (ULN) on Day 32

[d] If this sample is ADA positive, the subject will be asked to return to provide another sample at approximately 3 months after the end-of-study visit (post-study sample). If this sample is ADA positive, additional visit(s) every 3 months should continue until a sample tests negative for ADA.

[e] PK Sampling Schedule for MEDI0382:

- Day 1: Predose
- Day 5: Predose
- Day 12: Predose
- Day 19: Predose
- Day 32: Predose and at 0.5, 1, and 2 hours (± 15 min); 4, 6 and 8 (± 30 min) postdose
- Day 33: 24 hours (± 15 min) postdose

[f] Urine sample for urine albumin / creatinine ratio should be taken as an early morning specimen during the first void of the day.

[g] A urine pregnancy test should be conducted on any female subject of childbearing potential as detailed in the schedule. Pregnancy tests do not need to be conducted in women who are surgically sterile (ie, bilateral tubal ligation, bilateral oophorectomy, or complete hysterectomy) or are postmenopausal (defined as at least 1 year since last menses and/or having an elevated follicle stimulating hormone laboratory value which is in the postmenopausal range in previous laboratory test results).

4.3 Description of Study Procedures

4.3.1 Efficacy

4.3.1.1 Mixed-meal Tolerance Tests

A standardised MMTT will be used to assess change in glucose AUC measured from baseline (Day -5) to the end of 32 days of treatment. A detailed MMTT schedule is provided in the footnotes to Table 9 and Table 10.

Following a minimum 8-hour fast the subject will undergo an MMTT which will involve the consumption of a standardised liquid meal (Ensure Plus, a nutritional supplement containing the components of fat, carbohydrate, and protein, which make up a standard MMTT) within 15 minutes, and timed serial blood samples will be obtained for measurement of glucose through 240 minutes after consumption of the standardised meal (with no additional food intake during this time). Blood will be drawn within 15 minutes before consuming the standardised liquid meal (ie, “0 minutes”), and at 15, 30, 45, 60, 90, 120, 180, and 240 minutes (± 5 minutes) after consumption. Blood sampling should occur as close as possible to the specified times for the MMTT. Sampling ± 5 minutes of the specified time will not be considered a protocol deviation but the exact time of sampling should be recorded. At Day 32 the serial blood sampling will begin 2.5 hours after Investigational Product administration.

Subjects who use a quick acting or pre-mixed form of insulin with breakfast should receive their usual/current dose of breakfast-time insulin with the Ensure Plus milkshake ie, dose reduction of insulin is not required. Subjects who carbohydrate count or vary insulin dose in relation to meal type are to be advised that the Ensure Plus milkshake contains approximately

44.4 g of carbohydrate, 10.8 g of fat and 13.8 g of protein and to adjust their insulin dose on this basis. [redacted]

[redacted]

4.3.1.2 Blood Tests for Glucose Lowering Efficacy

Blood samples will be collected to evaluate blood glucose (fasting) and HbA1c levels (see Table 9, Table 10, and Table 11 for evaluation times).

4.3.1.3 Weight

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, the same calibrated scale should be used for each measurement for any given subject.

4.3.2 Medical History, Physical Examination, Electrocardiogram, Weight, and Vital Signs

4.3.2.1 Medical History and Physical Examination

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

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

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

The full physical examination including structured neurological examination is required at screening. Targeted/abbreviated 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.

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

4.3.2.2 Electrocardiograms

At the visits specified in Table 9, Table 10, and Table 11, 12-lead digital ECGs will be obtained after the subject has rested for 10 minutes in the supine position. Only a single ECG of 10 seconds' duration will be required at the specified time points.

The same centrally provided recorder will be used for each evaluation for each subject. Date and time settings should be checked at the start of each study day to ensure that they are set to the correct time.

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

Electrocardiograms will be digitally recorded but must be printed on paper. In this study lead II will be analysed and reported as primary. Lead V2 or V5 will be analysed, for all visits, as backup for the individual where analysis in lead II is not deemed possible for predose or significant parts of whole visits or whole visits. The following variables should be captured: heart rate, RR, PR, QRS, axis, ST-T morphology, and QT intervals from the primary lead of the digital 12-lead ECG. The investigator may add extra 12-lead ECG safety assessments if there are any abnormal findings or if the investigator considers it is required for any other safety reason.

4.3.2.3 Assessment of the Injection Site

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

4.3.2.4 Vital Signs

Vital sign measurements (BP, pulse, body temperature and respiratory rate) will be obtained after the subject has rested in the supine position for at least 10 minutes at the time points specified in the schedules of procedures (for time points where ECG recording precedes vital sign measurement, the 10-minute rest in the supine position prior to the ECG suffices for the rest prior to vital sign measurement). Route of body temperature measurement will be according to local protocols. Where indicated on Visit 4 (Day 1) predose and Visit 9 (Day 32) postural BP assessed supine and then standing should be measured.

4.3.3 Clinical Laboratory Tests

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

Clinical laboratory safety tests will be performed in a licensed central clinical laboratory. Urine pregnancy tests may be performed at the site using a licensed test (urine human chorionic gonadotropin [hCG]; dipstick). Abnormal 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 9, Table 10, Table 11 for the schedule of tests):

Serum Chemistry

Sodium	Bicarbonate
Potassium	Aspartate transaminase (AST)
Chloride	Phosphorus
Glucose	Blood urea nitrogen (BUN) or serum urea
Creatinine	Alkaline phosphatase (ALP)
Albumin	Alanine transaminase (ALT)
Calcium	Total bilirubin
Magnesium	

Hematology

Hematocrit	Platelet count
Hemoglobin	Mean corpuscular hemoglobin concentration
Red blood cells (RBC)	Mean corpuscular volume
White blood cells (WBC) count with differential	

Urinalysis

pH	Specific gravity
Bilirubin	Color
Glucose	Appearance
Ketones	WBC Casts
Blood	RBC Casts
Protein	

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

Pregnancy Test (females of childbearing potential only)

- Urine human chorionic gonadotropin (hCG)

Other Tests

- Urine albumin / creatinine ratio
- Urine drug screen (screening and Day -5 only)
- Alcohol screening test (screening and Day -5 only)
- Pancreatic amylase, lipase
- Calcitonin
- Lactate
- HIV-1 and -2 antibodies (screening only)
- Hepatitis B and C serology (screening only)
- Fasting lipid profile

4.3.4 Pharmacokinetic Evaluation and Methods

Blood will be collected to evaluate PK of MEDI0382 in plasma (see Table 10 and Table 11 for collection time points and timing with regard to dosing). The PK of MEDI0382 in plasma will be measured utilizing a validated liquid chromatography-tandem mass spectrometry (LC/MS-MS) method.

For those subjects who are taking metformin, blood samples will be collected and stored for measurement of metformin PK if the resulting analyses are deemed to be useful to further evaluate safety of MEDI0382 (see Table 10 for collection time points). Blood samples will be stored for up to 6 months after clinical study report finalisation. Evaluations will be performed using a validated LC/MS-MS assay.

Residual MEDI0382 PK samples will be retained for up to 5 years after clinical study report (CSR) finalisation.

4.3.5 Immunogenicity Evaluation and Methods

Blood samples will be collected to evaluate serum ADA responses to MEDI0382 (see Table 10 and Table 11 for collection time points). A screening assay will be used to determine ADA-positive samples. This will be in the form of a traditional ligand-binding "bridging" assay using electrochemiluminescence. Any positive samples will be tested in a confirmatory assay whereby the specificity of the ADA response will be confirmed as either positive or negative with respect to MEDI0382. Cross-reactivity of ADA-positive samples to GLP-1 and glucagon may also be assessed. Titer evaluation will be performed on samples that are confirmed positive for ADA.

At the end of study visit (Visit 12), if a subject's sample is confirmed 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 subject will be monitored until ADA levels have returned to baseline. Serum samples collected for ADA should be stored for 2 years after marketing approval, and they may be utilised for further characterisation of the antibody response.

4.3.6 Pharmacodynamic Evaluation and Methods

4.3.6.2 Training for Application and Wearing of ABPM Device

Subjects will be given training at their local study site about how to set up and apply the ABPM device. In brief, an appropriate size cuff encircling 80% to 100% of the arm will be selected and the device will be fitted to the subject (on the contralateral side to the CGM device), with the bladder placed over the artery and an initial test reading performed. The

subjects will be advised that for the first reading the device will inflate to a pressure of 180 mm Hg, and thereafter the device will adapt to inflate to a pressure just above the last recorded BP. The subject will be advised to undergo normal daily activities while wearing the cuff, and he/she will be advised to avoid any strenuous form of activity, bathing, or showering while wearing the cuff. The subject will be advised to remain still during a measurement with the arm relaxed at heart level. The subject will also be given advice on how to wear the device during the day and at night while sleeping, and what to expect in terms of frequency of readings during the day (every 15 minutes) and overnight (every 30 minutes). During ABPM, systolic BP, diastolic BP, heart rate pressure, heart rate, and mean arterial pressure readings will be recorded over a period of 24 hours.

[redacted]

4.3.10 Estimate of Volume of Blood to Be Collected

The estimated volume of blood to be collected from each subject over the entire course of the study is approximately 200.5 mL if the subject is taking metformin or approximately 180.5 mL if the subject is not taking metformin. An additional approximately 18.5 mL will be collected if a subject consents to optional genetic research and a further approximately 27 mL if a subject consents to optional future nongenetic research, yielding a maximum total volume collected of approximately 246 mL. If repeats of any blood tests are required, the volume of blood collection will increase accordingly.

4.4 Study Suspension or Termination

The sponsor reserves the right to temporarily suspend or permanently terminate this 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

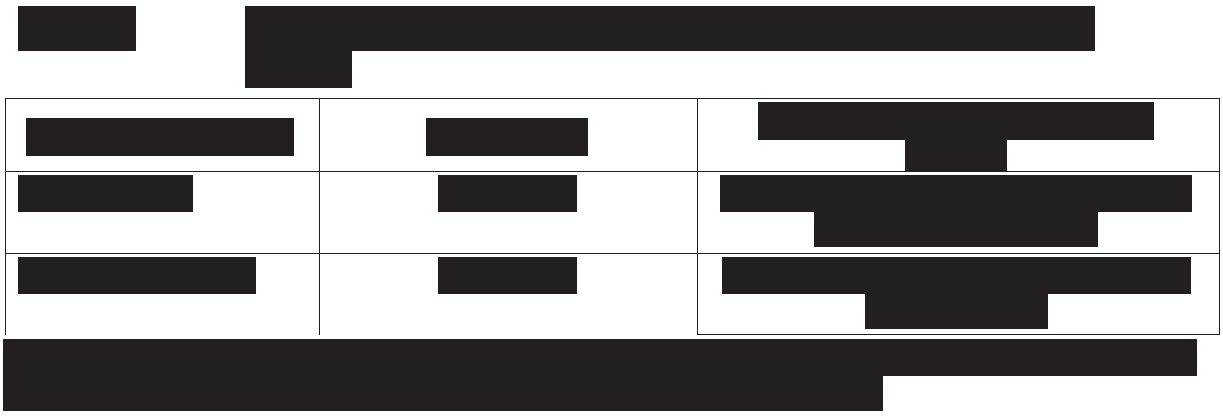
If MedImmune determines that temporary suspension or permanent termination of the study is required, MedImmune will discuss the reasons for taking such action with all participating investigators (or head of the medical institution, where applicable). When feasible, MedImmune will provide advance notice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

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

4.5 Investigational Products

4.5.1 Identity of Investigational Products

MedImmune will provide the investigators with investigational product, diluent, and placebo (Table 12 and Table 13) using designated distribution centres.



[redacted]

[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

4.5.1.1 In-clinic Vial Dosing, [redacted] MEDI0382: IP Handling, Inspection, and Dose Preparation

Investigational Product Handling

Investigational product kits should be stored at 2°C to 8°C in the original container. Investigational products do not contain preservatives, are supplied for single-dose use only, and any unused portion must be discarded.

Investigational Product Inspection

Each vial selected for dose preparation should be inspected. MEDI0382 is supplied as a sterile liquid solution [redacted]. The MEDI0382 or Placebo solution in vials should not be cloudy, discoloured, 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 4.5.1.6) for further instructions.

Dose Preparation: [redacted] Dose and Placebo

The final delivery volume and concentration for the [redacted] dose level are described in Table 14. The volume to be delivered will be withdrawn using a [redacted] syringe with a 27 gauge needle. Dilution and preparation of doses for administration is to be performed aseptically. Total in-use storage time from needle puncture of the investigational product vial to start of administration should not exceed 4 hours. If storage time exceeds these limits, a new dose must be prepared from a new vial.

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

4.5.1.5 Monitoring of Dose Administration

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

As with any exogenous peptide or biologic product, allergic reactions to dose administration are possible. Therefore, appropriate drugs and medical equipment to treat acute anaphylactic reactions must be immediately available at the study sites where the first 5 doses will be administered, and study personnel must be trained to recognize and treat anaphylaxis.

4.5.1.6 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.

In the case of discovery of a defect in a PFS at home, subjects should be instructed not to dispose of the defective device, but to store it safely and separately at 2-8°C. Arrangements will be made for the defective item to be returned to the clinic for further investigation as required.

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

Additional medications that may be used during the study, and management of their dose and potential toxicities, is discussed in Section 3.1.4.

4.5.3 Labelling

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. The label on the investigational product kit specifies the appropriate storage.

4.5.5 Treatment Compliance

Investigational product is administered at the study site by study site personnel for the first four doses, who will monitor compliance. Thereafter, study site personnel should monitor compliance through verbal report and drug accountability at each study visit.

4.5.6 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 or designee.

4.6 Treatment Assignment and Blinding

4.6.1 Methods for Assigning Treatment Groups

An IXRS will be used for randomisation to a treatment group and assignment of blinded investigational product kit numbers. A subject is considered randomised into the study when the investigator notifies the IXRS that the subject meets eligibility criteria and the IXRS provides the assignment of blinded investigational product kit numbers for the subject.

Subjects will be randomised using a 1:1 ratio to receive either MEDI0382 or placebo. Sufficient subjects will be invited to participate in the study such that in total approximately 40 subjects will be randomised and 20 will complete dosing in the active arm and 20 will complete dosing in the placebo arm. [redacted]

[redacted]

The first dose of investigational product (MEDI0382 or placebo) must be administered the same day the investigational product is assigned, within 4 hours after the investigational product 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 study monitor must be notified immediately.

4.6.2 Methods to Ensure Blinding

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

The different fill volumes of investigational product (MEDI0382 and placebo) and the relative position of the plunger rods will be visually distinct during administration. To maintain the blind, investigational product (MEDI0382 and placebo) PFS will be handled by an unblinded investigational product manager or unblinded study personnel that will not be involved in the treatment or clinical evaluation of subjects. An unblinded qualified designee may administer investigational product to subjects during in-clinic visits. An unblinded site monitor will perform investigational product accountability, and this will be a different person to the blinded site monitor who will oversee other aspects of the study at the clinical site (see Section 6.2). The site will maintain a written plan detailing which staff members are blinded/unblinded and the process of investigational product administration used to maintain the blind.

In the event that treatment allocation for a subject becomes known to the investigator or other study staff involved in the management of study subjects, the sponsor must be notified *immediately*.

4.6.3 Methods for Unblinding

4.6.3.1 Unblinding in the Event of a Medical Emergency

In the event of a medical emergency, the investigator may unblind an individual subject's investigational product allocation. Instructions for unblinding an individual subject's investigational product assignment are contained in the IXRS manual. In general, unblinding should only occur if management of the medical emergency would be different based on the investigational product administered to the subject. If the management of a medical emergency would be the same whether or not MEDI0382 was received by the subject, the treatment assignment should not be unblinded.

MedImmune retains the right to unblind the treatment assignment 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 site staff or blinded MedImmune/contract research organization (CRO) trial team, the subject should be discontinued from investigational product.

4.7 Restrictions During the Study and Concomitant Treatment(s)

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

4.7.1 Permitted Concomitant Medications

Investigators may prescribe concomitant medications or treatments deemed necessary to provide adequate supportive care except for those medications 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, anti-emetics, anti-diarrheals, and analgesics, and other care as deemed appropriate, and in accordance with their institutional guidelines.

4.7.2 Prohibited Concomitant Medications

Other than the medications described above, use of herbal supplements is not permitted. Subjects must be instructed not to take any medications, including over-the-counter products, without first consulting with the investigator.

[redacted]:

- Concurrent or previous use of a GLP-1 analogue containing preparation within the last 30 days or 5 half-lives of the drug, if known, whichever is longest, at the time of Visit 2
- Concurrent use of any herbal preparations or medicinal products licensed for control of body weight or appetite and within 1 week prior to the start of dosing (Visit 4)
- Concurrent or previous use of drugs approved for weight loss (eg, orlistat, bupropion-naltrexone, phentermine-topiramate, phentermine, lorcaserin) and within the last 30 days or 5 half-lives of the drug, whichever is longest, prior to the start of dosing (Visit 4)
- Concurrent use of opiates, domperidone, metoclopramide, or other drugs known to alter gastric emptying and within 2 weeks prior to the start of dosing (Visit 4)

- Concurrent use of aspirin (acetylsalicylic acid) at a dose greater than 150 mg once daily and within the last 3 days prior to the start of the run-in period (Visit 2)
- Concurrent use of paracetamol (acetaminophen) at a total daily dose greater than 3000 mg and within the last 3 days prior to the start of the run-in period (Visit 2)
- Concurrent use of ascorbic acid (vitamin C) at a total daily dose of > 1000 mg and within the last 3 days prior to the start of the run-in period (Visit 2)

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. Analyses of secondary and exploratory efficacy variables will be performed without any adjustment for multiplicity.

Analysis Populations

Intent to Treat: The intent-to-treat (ITT) population is defined as all subjects that are randomised and receive any amount of investigational product, analysed according to randomised treatment assignment. All efficacy analyses will be performed on the ITT population unless otherwise specified.

As-Treated Population: The as-treated population is defined as all subjects who received at least 1 dose of investigational product and will be analysed according to the treatment actually received. All safety analyses will be performed on the as-treated population.

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

Immunogenicity Population: The Immunogenicity population includes all subjects in the as-treated population who have at least one serum immunogenicity result.

4.8.2 Sample Size

Forty subjects (20 completers in the MEDI0382 group and 20 completers in placebo group) will provide > 85% power to detect 18.1% difference between the two treatment groups in percentage change in the MMTT glucose AUC from baseline (Day -5) to the end of 32 days of treatment (Day 32), with a two-sided significance level of 0.1 and assuming the standard deviation of 20%.

4.8.3 Efficacy

4.8.3.1 Primary Efficacy Analysis

The primary efficacy analysis will be performed using the ITT population. The primary efficacy endpoint, percentage change in MMTT glucose AUC from baseline (Day -5) to the end of 32 days of treatment will be analysed using an analysis of covariance (ANCOVA) model. The model will include fixed effect of treatment and baseline AUC as a covariate. The difference of the percent change in glucose AUC between the two treatment arms will be compared with a two-sided significance level of 0.10.

4.8.3.2 Secondary Efficacy Analyses

Secondary efficacy analyses will be performed using the ITT population. All secondary efficacy endpoints will be summarised by visit and by treatment group. The change in percentage of time spent within a target glucose range of 70 mg/dL (3.9 mmol/L) to 180 mg/dL (10 mmol/L) over a 7-day period at baseline to the final week of treatment will be analysed using a Wilcoxon rank-sum test. All other continuous endpoints will be analysed using a similar ANCOVA model as that for the primary analysis.

[redacted]

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.

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.

4.8.5 Analysis of Immunogenicity/Pharmacokinetics

4.8.5.1 Pharmacokinetic Analyses

Pharmacokinetic parameters such as maximum concentration (C_{max}), time to maximum observed concentration (T_{max}), and AUC_{tau}, will be estimated from plasma concentration-time data for MEDI0382 at the [redacted] dose level if data permit. Descriptive statistics will be generated for PK parameters for the MEDI0382 group at [redacted] and for C_{trough} at each dose level. Subjects who have at least one measurable concentration time point of investigational product will be used for this analysis.

4.8.5.2 Immunogenicity Analyses

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.

4.8.6 Additional Analyses

4.8.6.1 Vital Signs Analyses

The change in the 24-hour average systolic BP, diastolic BP, and pulse rate from the ABPM will be summarized for each post-baseline evaluation. Vital signs (blood pressure, pulse rate, temperature and respiration rate) will be summarized at each visit.

4.8.6.2 ECG Analyses

Frequencies of abnormal ECGs and descriptive statistics of changes in ECG variables heart rate and RR, PR, QRS, QT, and QTc intervals will be summarized.

4.8.7 Interim Analysis

No interim analysis is planned for this study.

5 ASSESSMENT OF SAFETY

5.1 Definition of Adverse Events

The ICH Guideline for Good Clinical Practice E6(R1) defines an AE as:

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

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

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

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

5.2 Definition of Serious Adverse Events

An SAE is any AE that:

- Results in death
- Is immediately life-threatening
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect in offspring of the subject

- Is an important medical event that may jeopardize the subject or may require medical intervention to prevent one of the outcomes listed above.

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

5.3 Definition of Adverse Events of Special Interest

An 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 the sponsor. An AESI may be serious or nonserious. The rapid reporting of AESIs allows ongoing surveillance of these events to characterise and understand them in association with the use of this investigational product.

All AESIs should be recorded in the eCRF within 24 hours. In addition, AESIs that are also SAEs should be reported to MedImmune Patient Safety within 24 hours. Instructions to the site on how to record (in the eCRF) and report AESI are provided in Section 5.4 and Section 5.5 respectively. The AESIs for this study are defined below.

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

5.3.1 Hepatic Function Abnormalities

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

5.4 Recording of Adverse Events

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 the sponsor (see Section 5.5). See Section 5.2 for the definition of SAEs and Section 10.3 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

AEs will be collected from time of signature of informed consent, throughout the treatment period, and including the follow-up period (Day 60±5).

All SAEs will be recorded from the time of informed consent.

For nontreatment-emergent AEs (ie, AEs that occur during the period from the time informed consent is signed but prior to the subject receiving investigational product), only AEs associated with protocol-related procedures should be reported. After the start of treatment, all treatment-emergent AEs (TEAEs; Section 5.1) should be reported.

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 Deaths

All deaths that occur during the study, including the protocol-defined follow-up period must be reported as follows:

- All deaths (including those that are clearly the result of disease progression) should be reported and documented in the eCRF and reported as an SAE within 24 hours. The report should contain a comment regarding the co-involvement of disease progression, if appropriate, and should assign main and contributory causes of death.

- Deaths with an unknown cause should always be reported as an SAE. A post-mortem (autopsy) may be helpful in the assessment of the cause of death, and if performed a copy of the post-mortem results should be forwarded to the sponsor representative(s) within the usual timeframes (refer to Section 5.5 for additional information).

5.5 Reporting of Serious Adverse Events

All SAEs must 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 sponsor representative works with the investigator to ensure that all the necessary information is provided to the sponsor's patient safety data entry site within

1 calendar day of initial receipt for fatal and life-threatening events and within 5 calendar days of initial receipt for all other SAEs.

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

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 inform appropriate sponsor representatives immediately, or 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, reporting must occur within 30 days.

5.6.2 Hepatic Function Abnormality

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

5.6.3 Pregnancy

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

5.6.3.1 Maternal Exposure

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 sponsor representative works with the investigator to ensure that all relevant information is provided to the sponsor's patient safety data entry site within 1 or 5 calendar days for SAEs (see Section 5.5) and within 30 days for all other pregnancies.

The same timelines apply when outcome information is available.

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

6 STUDY AND DATA MANAGEMENT

6.1 Training of Study Site Personnel

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

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, MedImmune representatives will have regular contacts with the study site. Both a blinded and unblinded site monitor will be assigned to each site. The blinded site monitor will oversee study conduct, 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
- 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 that any 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.
- Review of temperature logs for refrigerators and freezers to store investigational product or biological specimens

The unblinded site monitor will oversee management of the investigational product, including ensuring that study drug accountability checks are being performed.

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

6.2.1 Source Data

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

6.2.2 Study Agreements

The Principal Investigator at each/the centre 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 protocol shall prevail with respect to the conduct of the study and the treatment of subjects and in all other respects, not relating to study conduct or treatment of subjects, the terms of the Clinical Study Agreement will 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)or assessed for the primary endpoint of the study, regardless of the number of doses of investigational product that was received.

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

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

7 ETHICAL AND REGULATORY REQUIREMENTS

7.1 Subject Data Protection

Each subject will be assigned a SID to ensure that personally identifiable information is kept separate from the study data. Subject data that are relevant to the trial, eg, demographic information, physical or mental health condition, diagnosis, comorbidities, laboratory test results, etc. will only be collected with the subject's informed consent. The 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 IRB/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 IRB/IEC must also approve all advertising used to recruit subjects for the study. The investigator is responsible for submitting these documents to the applicable IRB/IEC, and distributing them to the study site staff.

The opinion of the IRB/IEC must be given in writing. The investigator must provide a copy of the written approval to MedImmune before enrolment 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 IRB/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, IRB/IEC, and principal investigators.

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

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

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.

Substantial changes must be documented in a study protocol amendment. MedImmune will distribute amended versions of the protocol to the principal investigator(s). Before implementation, amended protocols must be approved by relevant IRB/IEC (see Section 7.2)

and according to local requirements, the national regulatory authority approval. The IRB/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.

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

7.5 Audits and Inspections

Authorized representatives of MedImmune, a regulatory authority, or an IRB/IEC may perform audits or inspections at the centre, 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, analysed, and accurately reported according to the protocol, Good Clinical Practice (GCP), guidelines of the International Council for Harmonisation (ICH), and any applicable regulatory requirements. The investigator will contact MedImmune immediately if contacted by a regulatory agency about an inspection at the site.

8 REFERENCES

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

Center for Drug Evaluation and Research (CDER). Byetta Pharmacology Review. 2005.

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

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

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

Victoza (liraglutide) 6 mg/mL for injection in pre-filled pen (Summary of Product Characteristics [SPC]). Last updated 2016 December 07; Novo Nordisk Limited, West Sussex, United Kingdom. Available from: URL: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/001026/WC500050017.pdf

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

9 CHANGES TO THE PROTOCOL

9.1 Protocol Amendment 4, 12Nov2018

Key Details of Amendment	Reason for Amendment
Amendment 4 / 12Nov2018	
Section 3.2.2 Rationale for Study Population, Section 4.1.2 Inclusion Criteria, and Section 4.1.4 Subject Enrollment and Randomisation	"At least" has been changed to "Approximately" to provide additional flexibility to recruitment in view of lower than expected numbers of eligible subjects in the eGFR 30 to 45 mL/min/1.73 m^2category.

9.2 Protocol Amendment 3, 11Oct2018

Key changes to the protocol are summarized in the table below.

Key Details of Amendment	Reason for Amendment
Amendment 3 / 11Oct2018	
Protocol Synopsis, and Section 3.1.1 Overview, Section 4.6.3.2 Unblinding for Interim Analysis Purposes, and Section 4.8.7 Interim Analysis	The planned interim analysis has been cancelled as there is no longer a time pressure to have these data for Phase 3 planning. There are no emerging safety signals from the ongoing study.

9.3 Protocol Amendment 2, 06Apr2018

Text revisions resulting from this amendment have been made in response to recommendations made by the Medicines & Healthcare products Regulatory Agency (MHRA) and are incorporated in the body of Protocol Amendment 2. Key changes to the protocol are summarized in the table below.

Key Details of Amendment	Reason for Amendment
Amendment 2 / 06Apr2018	
Section 4.1.6 Discontinuation of Investigational Product	Updated in line with recommendations from MHRA: Clarified dose-limiting symptoms in the first bullet of criterion #3. Bullet removed regarding subjects who did not meet inclusion, or met exclusion criteria. Added bullet regarding subjects who meet Hy's Law. Added bullet regarding ECG abnormalities.
Section 4.2.2 Randomised Treatment Period, Table 10 (footnote f)	Updated to add a 2-hour post-dose ECG on Days 1 and 32.
Section 4.2.2 Randomised Treatment Period, Table 10	Addition of amylase and lipase sampling at Days 5, 12 and 19.
Section 5.4.3 Deaths	Updated to detail that all deaths (including those that are clearly the result of disease progression) will be reported as an SAE.

9.4 Protocol Amendment 1, 28Feb2018

Text revisions resulting from this amendment are incorporated in the body of Protocol Amendment 1. Key changes to the protocol are summarized in the table below.

Key Details of Amendment	Reason for Amendment
Amendment 1 / 28Feb2018	
[redacted]	[redacted]
Section 4.1.3 Exclusion Criteria	Exclusion criterion #8: typographic error adjustment
Section 4.2.2 Randomised Treatment Period	Addition of weight to schedule of assessments on Day 32
Section 4.3.2.2 Electrocardiograms	Amended to clarify that review of ECG is from lead II on V2
[redacted]	[redacted]
Section 4.7.2 Prohibited Concomitant Medication	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 Visit 2" (previously Visit 1)
[redacted]	Text modified to align with updated Company template and practice

10 APPENDICES

10.1 Appendix 1 - Signatures

Sponsor Signature(s)

A Phase 2a, Randomised, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy, Safety, and Pharmacokinetics of MEDI0382 in Subjects with Type 2 Diabetes Mellitus and Renal Impairment

I agree to the terms of this protocol.

Signature and date: Electronic signature attached

[redacted], [redacted] Vice President, Clinical Development

Clinical Therapeutic Area Head

One MedImmune Way, Gaithersburg MD, 20878, USA

Telephone number: [redacted]

10.2 Appendix 2 – Contraception Guidance

For females of childbearing potential:

- Females of childbearing potential are defined as those who are not surgically sterile (ie, surgical sterilization includes bilateral tubal ligation, bilateral oophorectomy, or hysterectomy) defined as 12 months with no menses without an alternative medical cause and/or have a follicle-stimulating hormone [FSH] levels in the safety laboratory's normal range for postmenopausal phase on prior laboratory testing

A highly effective method of contraception is defined as one that results in a low failure rate (ie, less than 1% per year) when used consistently and correctly. The acceptable methods of contraception are described in Table 10-2. 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 10-2 Highly Effective Methods of Contraception

Barrier Methods	Hormonal Methods
• Intrauterine device • Intrauterine hormone-releasing system (UIS) [a] • Bilateral tubal occlusion • Vasectomized partner [b] • Sexual abstinence [c]	Combined (estrogen and progestogen containing hormonal contraception) [d] ° Injectable ° Transdermal (patch) Progestogen-only hormonal contraception associated with inhibition of ovulation [d] ° Injectable ° Implantable ° Intravaginal

[a] This is also considered a hormonal method.

[b] With appropriate post-vasectomy documentation of surgical success (absence of sperm in ejaculate).

[c] Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of the study and if it is the preferred and usual lifestyle of the subject.

[d] Oral forms of contraception are not acceptable given that vomiting may arise as a potential side-effect of MEDI0382

10.3 Appendix 3 - 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).

Hospitalisation

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, hospitalisation, 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

Relationship to Investigational Product

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

10.4 Appendix 4 - National Institute of Allergy and Infectious Diseases and Food 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 Diseases (NIAID) 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, dyspnea, 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 patient (minutes to several hours):
   (a) Involvement of the skin-mucosal tissue (eg, generalized hives, itch-flush, swollen lips-tongue-uvula)
   (b) Respiratory compromise (eg, dyspnea, 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 patient (minutes to several hours):
   (a) Infants and children: low systolic BP (age specific) or greater than 30% decrease in systolic BP
   (b) Adults: systolic BP of less than 90 mm Hg or greater than 30% decrease from that person’s baseline

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

10.5.1 Introduction

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

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

The investigator participates, together with MedImmune clinical project representatives, in review and assessment of cases meeting potential Hy's Law criteria to agree whether Hy's Law 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 potential Hy's Law/Hy's Law cases and for reporting AEs and SAEs according to the outcome of the review and assessment in line with standard safety reporting processes.

10.5.2 Definitions

Potential Hy's Law

AST or ALT ≥ 3 × ULN together with TBL ≥ 2 × ULN at any point during the study following the start of study medication irrespective of an increase in alkaline phosphatase (ALP).

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.

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

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

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

10.5.3 Follow-up

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.

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. The Study Physician contacts the investigator, to provide guidance, discuss and agree an approach for the study subjects' follow-up and the continuous review of data. Subsequent to this contact the investigator will:

- Monitor the subject until liver biochemistry parameters and appropriate clinical symptoms and signs return to normal or baseline levels, or as long as medically indicated
- Investigate the etiology of the event and perform diagnostic investigations as discussed with the medical monitor. This includes deciding which the tests available in the Hy's Law lab kit should be used.
- Complete the Liver CRF Modules as information becomes available
- 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

10.5.4 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. 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 CRF
- If the alternative explanation is an AE/SAE, record the AE /SAE in the CRF accordingly and follow 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:

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

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

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

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

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

[redacted]

[redacted]

[redacted]

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 main 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 centre. 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/gene expression results to subjects, any insurance company, any employer, their family members, or 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/gene expression data generated in this study will be stored at a secure system at MedImmune and/or designated organisations to analyse 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 organisations 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 Organisations, 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.

10.7 Appendix 7 Biological Samples

Storage, Re-use and Destruction of Biological Samples

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

The results of biomarker research will be reported either in the CSR itself or as an addendum, or separately in a scientific report or publication. The results of this biomarker research may

be pooled with biomarker data from other studies with the study drug to generate hypotheses to be tested in future research. ADA samples will be stored for up to 2 years after marketing approval.

Labelling and Shipment of Biological Samples

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

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

Chain of Custody of Biological Samples

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

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

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

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

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