An Exploratory Phase 2a, Randomised, Double-blind, Placebo-controlled Study to Evaluate the Effect of MEDI0382 on Energy Balance in Overweight and Obese Subjects with Type 2 Diabetes Mellitus

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PROTOCOL SYNOPSIS

TITLE

An Exploratory Phase 2a, Randomised, Double-blind, Placebo-controlled Study to Evaluate the Effect of MEDI0382 on Energy Balance in Overweight and Obese Subjects

HYPOTHESES

Primary Hypothesis: Administration of MEDI0382 once daily titrated up to a dose level of [redacted] will result in negative energy balance as evidenced by weight loss versus placebo after 42 days of treatment in overweight and obese subjects with type 2 diabetes mellitus (T2DM).

Secondary Hypotheses: Administration of MEDI0382 once daily titrated up to a dose level of [redacted] in overweight and obese subjects with T2DM will:

- result in a reduction in energy intake versus placebo after 42 days of treatment
- result in an increase in energy expenditure (EE) versus placebo after 41 days of treatment
- result in a change in body composition (reduced body fat) versus placebo after 42 days of treatment
- result in a reduction in fasting and post-prandial glucose versus placebo after 42 days of treatment
- be well-tolerated in overweight and obese subjects

OBJECTIVES AND ENDPOINTS

Type	**Primary Objective**	**Primary Endpoint**
Efficacy	To assess the effect of MEDI0382 titrated up to a dose level of [redacted] on body weight versus placebo	Percentage change in body weight in kg from Day 17 to 59
Type	**Secondary Objectives**	**Secondary Endpoints**
Efficacy	To assess the effect of MEDI0382 titrated up to a dose level of [redacted] versus placebo on energy intake during ad libitum lunchtime meals	Percentage and absolute change in total energy intake in kJ from the ad libitum lunch from: • Day 16 to 32 • Day 16 to 59
Efficacy	To assess the effect of MEDI0382 titrated up to a dose level of [redacted] versus placebo on TEE, AEE, and REE	Percentage and absolute change in TEE, AEE, and REE as measured by whole room indirect calorimetry in kJ per kg of fat body mass from Day 15 to 58
Efficacy	To assess the effect of a 16-day period of MEDI0382 titrated up to a dose level of [redacted] versus placebo on REE	Percentage and absolute change in REE as measured by hood indirect calorimetry in kJ per kg of fat body mass in kJ from Day 16to 32
Efficacy	To assess the effect of MEDI0382 titrated up to a dose level of [redacted] versus placebo on TEE	Percentage and absolute change in total energy expenditure as measured by doubly labelled water in kJ per kg of fat body mass from baseline (Day 17) to the end of treatment (Day 58 or 59)
Efficacy	To assess the effect of MEDI0382 titrated up to a dose level of [redacted] on measures of body weight and composition versus placebo	• Absolute change in body weight in kg from Day 17 to 59 • Change in absolute and percentage change in total body fat mass as measured by DXA in kg from Day -1 to 59 • Change in absolute and percentage change in total body fat mass: lean mass ratio as measured by DXA from Day -1 to 59

Efficacy	To assess the effect of MEDI0382 titrated up to a dose level of 300 µg on glucose homeostasis versus placebo	• Change in fasting glucose during a MMTT from Day -1 to 59 • Percentage change in glucose AUC during a MMTT from Day -1 to 59
Safety	To evaluate the safety and tolerability of MEDI0382 titrated up to a dose level of 300 µg versus placebo	During treatment and follow-up: • Vital signs • ECGs • Safety laboratory analysis • TEAEs and TESAEs
Immunogenicity	[redacted]	[redacted]
Type	**Exploratory Objectives**	**Exploratory Endpoints**
Efficacy	[redacted]	[redacted]
PK	[redacted]	[redacted]
PD	[redacted]	[redacted]
PD	[redacted]	[redacted]

PD	[redacted]	[redacted]
PD	[redacted]	[redacted]
PD	[redacted]	[redacted]
PRO	[redacted]	[redacted]

AIRg = acute insulin response; $AUC_{0\text{-}10\ min}$ = area under the plasma concentration time curve at 0 to10 minutes; AUC_{4h} = area under the plasma concentration time curve at 4 hours; EE = energy expenditure; ExEE = exercise energy expenditure; GIP = glucose-dependent insulinotropic polypeptide; GLP-1 = Glucagon-like peptide-1; kJ = kilojoule; MMTT = mixed meal tolerance test; PD = pharmacodynamic; PK = pharmacokinetics; PRO = patient reported outcome; REE = resting energy expenditure; SG = glucose effectiveness; SI = insulin sensitivity; TEAE = treatment emergent adverse event; TESAE = treatment emergent serious adverse event; TEE = total energy expenditure.

STUDY DESIGN

This is an exploratory Phase 2a randomised, double-blind, placebo-controlled study to evaluate the effect of MEDI0382 titrated up to [redacted] on energy balance in overweight and obese subjects with T2DM.

The study is planned to randomise 24 subjects at 1 site in the United Kingdom. Subjects will be consented, screened for suitability, and if eligible, will be randomised within 28 days of screening to receive single-blind placebo for 16 days, and then either double-blind MEDI0382 titrated up to [redacted] or placebo in a 2:1 ratio administered once daily via subcutaneous (SC) injection for 42 days. Subjects randomised to MEDI0382 will receive [redacted]

Subjects will be in the study for approximately 16 weeks (114 days), including a screening period of up to 28 days, a 16-day single-blind placebo treatment period, a 42-day double-blind treatment period, and a 28-day (± 3 days) safety follow-up period. The study will include up to 10 inpatient visits with a minimum of 3 overnight stays; subjects will be permitted to stay overnight for study visits if more convenient for them. Subjects will be requested to abstain from caffeinated drinks from days -1 to 2, days 14 to 17, days 31 to 32, and days 56 to 58. If subjects use dual oral therapy for T2DM they will be expected to stop the non-metformin therapy 28 days prior to Visit 4. The non-metformin therapy will be restarted at the end of the study according to glycated haemoglobin (HbA1c) levels and at the discretion of the investigator. Metformin therapy will be continued throughout the study.

TARGET SUBJECT POPULATION

Subjects aged ≥ 30 and ≤ 75 years, with a diagnosis of T2DM and a body mass index ≥ 28 and ≤ 40 kg/m^2. Female subjects of childbearing potential must not be pregnant and/or lactating, and should be using at least one highly effective method of contraception.

TREATMENT GROUPS AND REGIMENS

Following randomisation on Day -1, all eligible subjects will use placebo once daily in the morning via SC injection for 16 days during the single-blind placebo treatment period.

After the completion of the single-blind placebo treatment period, subjects will enter the double-blind treatment period, and will use either MEDI0382 or placebo in a 2:1 ratio once daily in the morning via SC injection for 42 days, as follows:

- [redacted]
- Placebo for 42 days (N = 8)

STATISTICAL METHODS

Sample Size: Sixteen subjects in the MEDI0382 group and 8 subjects in the placebo group will provide > 90% power to detect a 2.5% weight change from baseline difference between MEDI038[redacted] and placebo at Day 59, assuming a standard deviation of 2.0%, a 2-sided 0.1 alpha.

Statistical Analyses: The efficacy analysis will be based on the Modified Intent-to-treat (mITT) population. The primary efficacy endpoint of percentage change in body weight from Day 17 to 59 will be compared between MEDI0382 and placebo groups using an analysis of covariance (ANCOVA) model adjusting for treatment group and measurement at baseline. Last observation carried forward will be used for missing data imputation for post-baseline values when applicable. The secondary efficacy endpoints will be based on the mITT population and analysed by an ANCOVA model similar to that used for the primary efficacy analysis. Selected secondary endpoints will also be analysed using the Per-protocol population. [redacted]

Safety and Immunogenicity: The safety analysis will be based on the As-treated population. Adverse events (AEs) and serious adverse events (SAEs) will be coded by the most updated version of the Medical Dictionary for Regulatory Activities (MedDRA) and the type, incidence, severity, and relationship to investigational product by will be summarized by MedDRA System Organ Class (SOC) and Preferred Term (PT). 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. All treatment-emergent adverse events will be summarised overall, by MedDRA SOC and PT, and by severity and relationship to investigational product. In addition, summaries of deaths, SAEs, and treatment discontinuations due to AEs will be provided.

Additional safety data including vital signs, safety laboratory analysis, and ECGs will be summarised descriptively at each time point by treatment group.

[redacted]

Patient Reported Outcomes (PRO): Analysis of PROs will be based on the mITT population. The exploratory PRO endpoints including change in self-reported hunger and satiety scores from Day 15 to 58 and the change in total energy intake in kilojoules (kJ) as recorded in a food diary from Day 16 to 32 and from Day 16 to 59 will be analysed by an ANCOVA model similar to that used for the primary efficacy analysis.

Interim Analysis: No interim analyses are planned.

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LIST OF ABBREVIATIONS

Abbreviation or Specialized Term	Definition
ADA	anti-drug antibody/antibodies
AEE	activity energy expenditure
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine transaminase
ANCOVA	analysis of covariance
AST	aspartate transaminase
AUC	area under the concentration-time curve
BMI	body mass index
BP	blood pressure
CI	confidence interval
CKD-EPI	Chronic Kidney Disease-Epidemiology Collaboration
CRO	contract research organization
C_{max}	maximal plasma concentration
DEBQ	Dutch Eating Behaviour Questionnaire
DLW	doubly-labelled water
DNA	deoxyribonucleic acid
DPPIV	dipeptidyl peptidase 4 inhibitor
DXA	dual X ray absorptiometry
ECG	electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
EE	energy expenditure
eGFR	estimated glomerular filtration rate
ExEE	exercise energy expenditure
GI	gastrointestinal
GIP	glucose-dependent insulinotropic polypeptide
GLP-1	glucagon-like peptide-1
HbA1c	glycated haemoglobin
HBsAg	hepatitis B surface antigen
HIV	human immunodeficiency virus
IB	Investigator's Brochure
ICF	informed consent form

Abbreviation or Specialized Term	Definition
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IFU	Instructions for Use
IVGTT	intravenous glucose tolerance test
IXRS	interactive voice/web response system
kg	kilogram (s)
kJ	kilojoule (s)
LS	least squares
MDRD	Modification of Diet in Renal Disease
MedDRA	medical dictionary for regulatory activities
mITT	Modified Intent-to-treat
MMTT	mixed-meal tolerance test
NOAEL	no-observed-adverse-effect level
Oxm	oxyntomodulin
PD	pharmacodynamic (s)
PK	pharmacokinetic(s)
PRO	patient reported outcome
PT	preferred term
REE	resting energy expenditure
RMR	resting metabolic rate
SAE	serious adverse event
SC	subcutaneous
SGLT2i	sodium-glucose co-transporter inhibitor(s)
SID	subject identification
SOC	system organ class
TEE	total energy expenditure
TBL	total bilirubin
T2DM	type 2 diabetes mellitus
TEF	thermic effect of feeding
TEAE	treatment-emergent adverse event
TEE	total energy expenditure
TESAE	treatment-emergent serious adverse event
TSH	thyroid stimulating hormone
ULN	upper limit of normal
VAS	Visual Analog Scale

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, major 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.

1.2 MEDI0382 Background

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

[redacted]

1.3 Summary of Nonclinical Experience

[redacted]

[redacted]

1.4 Summary of Clinical Experience

[redacted]

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

1.5 Rationale for Conducting the Study

Energy balance describes the relationship between EE and energy intake. Under normal physiological conditions, EE is equal to energy intake and promotes stable body weight. Energy expenditure is defined as the amount of energy the body requires to maintain essential bodily functions and to perform physical activity. Measured total energy expenditure (TEE) is a composite of resting energy expenditure (REE), activity energy expenditure (AEE) and the thermic effect of feeding (TEF). Resting energy expenditure, also known as resting metabolic rate (RMR), is the predominant contributor to TEE. Activity energy expenditure is variable and a composite of exercise energy expenditure (ExEE) and non-exercise activity thermogenesis. The TEF typically accounts for approximately 10% of TEE (Hill et al 2014). Generating a negative energy balance, either through increased EE or reduced energy intake or both favours weight loss and forms the basis of strategies to treat obesity. Indeed, diets and restriction of energy intake are the most common and first-line approaches to achieve weight loss. In seeking therapies to promote weight loss, previous studies of receptor agonists, Oxm,

and glucagon have shown differing effects on EE and energy intake. In a prior study of Oxm injections administered to healthy subjects, significant weight loss was achieved and this effect was attributed to both reduced energy intake and increased AEE, but not REE (Wynne et al 2006). A second study evaluating short-term administration of either Oxm, GLP-1, glucagon or co-infusion of GLP-1 and glucagon demonstrated reduced energy intake for all drugs tested, but minimal effects on REE (Bagger et al 2015). Studies evaluating the effect of GLP-1 analogues have consistently shown a reduction in energy intake, but have revealed conflicting results with respect to the effect on EE (Farr et al 2016; Horowitz et al 2012). However, studies evaluating the impact of glucagon have recorded an increase in REE (Chakravarthy et al 2017), which has been shown to be independent of brown adipose tissue activity (Salem et al 2016).

[redacted] like Oxm, promotes weight loss through an effect on energy intake and/or an increase in EE.

1.6 Benefit-risk and Ethical Assessment

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

[redacted]

[redacted]

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 SC once daily titrated up to a dose level of [redacted] will result in negative energy balance as evidenced by weight loss versus placebo after 42 days of treatment in overweight and obese subjects with T2DM.

1.7.2 Secondary Hypotheses

Administration of MEDI0382 SC once daily titrated up to a dose level of [redacted] in overweight and obese subjects with T2DM will:

- result in a reduction in energy intake versus placebo after 42 days of treatment
- result in an increase in EE versus placebo after 41 days of treatment
- result in a change in body composition (reduced body fat) versus placebo after 42 days of treatment
- result in a reduction in fasting and post-prandial glucose versus placebo after 42 days of treatment
- be well-tolerated in overweight and obese subjects

2 OBJECTIVES AND ENDPOINTS

The primary, secondary, and exploratory objectives with associated endpoints are included in Table 1, Table 2, and Table 3 below.

2.1 Primary Objective and Endpoint

Table 1 Primary Objective and Endpoint

Type	Objective	Endpoint
Efficacy	To assess the effect of MEDI0382 [redacted] on body weight versus placebo	Percentage change in body weight in kg from Day 17 to 59

2.2 Secondary Objectives and Endpoints

Table 2 Secondary Objectives and Endpoints

Type	Objective	Endpoint
Efficacy	To assess the effect of [redacted] versus placebo on energy intake during ad libitum lunchtime meals	Percentage and absolute change in total energy intake in kJ from the ad libitum lunch from: • Day 16 to 32 • Day 16 to 59
Efficacy	To assess the effect of [redacted] versus placebo on TEE, AEE, and REE	Percentage and absolute change in TEE, AEE, and REE as measured by whole room indirect calorimetry in kJ per kg of fat body mass from Day 15 to 58
Efficacy	To assess the effect of a 16-day period of [redacted] versus placebo on REE	Percentage and absolute change in REE as measured by hood indirect calorimetry in kJ per kg of fat body mass in kJ from Day 16 to 32
Efficacy	To assess the effect of [redacted] versus placebo on TEE	Percentage and absolute change in total energy expenditure as measured by doubly labelled water in kJ per kg of fat body mass from baseline (Day 17) to the end of treatment (Day 58 or 59)
Efficacy	To assess the effect of [redacted] on measures of body weight and composition versus placebo	• Absolute change in body weight in kg from Day 17 to 59 • Change in absolute and percentage change in total body fat mass as measured by DXA in kg from Day -1 to 59 • Change in absolute and percentage change in total body fat mass: lean mass ratio as measured by DXA from Day -1 to 59
Efficacy	To assess the effect of [redacted] on glucose homeostasis versus placebo	• Change in fasting glucose during a MMTT from Day -1 to 59 • Percentage change in glucose AUC during a MMTT from Day -1 to 59
Safety	To evaluate the safety and tolerability of [redacted] versus placebo	During treatment and follow-up: • Vital signs • ECGs • Safety laboratory analysis • TEAEs and TESAEs
Immunogenicity	To characterise the [redacted] versus placebo	Development of ADA and titre (if confirmed ADA-positive) during treatment and follow-up

ADA = anti-drug antibodies; AEE = activity energy expenditure; AUC = area under the plasma concentration time curve; DXA = dual-energy X-ray absorptiometry; ECG = electrocardiogram; kg = kilogram; kJ = kilojoule; MMTT= mixed-meal tolerance test; REE = resting energy expenditure; TEAE = treatment-emergent adverse event; TESAE = treatment-emergent serious adverse event; TEE = total energy expenditure.

2.3 Exploratory Objectives and Endpoints

Table 3 Exploratory Objectives and Endpoints

Type	Objective	Endpoint
Efficacy	[redacted]	[redacted]
PK	[redacted]	[redacted]
PD	[redacted]	[redacted]
PD	[redacted]	[redacted]
PD	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

Table 3 Exploratory Objectives and Endpoints

Type	Objective	Endpoint
		• [redacted]
PD	[redacted]	[redacted]
PRO	[redacted]	[redacted]

AIRg = acute insulin response; $AUC_{0\ 10\ min}$ = area under the plasma concentration time curve at 0 to10 minutes; AUC_{4h} = area under the plasma concentration time curve at 4 hours; EE = energy expenditure; ExEE = exercise energy expenditure; GIP = glucose-dependent insulinotropic polypeptide; GLP-1 = Glucagon-like peptide-1; kJ = kilojoule; MMTT = mixed-meal tolerance test; PD = pharmacodynamic; PK = pharmacokinetics; PRO = patient reported outcome; REE = resting energy expenditure; SG = glucose effectiveness; SI = insulin sensitivity.

3 STUDY DESIGN

3.1 Description of the Study

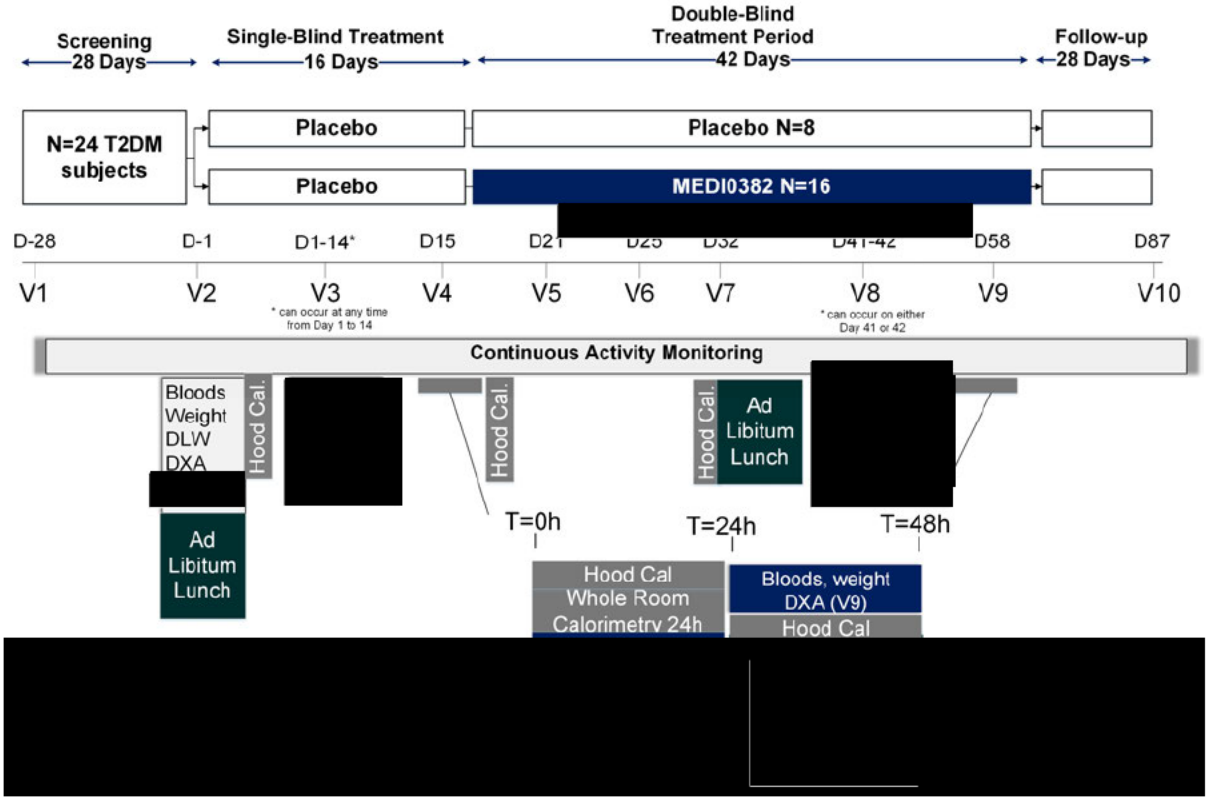
3.1.1 Overview

This is an exploratory Phase 2a randomised, double-blind, placebo-controlled study to evaluate the effect of [redacted] on energy balance in overweight and obese subjects with T2DM.

The study is planned to randomise 24 subjects at 1 site in the United Kingdom. Subjects will be consented, screened for suitability, and if eligible, will be randomised within 28 days of screening to receive [redacted], or placebo in a 2:1 ratio administered once daily via [redacted] for 42 days (16-day single-blind and 42-day double-blind treatment periods). Subjects randomised to [redacted].

Subjects will be in the study for approximately 16 weeks (114 days), including a screening period of up to 28 days, a 16-day single-blind placebo treatment period, a 42-day double-blind treatment period, and a 28-day (± 3 days) safety follow-up period. The study will include up to 10 inpatient visits with a minimum of 3 overnight stays; subjects will be permitted to stay overnight for study visits if more convenient for them. Subjects will be requested to abstain from caffeinated drinks from days -1 to 2, days 14 to 17, days 31 to 32, and days 56 to 58. If subjects use dual oral therapy for T2DM they will be expected to stop the non-metformin therapy 28 days prior to Visit 4. The non-metformin therapy will be restarted at the end of the study according to glycated haemoglobin (HbA1c) levels and at the discretion of the investigator. Metformin therapy will be continued throughout the study.

Figure 1 Study Flow Diagram and Additional Design Details



7/7 = 7 days, 28/7 = 28 days, Hood Cal = Hood-based calorimetry, DLW = doubly-labelled water, DXA = Dual X-ray absorptiometry, h = hours, [redacted], GET = gastric emptying time, T = time, V = visit.

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

3.1.2 Treatment Regimen

[redacted]

- [redacted]
- Placebo for 42 days (N = 8)

3.1.3 Dose Escalation

[redacted]

3.1.4 Management of Study Medication Related Toxicities

3.1.4.1 Tolerability

[redacted]

3.1.4.2 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. Spontaneous and clinically significant hypoglycaemia, defined as blood glucose < 3.0 mmol/L or 54 mg/dL with or without symptoms (hunger, dizziness, shaking, sweating, or irritability) (Skyder et al 2017), [redacted]. However, 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 or feel unwell, and will be expected to record the level in their diary. Local procedures for treatment and follow-up of any hypoglycaemic episode should be followed. Any blood glucose level of < 3.0 mmol/L (54 mg/dL) is considered

clinically significant hypoglycaemia and should be reported by investigators as an AE, regardless of whether or not subjects experience symptoms. Pharmacological treatments administered for hypoglycaemia, eg, dextrose/glucose tablets, glucagon etc, should be recorded in the electronic case report form (eCRF) as concomitant medications.

3.1.4.3 Hyperglycaemia

In the event of suspected persistent hyperglycaemia in a subject based on either symptoms of hyperglycaemia (eg, thirst, polyuria, blurred vision) or capillary plasma glucose readings (eg, 3 readings > 14 mmol/L [260 mg/dL] within 1 week), the investigator should perform additional fasting blood glucose level tests as necessary. If 2 or more laboratory plasma fasting glucose levels of > 14 mmol/L (260 mg/dL) more than 3 days apart are detected, the investigator should consider rescue therapy following discussion with the medical monitor.

In the unlikely event that a subject is unwell and severe persistent hyperglycaemia (eg, fasting glucose > 14 mmol/L [260 mg/dL]) is suspected by the investigator, the subject should be advised to monitor capillary plasma glucose levels up to 5 times per day and rescue therapy should be administered within a 24- to 48-hour time frame if required.

3.2 Rationale for Dose, Population, and Endpoints

MEDI0382 is being developed for the treatment of T2DM and obesity. [redacted]

3.2.1 Dose Rationale

[redacted]

[redacted]

[redacted] (Table 4).

Table 4 Proposed Study Dose and Predicted Safety Margin Based on Safety Data from the Cynomolgus Monkey

[redacted]

3.2.2 Rationale for Study Population

Subjects aged ≥ 30 and ≤ 75 years, with BMI > 28 and ≤ 40 kg/m^2 will be included in the study population to balance recruitment potential with projected variability in EE measurements. Conflicting reports exist with respect to the impact of obesity on EE (Carneiro et al 2016) and subjects with T2DM have differing REE and AEE, and this may be influenced by glycaemic control (Caron et al 2016). In view of this, subjects without poor glycaemic control (HbA1c ≤ 8.0%) using metformin, dipeptidyl peptidase-4 (DPPIV) inhibitors, sodium-glucose co-transporter inhibitors (SGLT2i), sulfonylurea, or glitinide will be enrolled; if they are on dual therapy, the non-metformin therapy will be washed out 4 weeks prior to dosing of MEDI0382 (Visit 4). In addition, subjects that partake in high intensity exercise (and likely have a high BMI due to excess muscle bulk) will be excluded.

3.2.3 Rationale for Endpoint(s)

3.2.3.1 Primary Endpoint

[redacted] eight loss is an established surrogate measure of energy balance and therefore percentage change in body weight will provide an overview of net energy balance versus placebo across the course of 42 days of MEDI0382 dosing (Hill et al 2014).

3.2.3.2 Secondary Endpoints

Energy Intake

Given that prior studies undertaken with GLP-1 and glucagon receptor-agonists and oxm have revealed significant effects on energy intake, it is likely that MEDI0382 influences energy intake. Energy intake may be measured in a more robust way than self-report through single-blind assessment of ad libitum meal consumption.

Energy Expenditure

Given the findings of prior research describing an increase in differential components of EE it will be important to determine the effect of MEDI0382 on TEE, AEE, and REE (Section 1.2). Gold standard methodology including whole room indirect calorimetry and DLW will be used in addition to an activity monitor to obtain estimates of EE as secondary and exploratory endpoints during the study. As fluctuations in weight and fat mass may influence estimates of EE, [redacted] and all measurements will be adjusted for total body fat mass as measured by dual X-ray absorptiometry (DXA) scanning. In addition, subjects will be asked to abstain from caffeinated drinks for at least 24 hours prior to measurements as caffeine may increase EE and dietary advice will be given to ensure subjects have a neutral energy balance prior to whole calorimetry assessments.

Body Weight and Composition

In addition to the primary endpoint of percentage change in body weight, absolute change in body weight will also provide an overview of net energy balance versus placebo across the course of 42 days of MEDI0382 dosing.

[redacted]

Glucose Homeostasis

[redacted]

Safety and Tolerability

As MEDI0382 remains under development, safety and tolerability will be assessed throughout this study.

Standard safety endpoints including vital signs, safety laboratory analysis, treatment-emergent adverse events (TEAEs), treatment-emergent serious adverse events (TESAEs), and electrocardiograms (ECGs) will be assessed during treatment and follow-up. [redacted]

Immunogenicity

[redacted]

3.2.3.3 Exploratory Endpoints

MEDI0382 Exposure

[redacted]

[redacted]

[redacted]

[redacted]

[redacted] **Satiety**

[redacted]

4 MATERIALS AND METHODS

4.1 Subjects

4.1.1 Number of Subjects

Enrolment of approximately 24 subjects is planned.

4.1.2 Inclusion Criteria

Subjects must meet all of the following criteria:

1 Subjects aged ≥ 30 and ≤ 75 years at screening

2 Provision of signed and dated written informed consent (except for consent for genetic and non-genetic research and additional optional assessments) prior to any protocol-related procedures

3 Body Mass Index > 28 and ≤ 40 kg/m^2 at screening

4 Glycated haemoglobin (HbA1c) ≤ 8.0% at screening

5 Diagnosed with T2DM with glucose control managed with metformin, with or without a DPPIV inhibitor, SGLT2i, sulfonylurea, or glitinide, where no significant dose change (increase or decrease > 50%) has occurred in the 3 months prior to screening; if the

subject is on dual therapy, a 4-week washout of the non-metformin therapy (DPPIV inhibitor, SGLT2i, sulfonylurea, or glitinide) will be required prior to Visit 4

6 Female subjects of childbearing potential must have a negative pregnancy test at screening and randomisation, and must not be lactating

7 Female subjects of childbearing potential who are sexually active with a non-sterilised 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 must agree to continue using such precautions up until 4 weeks after the last dose of investigational product

4.1.3 Exclusion Criteria

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

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

2 Any subject with a cardiac pacemaker or implanted/portable electronic device

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 (whichever is longer) at the time of screening (Visit 1)

4 Any subject who has received any of the following medications within the specified time frame prior to Visit 2: herbal preparations or drugs licensed for control of body weight or appetite (eg, orlistat, bupropion, naltrexone, phentermine-topiramate, phentermine, lorcaserin, opiates, domperidone, metoclopramide, or other drugs known to alter gastric emptying)

5 Concurrent participation in another study with an investigational product and prior randomisation in this study is prohibited

6 Severe allergy/hypersensitivity to any of the proposed study treatments, excipients, or standardised meals

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

8 Abnormal thyroid stimulating hormone (TSH) level of < 0.03 mIU/L or > 10 mIU/L confirmed on two consecutive tests

9 Regularly engage in high intensity exercise at least three times per week or have done so in the prior three months

10 Clinically 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

11 Acute or chronic pancreatitis with or without amylase > 1000 IU/L and/or lipase > 600 IU/L at screening

12 Significant hepatic disease (except for nonalcoholic steatohepatitis or nonalcoholic fatty liver disease without portal hypertension or cirrhosis) and/or subjects with any of the following results at screening:

(a) Aspartate transaminase (AST) ≥ 3 × upper limit of normal (ULN)

(b) Alanine transaminase (ALT) ≥ 3 × ULN

(c) Total bilirubin ≥ 2 × ULN

13 Impaired renal function defined as estimated glomerular filtration rate (eGFR) < 45 mL/minute/1.73 m^2 at screening (GFR estimated according to the Chronic Kidney Disease-Epidemiology Collaboration (CKD-EPI) or the Modification of Diet in Renal Disease (MDRD) using MDRD Study Equation isotope dilution mass spectrometry-traceable [SI units]

14 Poorly controlled hypertension defined as:

(a) Systolic BP > 180 mm Hg

(b) Diastolic BP or > 100 mm Hg

After 10 minutes of supine rest and confirmed by repeated measurement at screening. Subjects who fail BP screening criteria may be considered for 24-hour ambulatory blood pressure monitoring at the discretion of the investigator. Subjects who maintain a mean 24-hour BP ≤ 180/100 mmHg with a preserved nocturnal dip of > 15% will be considered eligible

15 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

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

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

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

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

20 Substance dependence or history of alcohol abuse and/or excess alcohol intake

21 Involvement of any AstraZeneca, MedImmune, contract research organization (CRO), or National Institute for Health Research/Wellcome Trust Cambridge Clinical Research Facility employee or their close relatives

4.1.4 Subject Enrolment 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 an interactive voice/web response system (IXRS). The SID number will be assigned prior to the beginning of screening evaluations to assess study eligibility (inclusion/exclusion) criteria. The SID number will be used to identify the subject during the screening process and throughout study participation, if applicable.

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

Subjects who fail to meet the eligibility criteria (ie, screening failures) should not be randomised or receive investigational product. Subjects may be rescreened once and receive a new SID number if, in the opinion of the investigator, there is a reason to believe they may be eligible.

Subjects who are enrolled, but subsequently found not to meet all the eligibility criteria must not be randomised or receive investigational product, and must be withdrawn from the study.

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 AEs. After consent is withdrawn, no further study visits or data collection should take place.

4.1.6 Discontinuation of Investigational Product

An individual subject will not receive any further investigational product if any of the following occur in the subject 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, contraindicates further dosing: specific examples include:

- Dose-limiting symptoms with respect to GI tolerability and in particular if a subject requires intravenous fluids for more than 48 hours 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

- Any subject where Hy's law criteria on liver function tests is met: AST or ALT ≥ 3 × ULN **together with** total bilirubin ≥ 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 with persistent fasting glucose level of > 260 mg/dL(14.4 mmol/L) despite a maximum tolerated dose of rescue therapy to enable optimisation of the subject's glycaemic control

4 Subject noncompliance that, in the opinion of the investigator or sponsor, warrants withdrawal (eg, refusal to adhere to scheduled visits)

5 Pregnancy in a female subject

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 clinical study.

4.1.7 Replacement of Subjects

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

4.1.8 Withdrawal of Informed Consent for Data and Biological Samples

Biological Samples Obtained for the Main Study

Study data are protected by the use of a SID number, which is a number specific to the subject. The investigator is in control of the information that is needed to connect a study sample to a subject. A subject's consent to the use of data does not have a specific expiration date, but the subject may withdraw consent at any time by notifying the investigator. If consent is withdrawn, any samples collected prior to that time may still be given to and used by the sponsor but no new data or samples will be collected unless specifically required to monitor safety of the subject (Section 10.6).

Plasma and Muscle Biopsy Samples Obtained for Genetic Research or Future Non-genetic Research

Samples obtained for genetic research or future non-genetic research will be labelled with a sample identification number linked to the SID number but will not be labelled with personal identifiers such as the subject's name (Section 10.7). If the subject withdraws consent for participating in the genetic research or future non-genetic research, the sponsor will locate the

subject's sample and destroy it. The coding of samples and results is to ensure that these research results are kept confidential by keeping the subject's identity and these results separate.

If the subject consents to have his/her samples used for genetic research or future non-genetic research, this additional research may not start immediately and may start at any time during the storage period. The subject's sample(s) including any specimens of extracted deoxyribonucleic acid (DNA) will be stored by the sponsor with similar samples from other subjects at a secure central laboratory. The subject's samples will not be kept for more than 15 years after the end of the study in which they were collected. If the subject chooses not to allow his/her study samples to be used for genetic research or future non-genetic research, the samples will be destroyed by the sponsor once they are no longer required for the main study.

If consent is withdrawn after a sample has been taken but before the subject's sample is sent to the sponsor for genetic research or future non-genetic research, the investigator will arrange to have it destroyed. If consent is withdrawn after the subject's sample(s) have been sent to the sponsor for genetic research or future non-genetic research, the sponsor and the investigator will ensure that these sample(s) are destroyed unless the sample identification number has been removed and the subject can no longer be linked to any sample(s). However, if the subject's samples have already been used for research, the sponsor is not required to destroy results of this research. In this case only the remaining sample(s) will be destroyed.

4.2 Schedule of Study Procedures

4.2.1 Enrolment/Screening Period

Table 5 shows all procedures to be conducted at the screening visit.

Table 5 Schedule of Screening Procedures

Study Period	Screening
Visit Number	**V1**
Procedure / Study Day	**Day -28 to Day -1**
Written informed consent/ assignment of SID number	X
Optional informed consent for blood samples for future genetic research [a]	X
Optional informed consent for blood samples for future non-genetic research [a]	X
[redacted]	[redacted]
[redacted]	[redacted]
Medical history, including smoking and alcohol history	X
Physical examination (full) including structured neurological examination [b]	X
Verify eligibility criteria	X
Weight, height and BMI calculation	X

Study Period	Screening
Visit Number	**V1**
Procedure / Study Day	**Day -28 to Day -1**
Demographics	X
12-lead ECG [c]	X
Vital signs (BP [d], pulse, body temperature, respiration rate)	X
Alcohol breath test	X
Collect blood for:	
LFTs, Cr and eGFR calculation only	X
TSH	X
HbA1c	X
Calcitonin	X
…Pancreatic lipase and amylase	X
HIV-1 and -2 antibodies; hepatitis B and C serology	X
Serum pregnancy test	X
Collect urine for:	
Urine drug screen	X
Urine pregnancy test if applicable	X
SC injection self-administration training [e]	X
Advise on washout of second non-metformin diabetes therapy if applicable [f]	X
Assessment of AEs and SAEs [g]	X
Concomitant medications	X

AE = adverse event; BMI = body mass index, BP = blood pressure, Cr = creatinine, DPPIV = dipeptidyl peptidase 4 inhibitor; ECG = electrocardiogram, eGFR = estimated glomerular filtration rate, FBC = full blood count, HbA1c = glycated haemoglobin, HIV = human immunodeficiency virus, LFTs = liver function tests (albumin, alanine transaminase [ALT], aspartate aminotransferase [AST], alkaline phosphatase [ALP] and total bilirubin), SAE = serious adverse event; SC = subcutaneous; SGLT2i = sodium-glucose co-transporter inhibitor(s); SID = subject identification, TSH = Thyroid stimulating hormone; V = Visit.

[a] During the informed consent process subjects will be asked to provide consent for the main study as well as for the optional components: future genetic research and future non-genetic research. Only sample(s) for which the subject has consented will be taken.

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

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

[d] Blood pressure should be measured once at heart level in the non-dominant group where possible, with the subject either seated or supine and rested for 10 minutes prior to the measurement.

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

[f] Once the subject's eligibility has been confirmed, subjects who take a second agent for their diabetes in addition to metformin (ie, a DPPIV inhibitor, SGLT2i, sulfonylurea, or glitinide), should be advised to stop the therapy 28 days before Visit 4.

[g] AEs and SAEs will be assessed from the time informed consent form is signed.

4.2.2 Randomised Treatment Period

Table 6 shows all procedures to be conducted during the treatment period.

Table 6 Treatment Period Study Procedures

Study Period	Placebo Period				Treatment Period						
Visit Number	**V2**	**V3 (optional)**	**V4**			**V5**	**V6**	**V7**	**V8**	**V9**	
Procedure / Study	**Day -1**	**Day 1-14**	**Day 15**	**Day 16**	**Day 17**	**Day 21**	**Day 25**	**Day 32**	**Day 41 or 42**	**Day 58**	**Day 59**
Admit to clinical unit			X							X	
Discharge from clinical unit					X						X
Outpatient visit to clinical unit	X	X				X	X	X	X		
Fasting on the night before required [a]	X	X	X	X	X			X	X	X	X
Physical examination (abbreviated)	X				X			X		X [b]	
Weight [c]	X				X			X			X
ECG					X						X
Vital signs (BP, pulse, body temperature, respiration rate) [d]	X				X			X			X
Collect Blood for											
Serum chemistry	X				X			X			X
Haematology	X				X			X			X
Pancreatic lipase and amylase					X			X			X
HbA1c					X						X
Serum calcitonin					X						X
Fasting lipid profile					X						X
Serum pregnancy test	X				X						
Optional for genetic testing	X										

Table 6 Treatment Period Study Procedures

Study Period	Placebo Period				Treatment Period						
Visit Number	V2	V3 (optional)	V4		V5	V6	V7	V8	V9		
Procedure / Study	Day -1	Day 1-14	Day 15	Day 16	Day 17	Day 21	Day 25	Day 32	Day 41 or 42	Day 58	Day 59
Optional non-genetic testing	X										X
[redacted]					[redacted]			[redacted]			[redacted]
[redacted]					[redacted]			[redacted]			[redacted]
Collect urine for:											
Urinalysis					X			X			X
Urine pregnancy test	X				X			X			X
Alcohol breath and urinary illicit drug test	X										
DLW assessment [g]	X				X				X	X	X
24-hour protein estimation			X							X	
DLW administration [h]	X								X		
[redacted]		X							X		
Fixed standardised breakfast (Meal Type A) [j]	X			X				X			X
[redacted] [k]	X										X
Ad libitum lunch (Meal Type C) [l]	X			X				X			X
Food diary provision and completion [m]	X			X				X			X

Table 6 Treatment Period Study Procedures

Study Period	Placebo Period				Treatment Period						
Visit Number	**V2**	**V3 (optional)**	**V4**		**V5**	**V6**	**V7**	**V8**	**V9**		
Procedure / Study	**Day -1**	**Day 1-14**	**Day 15**	**Day 16**	**Day 17**	**Day 21**	**Day 25**	**Day 32**	**Day 41 or 42**	**Day 58**	**Day 59**
SmartPill™ capsule administration to assess gastric emptying			X							X	
Fixed standardised meals (Meal Type B) [n]			X							X	
Advice on diet prior to whole room calorimetry (remote contact or during visit)		X (Day 4-11)							X		
Subject enters whole room calorimeter [o]			X							X	
Exercise sessions [p]			X							X	
Hunger/satiety questionnaires [q]			X							X	
DXA scan [r]	X										X
Optional muscle biopsy [s]		X							X		
Hood-based indirect calorimetry [t]	X		X	X	X			X		X	X
Provision of activity monitor and device training	X										
Activity monitoring	Subjects will be expected to wear the activity monitoring device until the final study visit (V10)										
Activity monitoring device battery check/ charging (as required) [u]				X				X		X	
Weight measurement at home	Subjects will be expected to weigh themselves every 72 hours whilst at home										

Table 6 Treatment Period Study Procedures

Study Period	Placebo Period				Treatment Period						
Visit Number	V2	V3 (optional)	V4		V5	V6	V7	V8	V9		
Procedure / Study	Day -1	Day 1-14	Day 15	Day 16	Day 17	Day 21	Day 25	Day 32	Day 41 or 42	Day 58	Day 59
Glucose meter provision and device training	X										
Provision of paper diary or digital device for collection of capillary glucose and weight measurements	X										
Capillary glucose measurements	Subjects will be requested to measure pre-breakfast capillary plasma glucose measurements every 72 hours whilst at home and if they feel unwell or experience symptoms of hypoglycaemia until Visit 10										
Assessment of TEAEs/TESAEs [v]	Will be collected continuously throughout the study										
Concomitant medications	Will be collected continuously throughout the study										
Subcutaneous injection training	X										
Verify eligibility criteria	X										
Randomisation	X										
[redacted]	[redacted]										
[redacted]	[redacted]										
[redacted]	[redacted]										
[redacted]	[redacted]										
[redacted]	[redacted]										

ADA = anti-drug antibody; AE = adverse event; BP = blood pressure; DLW = doubly labelled water; DXA = dual X ray absorptiometry; ECG = electrocardiogram; eCRF = electronic case report form; GIP = glucose-dependent insulinotropic polypeptide; GLP-1 = glucagon-like peptide-1; IVGTT = intravenous glucose tolerance test; LFT = liver function tests, min = minutes; MMTT = mixed-meal tolerance test; PK = pharmacokinetic(s); SAE = serious adverse event; TEAE = treatment-emergent adverse event; TESAE = treatment-emergent serious adverse event; V = Visit; VAS = Visual Analog Scale.

[a] Fasting for at least 12 hours is required the night before on Days -1, 15, 16, 17, 32, 58, and 59; on Day 17 subjects should be fasted overnight for at least 8 hours prior to investigational product administration and for a further 4 hours after investigational product administration as described in footnote s. For [redacted]

[b] Physical exam on Day 58 can occur at any time on Day 58 or 59.

[c] Body weight should be measured in the morning prior to breakfast or any of the standardised meals (predose on Day17); the subject should take off their shoes and remove bulky clothing. Calibrated scales should be used.

[d] Vital signs should be performed predose and 4 hours postdose on Day 17.

[e] PK samples should be taken predose.

[f] If possible, [redacted] See Section 4.3.7 for additional details.

[g] Urine samples for doubly labelled water assessment should be taken at baseline (T = 0) prior to administration of the doubly labelled water and further samples should be collected at T = 2, 3 and 4 hours ± 15 min afterwards and then a single sample should be taken 17 days± 4 hours later (eg, if DLW was given on Day -1 at 1000 hours, collection of urine would occur prior to 1000 hours and then at 2, 3, and 4 hours afterwards and then again on Day 17 at 1000 hours ± 4 hours). Visit 8 may occur on either Day 41 or 42, and if more convenient, the subject may be provided with instructions to perform the urine collections themselves at home after administration of DLW at the specified time points. The subsequent follow-up urine sample should be 17 days later eg, if the DLW was administered on Day 42, the follow-up sample should be taken on Day 59.

[h] DLW may be administered at any time.

[i] [redacted]

[j] A fixed standardised breakfast (as part of the MMTT) (Meal Type A) should be given to all subjects on Day -1 upon arrival to the study unit following the hood calorimetry assessment.

[k] [redacted]

[l] Ad libitum meal (Meal Type C) consumption will be measured in a single-blind fashion (see Section 4.3.2.2 for further details). The meal should commence at 1300 ± 2 hour. Subjects will be requested to eat until they feel comfortably full and the meal duration should be flexible according to subject preference.

[m] Subjects should be provided with a food diary after the ad libitum lunch on days -1, 16, 32 and 59 requested to record all food and drink they consume that day for the remainder of the day until midnight.

[n] Fixed standardised meals (Meal Type B) should be given at 0900 ± 30 min, 1300 ± 30 min and 1800 ± 30 min while the subject is in the whole room calorimeter. The meal type should be the same for all subjects and contain fixed ratios of carbohydrate, fat and protein, but energy content should be matched to the mean 24-hour energy expenditure recorded for the subject (see Section 4.3.2.2 for further details). The precise timings of these procedures may vary, provided that meals and exercise sessions are planned with similar time intervals and kept consistent for all subjects.

[o] Subjects should remain in the whole room calorimeter for the entire duration of up to 36 hours and not leave the room during this period including for meal times; a commode should be supplied for the subject to undergo toilet visits, and study site staff should minimise the time they spend within the whole room calorimeter. On Day 15 subjects should enter the calorimeter early in the morning to allow for calibration of the chamber and are permitted to stay overnight if more convenient for them. The measurement on Day 15 will begin after a 2-hour calibration period and last for 24 hours. On Day 58 subjects will enter the whole room calorimeter the night before to allow for calibration and the 24-hour of measurement will begin at 0800 ± 1 hour. The physical exam can be performed anytime on Day 58 or 59. The MMTT on Day 59 should begin after the 24-hour calorimetry measurement period has been completed.

[p] Subjects will be requested to use an exercise bike whilst inside the whole room calorimeter for exactly 15 min continuously at 1130 ± 15 min and 1430 ± 15 min, 1730 ± 15 min and 2030 ± 15 min. The same resistance level (eg, the lowest resistance level on the bike) should be used for all subjects and subjects should aim to exercise at 65% of maximal heart rate and complete the full 15 min of exercise. The precise timings of these procedures may vary, provided that meals and exercise sessions are planned with similar time intervals and kept consistent for all subjects.

[q] Subjects should be given hunger and satiety questionnaires as they enter the calorimeter to be completed prior to the first meal. The VAS questionnaires should be repeated during the day.

[r] Subjects should remove their outer clothing and jewelry/watch and dress in a surgical gown or scrubs to undergo DXA scanning.

[s] [redacted]

[t] Indirect calorimetry using a hood should be performed with the subject rested. On Day 17 hood calorimetry should be performed at any time predose while the subject is fasted and at 4 hours postdose ± 15 min. Subjects should remain fasted in between measurements, but are permitted to drink caffeine-free clear liquids during this time. See Section 4.3.2.6 for additional details.

[u] During study visits, staff should check that the activity monitor is adequately charged and top up charging where needed; charging times should be kept to a minimum to ensure continuity of measurements.

[v] AEs and SAEs will be assessed from the time of signed informed consent form.

[w] [redacted]

4.2.3 Follow-up Period

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

Table 7 Schedule of Follow-up Procedures

Study Period	Follow-up Period
Visit Number	**Final Visit (V10)**
Procedure / Study Day	**28 days post last dose (± 3 days)**
Physical examination (abbreviated)	X
Remove activity monitoring device	X
Weight	X
ECG	X
Vital signs (BP, pulse, body temperature, respiration rate) [a]	X
Serum chemistry panel	X
Calcitonin [b]	X
Haematology	X
Urinalysis	X
HbA1c	X
Urine pregnancy test	X
[redacted]	[redacted]
Assessment of TEAEs/TESAEs [d]	X
Concomitant medications [e]	X

ADA = anti-drug antibody; AE = adverse event; BP = blood pressure; ECG = electrocardiogram; HbA1c = glycated haemoglobin, SAE = serious adverse event; TEAE = treatment-emergent adverse event; TESAE = treatment-emergent serious adverse event; ULN = upper limit of normal; V = visit.

[a] Blood pressure should be measured once at heart level in the non-dominant arm where possible, with the subject seated and rested for 10 minutes prior to the measurement.

[b] Only to be repeated if the calcitonin level was > ULN in the sample taken at the end of dosing.

[c] See Section 4.3.7 for details.

[d] AEs and SAEs will be assessed from the time of signed informed consent form.

[e] If a second non-metformin agent was washed out during the screening period the investigator and/or study team should consider whether it is appropriate to re-start this therapy.

4.2.4 Early Discontinuation Visit or Unscheduled Study Visit

The following study procedures may be conducted for subjects who prematurely discontinue from the study or for subjects who require an unscheduled study visit. The types of procedures required will be at the discretion of the investigator.

- Targeted physical examination
- ECG

- Vital signs
- Body weight
- [redacted]
- Blood tests including chemistry and haematology panel
- [redacted]
- Assessment of AEs/serious adverse events (SAEs)
- Concomitant medications
- Urine pregnancy test (if applicable)

4.3 Description of Study Procedures

4.3.1 Screening/Enrolment, Treatment, and Follow-up

On Day -1 subjects will attend the clinical unit having fasted for 12 hours overnight (ideally subjects will stay at the research facility the night before but have the option to arrive the morning of Day -1 if more convenient). Subjects will be weighed and will undergo a hood calorimetry assessment (after at least one hour of rest) to measure REE. Subjects will then receive a standardised solid meal (Meal Type A) as part of a MMTT with serial blood sampling followed by a lunchtime meal on an ad libitum basis (Meal Type C); food consumption will be measured in a single-blind fashion and subjects will be expected to complete a food diary for the remainder of the day after the ad libitum lunch. During the visit subjects will also undergo a DXA scan, blood tests for safety and they will receive a drink of doubly labelled water (DLW [$^{2}H_{2}{}^{18}O$]) and will be required to provide urine samples before and after the drink of DLW. In addition, an activity monitor will be fitted and subjects will be expected to wear the monitor continuously until the final study visit. Subjects will also be required to perform periodic measurements of weight and capillary glucose measurements whilst at home for the duration of the study, the results of which will either be recorded digitally or in a paper diary. [redacted]

[redacted]

Between Day 4 and 11, subjects will be contacted by the study team at any time to advise them on diet in the 72 hours prior to their admission on Day 15 to ensure that they are in a neutral energy balance before this visit. On Day 15, subjects will be admitted following a 12-hour overnight fast to the clinical unit for approximately 48 hours. Upon arrival, subjects will enter the whole room calorimeter and remain inside for up to 36 hours. A hood

calorimetry assessment will be performed initially and collection of urine for protein estimation (on Day 15/16) and DLW assessments (on Day 17) will be undertaken. Subjects will receive standardised meals at fixed times (Section 4.3.2.2). Meals (Meal Type B) will be formulated to match individual energy requirements using baseline energy expenditure readings from the activity monitor or using population-based energy requirement equations. Immediately after the first meal subjects will be required to swallow a SmartPill™ to measure gastric emptying and they will be restricted to drinking 200 mL water for the first 2 hours after swallowing the SmartPill™, but will be permitted to drink unlimited amounts of sugar-free, decaffeinated drinks for the remainder of the day after this time. During the time in the calorimeter, subjects will be expected to exercise on an exercise bike for 4 × 15-minute intervals and to fill out questionnaires to assess hunger and satiety. On Day 16 subjects will undergo a hood calorimetry assessment and afterwards will receive a fixed standardised breakfast (Meal Type A) followed by a lunch-time meal on an ad libitum basis (Meal Type C); food consumption will be measured in a single-blind fashion and subjects will be expected to fill in a food diary for the remainder of the day after the ad libitum lunch. On Day 17, following an overnight fast of at least 8 hours, [redacted]

On Day 32, subjects will attend for a long day visit following an overnight fast of at least 12 hours. Subjects will undergo hood calorimetry upon arrival (after at least one hour of rest) and afterwards they will receive a fixed standardised breakfast (Meal Type A) followed by an ad libitum lunch (Meal Type C); again, food consumption will be measured in a single-blind fashion. [redacted]

Subjects will either receive a home visit or re-attend for a short visit on either Day 41 or 42 to receive DLW and will be requested to provide urine samples before and afterwards. Subjects will also be advised on diet in the 72 hours prior to their admission on Day 58 to ensure that subjects are in a neutral energy balance before this visit. [redacted]

On Day 58, subjects will be re-admitted to the clinical unit for approximately 48 hours but will be permitted to arrive the evening before and stay overnight if that is more convenient for them. Upon arrival, subjects will enter a whole room calorimeter for up to 36 hours and

undergo the same procedures as before including urine sampling for protein estimation and as part of the DLW assessment.

On Day 59 subjects will be weighed and then receive a fixed solid standardised meal (Meal Type A) as part of a MMTT with serial blood sampling followed by a lunchtime ad libitum meal (Meal Type C) with a single-blind measure of food consumption and completion of a food diary for the remainder of the day. Subjects will also undergo a repeat DXA scan and safety bloods will be taken at the same time as the MMTT. A follow-up visit will be performed for final safety assessments approximately 28 days after the last dose of investigational product.

4.3.2 Efficacy

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

4.3.2.1 Mixed-meal Tolerance Test

Following a minimum 12-hour fast the subject will undergo a MMTT at the times specified in the schedule of treatment period study procedures (Table 6) which will involve the consumption of a standardised solid meal (Meal Type A) within 5 minutes, and timed serial blood samples will be obtained for measurement of glucose and gut and pancreatic hormone levels through 240 minutes with no additional food intake during this time. Subjects will be permitted to drink water during this assessment.

4.3.2.2 Standardized Meals

Meal Type A:

A standardised solid breakfast meal that will be provided to subjects at the time points specified in the schedule of treatment period study procedures and during the MMTTs (Table 6). The same meal should be used for all subjects at the beginning and end of the study.

Meal Type B:

Meal Type B describes the standardised meals that will be administered to subjects during their stay in the whole room calorimeter at the time points specified in the schedule of treatment period study procedures (Table 6). The solid meals should be balanced nutritionally and contain fixed ratios of carbohydrate, fat and protein. The total daily calorie content of meals should be matched to the subjects EE recorded on the activity monitor worn during the single-blind placebo treatment period to ensure neutral energy balance. Alternatively, population-based estimates of energy requirement equations may be made. For example, if the subject's average daily calorie expenditure (predicted or measured) = 2000 kcals during the placebo treatment period, the total daily calorie content of meals administered while the subject is in the calorimeter should equal approximately 2000 kcals. Subjects will be expected to consume each meal within 30 minutes. The actual meal choices provided may vary by

meal, but ideally subjects should be given the same type of meal at the same time; and the same menu should be used between the baseline assessments and at the end of the treatment period. If a subject has a strong dislike of a particular meal, it is permissible to substitute the meal with an alternative providing that the meal contains the same ratio of carbohydrate, fat, and protein. Inter-meal snacks should be avoided while the subject is in the calorimeter; however, sugar-free caffeine-free drinks are allowed freely during this time (with the exception of the 2-hour period after ingestion of the SmartPill™ to measure gastric emptying).

Meal Type C:

Meal type C is the ad libitum lunch that will follow breakfast (Meal Type A) that will be served as a meal with food of known macronutrient content at the time points specified in the schedule of treatment period study procedures (Table 6). Subjects will be advised to eat freely until they feel comfortably full. There will be no time limit on the duration of the meal. During the meal, the quantity of food ingested will be recorded by study site staff; the subjects will not be aware food consumption is being recorded. When subjects are finished eating their ad libitum lunch, they will be provided with a food diary to complete for the remainder of the day (Section 4.3.3.2).

4.3.2.3 Dual X-ray Absorptiometry

The change in total body fat mass will be measured in kilograms (kg) using DXA at the beginning of the study and end of the study according to the time points specified in the schedule of treatment period study procedures (Table 6). Dual X ray absorptiometry scanning will be conducted using a Lunar iDXA scanner (GE healthcare). A single scan is equivalent to 2 days of background radiation. Subjects will be asked to remove all metal on their body and will be provided with surgical scrubs to wear when necessary. Subjects will align themselves on the scanner so that the centre of their body is lying on the middle of the scanner. Subjects will be advised to be as still as possible for the duration of the scan, which will take between 5 and 10 minutes depending on the size of the participant. There will be no requirement for sedation during the scan.

Analysis of the result will involve alignment of standard lines to outline the following sections in the body: left leg, right leg, right trunk, left trunk, right arm, left arm, and head. A read-out of the estimated mass of total body tissue, fat, and lean mass fat mass will be generated and recorded in the eCRF.

4.3.2.4 [redacted]

[redacted]

4.3.2.5 Activity Monitor

A wrist-band activity monitor will be worn for the duration of the study and will be used to measure EE generated on the device as a function of monitored physical activity. The device, which is an accelerometer, will also be used to monitor time spent in activity and energy expenditure at different phases in the study.

The subject may be required to periodically re-charge the activity monitor at home and will be provided with additional written instructions for use of the device (eg, what to do with the monitor while bathing, etc). The device is not waterproof and will need to be removed during showering, bathing and swimming.

4.3.2.6 Whole-Room and Hood-Based Indirect Calorimetry

A whole room calorimetry assessment will be used to measure gaseous exchange and therefore indirect estimates of EE over a 24-hour period. Subjects will enter the whole room calorimeter for up to 36 hours and reside inside for this entire duration (this will include toilet visits too). An equilibration period will be required prior to recording gaseous exchange. Study site staff will not enter the calorimeter during this time unless this is required for safety reasons.

During the time in the calorimeter subjects will be asked to exercise on an exercise bike for 15-minute intervals at 4 times. During these sessions subjects will be asked to aim for a heart rate of 65% of maximum (defined as 220 beats per minute minus age) and complete the full 15-minute session. The exercise bike should be placed inside the calorimeter ideally prior to the subject entering the chamber and the settings on the exercise bike should be calibrated to the lowest resistance setting for all subjects at the beginning and end of the study.

Hood indirect calorimetry assessments will be performed according to the days and times specified in the schedule of treatment period study procedures (Table 6). Subjects should be rested for at least 1 hour prior to hood calorimetry measures; during a hood calorimetry assessment the subject will be asked to remain quiet and rested for 40 minutes in total with 10 minutes before and after the assessment to allow for room air assessment. A large plastic hood is placed over their head for 20 minutes and measurements of gaseous exchange are undertaken. A hood calorimetry assessment may also be performed at times whilst the subject is in the whole room calorimeter to obtain an estimate of REE if required.

4.3.2.7 Muscle Biopsy

[redacted]

[redacted]

4.3.2.8 Body Weight

Body weight in kilograms (kg) will be measured at clinic visits at the time points specified in the schedules of study procedures (Section 4.2) after the subject have removed bulky clothing including shoes. Whenever possible, the same (properly calibrated) scale should be used for each measurement for any given subject.

Body weight will also be measured by the subject at home every 72 hours; and the subject should be given similar instructions for undertaking measurements. Collection of home-recorded weights will either be electronic or recorded in a paper diary.

4.3.2.9 Intravenous Glucose Tolerance Test

To measure first phase insulin release, insulin sensitivity, and glucose, at the time points specified in the schedule of treatment period study procedures (Table 6), subjects will attend the clinical unit having fasted for 12 hours overnight for an intravenous glucose tolerance test (IVGTT). During this assessment, an intravenous cannula will be inserted into a vein in the antecubital fossa and patency will be checked with a normal saline flush. Once confirmed, a bolus of 300 mg/kg (based on body weight or lean mass) of 20% to 30% glucose or dextrose solution will be administered intravenously. Blood samples will be drawn before and for up to 180 minutes after the glucose infusion at time-points detailed in the schedule of procedures.

4.3.2.10 Gastric Emptying Assessment

At the time points specified in the schedule of treatment period study procedures (Table 6), subjects will be admitted to the clinical unit following a 12-hour overnight fast and be required to swallow a SmartPill™ to measure gastric emptying. The SmartPill™ will be consumed immediately after the first standardised meal (Meal type B) while the subject is in the whole room calorimeter. After consuming the SmartPill™, the subject will be restricted to drinking 200 ml of water for the preceding 2 hours, but thereafter may drink sugar-free and decaffeinated drinks freely. If a subject is unable/ unwilling to complete this procedure, they should not be withdrawn or discontinued from the study.

The SmartPill™ motility capsule (referred to as a SmartPill™) is part of the SmartPill™ Motility Testing System (Medtronic) used to measure gastric emptying. The system consists of a SmartPill™ which the subject ingests, a receiver worn around the waist and a laptop including a docking station. The SmartPill™ measures pressure, pH, transit time, and temperature as it passes through the entire GI, sending a signal to the receiver once it has been

expelled from the body (through the faeces). Once the receiver has indicated that the SmartPill™ has been passed out of the body, the subject will return the receiver to the site who will download the data (the SmartPill™ is a disposable device and should pass through the faeces un-noticed; it does not need to be recovered following elimination through the faeces). The gastric emptying time is computed automatically by the system software and can be verified from the resulting trace which is a feature of the output dataset.

In the event that a subject cannot or will not swallow the SmartPill™ capsule, they may continue in the study without it constituting a deviation from the protocol. If for any reason a subject is unable to tolerate the SmartPill™ they should not be discontinued from the study.

4.3.3 Patient Reported Outcomes

4.3.3.1 Hunger and Satiety

Questionnaires will provide information on whether MEDI0382 affects hunger, satiety or both. Change in hunger and satiety scores at the time points specified in the schedules of procedures will be obtained. Results will be recorded in the eCRF.

Dutch Eating Behaviour Questionnaire

The Dutch Eating Behaviour Questionnaire (DEBQ) is a 33-item self-report questionnaire that was developed to assess three distinct eating behaviours in adults: (1) emotional eating, (2) external eating, and (3) restrained eating. Items on the DEBQ range from 1 (never) to 5 (very often), with higher scores indicating greater endorsement of the eating behaviour (Van Strien et al 1986) (Section 10.8.1). Results will be recorded in the eCRF.

Visual Analogue Scale

A Visual Analogue Scale (VAS) that will be used in this study is a 4-item self-report questionnaire that assesses hunger on a scale from ‘not at all’ to ‘extremely.’ A copy of this VAS is included in Section 10.8.2. Results will be recorded in the eCRF.

4.3.3.2 Food Diary

Subjects will be provided with a food diary following the ad libitum meal assessment and ask to record the amount of food and any drinks consumed for the remainder of the day where indicated in the schedule of assessments. The total calories consumed in joules will be calculated and recorded in the eCRF.

4.3.4 Safety Assessments

4.3.4.1 Medical History and Physical Examination

Complete medical history will include history (including smoking and alcohol history) and current medical conditions, past or present cardiovascular disorders, respiratory, gastrointestinal (GI), renal, hepatic, neurological, endocrine, lymphatic, haematologic,

immunologic, dermatological, psychiatric, genitourinary, drug and surgical history, or any other diseases or disorders.

The full physical examination including a structured neurological examination is required at screening (Table 5). Abbreviated physical 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 (ie, randomised treatment and follow-up periods) (Table 6 and Table 7). Physical examinations will be performed by a physician or qualified designee and will include examination of the following body systems: immunologic/allergy; head, ears, eyes, nose, and throat; respiratory; cardiovascular; GI; musculoskeletal; neurological (structured neurological examination to encompass mental status, cranial nerves, nystagmus; motor system-muscle strength, sensory system-sensation, bowel and bladder function, deep tendon reflexes, gait, station, coordination, fundoscopy, and cerebellar function); psychiatric (to the extent of determining whether or not the subject is willing and able to cooperate with the required study procedures in the investigator's judgment); dermatological; haematologic/lymphatic; and, endocrine.

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

Clinically significant abnormal findings will be recorded.

4.3.4.2 Assessment of the Injection Site

Study centre staff will check the injection site for 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 changes.

4.3.4.3 Electrocardiograms

At the visits specified in the schedules of study procedures (Table 5, Table 6, and Table 7), ECGs will be obtained after 10 minutes supine rest. Only a single digital ECG recording will be required at the specified time points.

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

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

In this study lead II or V2 will be analysed and reported as primary. Lead V5 will be analysed, for all visits, as backup for the individual where analysis in lead II or V2 is not deemed possible for pre-dose or significant parts of whole visits or whole visits.

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

4.3.4.4 Vital Signs

Vital sign measurements (BP, pulse rate, body temperature, and respiration rate) will be obtained after the subject has rested in either a seated or supine position for at least 10 minutes at the time points specified in the schedules of study procedures (Section 4.2). 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). Blood pressure should be measured once at heart level in the non-dominant arm where possible, with the subject seated or supine and rested for 10 minutes prior to the measurement. Route of body temperature measurement will be according to local procedures.

4.3.4.5 Weight, Height, and Body Mass Index Calculation

Weight (kg), height (cm), and BMI (kg/m^2) will be measured at screening. Weight will be measured at all other time points as specified in the schedules of study procedures (Section 4.2).

4.3.5 Clinical Laboratory Tests

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

Clinical laboratory safety tests will be performed in a licensed central or licensed local clinical laboratory. Urine pregnancy tests may be performed at the site using a licensed test (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 (refer to time points in the schedules of study procedures (Section 4.2):

Serum Chemistry

- Potassium
- Sodium
- ALT
- AST
- ALP
- Total bilirubin
- Creatinine
- Blood urea
- Albumin

ALP = alkaline phosphatase; ALT = alanine transaminase; AST = aspartate transaminase.

Notes:

Liver function tests = AST, ALT, ALP, total bilirubin, and albumin

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

Haematology

- White blood cell count with differential
- Red blood cell count
- Haematocrit
- Haemoglobin
- Platelet count
- Mean corpuscular volume
- Mean corpuscular haemoglobin concentration

Urinalysis

- Protein
- Glucose
- Blood
- Urine drug screen [a]
- Ketones

Notes:

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

[a] Illicit drug panel will test for the following drugs; amphetamines, barbituates, benzodiazepines, cocaine, opiates (morphine, heroin), methamphetamine, cannabinoids (marijuana), methodone, phencyclidene, methylenedioxy-methamphetamine (ecstasy), propoxyphene, and tricyclic antidepressants. 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.

Additional Urine Samples

- Urine samples for DLW assessment
- 24-hour urine collection for protein assessment

Pregnancy Test (females of childbearing potential only)

- Serum human chorionic gonadotropin (hCG; screening if applicable, and Day -1 and 17 only)
- Urine hCG

Other Laboratory/Blood Tests

- Calcitonin
- Alcohol screening test (breath- or urine-based test)
- Pancreatic amylase and lipase
- Glycated haemoglobin
- Anti-drug antibodies (immunogenicity)
- Hepatitis B surface antigen, hepatitis C antibody (screening only)
- Human immunodeficiency virus-1, -2 antibodies (screening only)
- Metabolism panel for MMTT: Timed glucose; insulin, C-peptide, glucagon, GIP, active and total GLP-1, and ghrelin
- Fasting lipid profile: high-density lipoprotein, low-density lipoprotein, triglycerides, total cholesterol, and Apo lipoprotein B
- Thyroid stimulating hormone (TSH; screening only)

4.3.5.1 Glucose Meter Measured Capillary Plasma Glucose Readings

At the start of the study, each subject will be issued a standardised glucose meter, testing strips, and a diary. Subjects will be requested to record a capillary glucose reading pre-breakfast every 72 hours and will also be encouraged to perform finger-prick tests if they feel unwell, and in particular if they feel the symptoms may be due to hypoglycaemia for the duration of the study (Section 3.1.4.2). If the investigator/site staff feel that a subject could be experiencing hypo- or hyperglycaemia, capillary plasma glucose should be tested with a standardised glucose meter. Capillary plasma glucose levels of < 3 mmol/L (54 mg/dL) should be recorded as an AE regardless of whether the subject has symptoms or not. Readings taken by the subject at home will be recorded electronically or in a paper diary.

4.3.6 Pharmacokinetic Evaluation and Methods

[redacted]

4.3.7 Immunogenicity Evaluation and Methods

[redacted]

[redacted]

4.3.8 Biomarker Evaluation and Methods

[redacted]

4.3.9 Genetics

The subject's consent to participate in the genetic research components of the study is optional. See Section 10.6.3 for further information.

4.3.10 Estimate of Volume of Blood to Be Collected

[redacted] Additional blood samples may be collected at the discretion of the investigator in the event of abnormal laboratory findings or an AE.

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:

- The incidence or severity of AEs in this or other studies indicates a potential health hazard to subjects
- Subject enrolment is unsatisfactory
- Non-compliance that might significantly jeopardize the validity or integrity of the study
- Sponsor decision to terminate development of the investigational product for this indication
- Sponsor decision to terminate the study based on a planned futility analysis

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 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 (IECs when applicable) will be obtained prior to resuming the study.

4.5 Investigational Products

4.5.1 Identity of Investigational Product(s)

MedImmune will provide the investigator(s) with investigational product (Table 8) using designated distribution centres.

Table 8 Identification of Investigational Products

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

[a] Final Qualified Person certification and responsible manufacturer is MedImmune.

[redacted]

4.5.1.1 Investigational Product Handling

In-clinic Investigational Product Handling

[redacted]

At-home Investigational Product Handling

[redacted]

[redacted]

4.5.1.2 Investigational Product Inspection

[redacted]

[redacted]

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

4.5.1.3 Treatment Administration

In-clinic Treatment Administration

[redacted]

[redacted]

At-home Treatment Administration

[redacted]

[redacted]

[redacted]

4.5.1.4 Monitoring of Dose Administration

[redacted]

[redacted]

4.5.1.5 Reporting Product Complaints

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

MedImmune contact information for reporting product complaints:

Email: productcomplaints@medimmune.com

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

Fax: +1-301-398-8800

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

4.5.2 Additional Study Medications

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

4.5.3 Labelling

Labels for the investigational product will be prepared in accordance with Good Manufacturing Practice and local regulatory guidelines.

4.5.4 Storage

All investigational product should be stored at 2°C to 8°C in a secure place under appropriate storage conditions. The label on the investigational product kit specifies the appropriate storage requirements.

4.5.5 Treatment Compliance

In-clinic Administration

[redacted]

At-home Administration

[redacted]

4.5.6 Accountability

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

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

4.6 Treatment Assignment and Blinding

4.6.1 Methods for Assigning Treatment Groups

An IXRS will be used for randomisation to a treatment group and assignment of 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 investigational product kit numbers for the subject.

4.6.2 Methods to Ensure Blinding

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

The different fill volumes of investigational product (MEDI0382 and placebo) and the relative position of the plunger rods will be visually distinct during administration. Neither the subject/legal representative 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 blinding mechanism will be implemented through the IXRS to ensure that treatment groups are not revealed to the site. In the event that treatment allocation for a subject becomes known to the investigator or other study staff involved in the management of study subjects, the sponsor must be notified *immediately*. If the treatment allocation for a subject needs to be known to treat an individual subject for an AE, the investigator must notify the sponsor *immediately* and, if possible, before unblinding the treatment allocation.

In addition, to maintain the blind, investigational product (MEDI0382 and placebo) prefilled syringes will be handled by an unblinded investigational product manager or unblinded study personnel who will not be involved in the treatment or clinical evaluation of subjects. 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. The site will maintain a written plan detailing which staff members are blinded/unblinded and the process of investigational product administration used to maintain the blind.

4.6.3 Methods for Unblinding

4.6.3.1 Unblinding in the Event of a Medical Emergency

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

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

Instructions for unblinding an individual subject's investigational product allocation are contained in the IXRS manual.

4.6.3.2 Unblinding for Pharmacokinetic Analysis

[redacted]

4.7 Restrictions During the Study and Concomitant Treatment(s)

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

4.7.1 Permitted Concomitant Medications

Investigators may prescribe concomitant medications or treatments deemed necessary to provide adequate supportive care except for those medications 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-diarrhoeals, 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 concomitant medications or herbal supplements at the times specified in the list below is not permitted. Subjects must be instructed not to take any medications, including over-the-counter products, without first consulting with the investigator.

- Concurrent or previous use of a GLP-1 analogue containing preparation within the last 30 days or 5 half-lives of the drug, whichever is longest, prior to the start of screening (Visit 1)
- Concurrent 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 the single-blind placebo treatment period (Visit 2)
- 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 the single-blind placebo treatment period (Visit 2)

- Concurrent use of opiates, domperidone, metoclopramide, or other drugs known to alter gastric emptying within 2 weeks prior to the start of Visit 2

4.8 Statistical Evaluation

4.8.1 General Considerations

Data will be provided in listings sorted by treatment group and subject number. Tabular summaries will be presented by treatment group and visit. Categorical data will be summarized by the number and percentage of subjects in each category. Continuous variables will be summarized by descriptive statistics, including mean, standard deviation, median, minimum, and maximum. Baseline values will be defined as the last valid assessment prior to the first administration of investigational product unless otherwise specified. Additional details of statistical analyses will be described in the statistical analysis plan.

4.8.2 Analysis Populations

The Intent-to-treat population will include all subjects who receive any investigational product analysed according to randomised treatment group.

The Modified Intent-to-treat (mITT) population will include all subjects who receive at least one dose of investigational product in the double-blind treatment period analysed according to randomised treatment group.

The As-treated population will include all subjects who receive any investigational product analysed according to the treatment they actually receive.

The Per-protocol population will include all subjects in the mITT population who complete treatment with investigational product up to Day 58.

The PK population will include all subjects in the As-treated population and have at least one PK sample taken that is above the lower limit of quantitation.

The Immunogenicity population will include all subjects in the As-treated population who have at least one serum sample for immunogenicity testing.

4.8.3 Sample Size

[redacted]

4.8.4 Efficacy

4.8.4.1 Primary Efficacy Analysis

The efficacy analysis will be based on the mITT population. The primary efficacy endpoint of percentage change in body weight from Day 17 to 59 will be compared between MEDI0382 and placebo groups using an analysis of covariance (ANCOVA) model adjusting for treatment group and measurement at baseline. Last observation carried forward will be used for missing data imputation for post-baseline values when applicable.

4.8.4.2 Secondary Efficacy Analyses

The secondary efficacy endpoints will be based on the mITT population and analysed by an ANCOVA model similar to that used for the primary efficacy analysis. Selected secondary endpoints will also be analysed using the Per-protocol population.

4.8.4.3 Exploratory Efficacy and Pharmacodynamic Analyses

[redacted]

4.8.5 Safety

4.8.5.1 Analysis of Adverse Events

The safety analysis will be based on the As-treated population. Adverse events and SAEs will be coded by the most updated version of the Medical Dictionary for Regulatory Activities (MedDRA) and the type, incidence, severity, and relationship to investigational product by will be summarized by MedDRA System Organ Class (SOC) and Preferred Term (PT). 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. All TEAEs will be summarized overall, by MedDRA SOC and PT, and by severity and relationship to investigational product. In addition, summaries of deaths, SAEs, and treatment discontinuations due to AEs will be provided.

4.8.5.2 Analysis of Clinical Laboratory Parameters

Additional safety data including vital signs, safety laboratory analysis, and ECGs will be summarised descriptively at each time point by treatment group.

4.8.6 Analysis of Immunogenicity

[redacted]

4.8.7 Analysis of Pharmacokinetics

[redacted]

4.8.8 Patient Reported Outcomes

Analysis of patient reported outcomes (PROs) will be based on the mITT population. The exploratory PRO endpoints including change in self-reported hunger and satiety scores from, Day 15 to 58 and the change in total energy intake in kilojoules (kJ) as recorded in a food diary from Day 16 to 32 and from Day 16 to 59 will be analysed by an ANCOVA model similar to that used for the primary efficacy analysis.

4.8.9 Interim Analysis

No interim analyses are planned.

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 serious adverse event (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 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 (Section 5.4). 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.

5.3.1 Time Period for Collection of Adverse Events

AEs and SAEs will be collected from time of signature of informed consent throughout the study including the follow-up period as described above.

5.3.2 Follow-up of Unresolved Adverse Events

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

5.3.3 Deaths

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

- An AE causing the death must be reported as an SAE within 24 hours. The report 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 5.4 for additional information).

5.4 Reporting of Serious Adverse Events

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

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.

5.5 Other Events Requiring Immediate Reporting

5.5.1 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 CRF and on the Overdose CRF module.
- An overdose without associated symptoms is only reported on the Overdose CRF 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 5.4. For other overdoses, reporting must occur within 30 days.

5.5.2 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.

5.5.3 Pregnancy

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

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

5.5.3.1 Maternal Exposure

If a subject becomes pregnant during the course of the study, the 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, i.e., 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 (Section 5.4) 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) utilized.

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

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

6.2 Monitoring of the Study

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

- Provide information and support to the investigator(s)
- Confirm that facilities remain acceptable
- Confirm that the investigational team is adhering to the protocol, that data are being accurately and timely recorded in the eCRFs, that biological samples are handled in

accordance with the Laboratory Manual and that study drug accountability checks are being performed

- Perform source data verification (a comparison of the data in the eCRFs with the subject's medical records at the hospital or practice, and other records relevant to the study) including verification of informed consent of participating subjects. This will require direct access to all original records for each subject (eg, clinic charts)
- Ensure withdrawal of informed consent to the use of the subject's biological samples is reported and biological samples are identified and disposed of/destroyed accordingly, and the action is documented, and reported to the subject

The MedImmune representative will be available between visits if the investigator(s) or other staff at the centre 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 shall prevail.

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

6.2.3 Archiving of Study Documents

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

6.3 Study Timetable and End of Study

An individual subject will be considered to have completed the study if the subject was followed through their last protocol-specified visit/assessment at Visit 10, regardless of the number of doses of investigational product that was received.

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

The end of the study ('study completion') is defined as the date of the last protocol-specified visit/assessment (Visit 10) for the last subject in the study.

6.4 Data Management

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

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

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

6.5 Medical Monitor Coverage

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

7 ETHICAL AND REGULATORY REQUIREMENTS

7.1 Subject Data Protection

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

Extra precautions will be taken to preserve confidentiality and prevent genetic data being linked to the identity of the subject. MedImmune will not provide individual genotype results to subjects, any insurance company, any employer, their family members, general physician or any other third party, unless required to do so by law.

7.2 Ethics and Regulatory Review

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

The opinion of the IEC must be given in writing. The investigator must provide a copy of the written approval to MedImmune before 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 IEC annually.

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

Each Principal Investigator is responsible for providing reports of any serious and unexpected adverse drug reactions from any other study conducted with the investigational product to the IEC. 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 ICF (s) is/are stored in the Investigator's Study File
- Ensure a copy of the signed ICF is given to the subject
- Ensure that any incentives for subjects who participate in the study as well as any provisions for subjects harmed as a consequence of study participation are described in the IFC that is approved by an IEC

7.4 Changes to the Protocol and Informed Consent Form

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

Substantial changes must be documented in a study protocol amendment. MedImmune will distribute amended versions of the protocol to the principle investigator(s). Before implementation, amended protocols must be approved by relevant IRB/IEC (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 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 ICH, and any applicable regulatory requirements. The investigator will contact MedImmune immediately if contacted by a regulatory agency about an inspection at the site.

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9 CHANGES TO THE PROTOCOL

9.1 Protocol Amendment 5, 20Mar2019

The changes to text summarised below have been incorporated in the body of Protocol Amendment 5.

Table 9 Summary of Revisions to the Protocol

Section of the Protocol Affected	Reason for Amendment
Protocol Synopsis (Objectives and Endpoints; Statistical Methods), Section 2.2 (Secondary Objectives and Endpoints, Table 2, Secondary Objectives and Endpoints), Section 2.3 (Exploratory Objectives and Endpoints, Table 3, Exploratory Objectives and Endpoints), Section 3.2.3.2 (Secondary Endpoints), Section 4.8.1 (General Considerations), Section 4.8.2 (Analysis Populations), Section 4.8.4 (Efficacy), and Section 4.8.8 (Patient Reported Outcomes)	To correct errors identified in the planned statistical analyses: • The objectives and endpoints were updated. • The secondary objective and related endpoint pertaining to the effect of placebo treatment on ad libitum lunchtime energy intake was removed. • The rationale for the single-group crossover analyses was removed. • Text describing which subjects were to be included in the treatment groups for certain endpoints was removed. • Analysis populations were added and revised. • The analysis populations were changed for the efficacy and PRO analyses.
Protocol Synopsis (Treatment Groups and Regimens) and Section 3.1.2 (Treatment Regimen)	The text was revised: • To correct a typographic error in the treatment groups and regimens section of the protocol synopsis. • To better clarify the regimen for the single-blind placebo treatment group.
[redacted]	[redacted]
Protocol Synopsis (Statistical Methods) and Section 4.8.5.1 (Analysis of Adverse Events)	The terminology for AEs was reconciled to improve consistency and correct typographic errors.
Section 3.1.3 (Dose Escalation)	The text was revised to better clarify how dose escalation will occur from Day 17 onwards.
[redacted]	[redacted]

Table 9 Summary of Revisions to the Protocol

Section of the Protocol Affected	Reason for Amendment
Section 4.2.2 (Randomised Treatment Period, Table 6 Treatment Period Study Procedures), Section 4.3.2.7 (Muscle Biopsy), and Section 4.3.2.9 (Intravenous Glucose Tolerance Test)	Minor procedural changes were made: • To align with the capabilities of the study site in completing procedures. • To correct typographic errors.
Section 4.3.8 (Biomarker Evaluation and Methods)	Upon further consideration after authoring the original protocol, the text was revised to clarify the biomarker evaluation.
Section 4.5.1.3 (Treatment Administration)	Text describing the type of treatment to be administered on Day 1 was deleted to correct typographic error.
Section 10.5 Appendix 5 (Actions Required in Cases of Increases in Liver Biochemistry and Evaluation of Hy's Law)	The processes for the evaluation of Hy's Law were updated to reflect changes in the sponsor's standard operating procedures.

ADA = anti-drug antibodies; AE = adverse event; PRO = patient reported outcome.

9.2 Protocol Amendment 4, 31Aug2018

The changes to text summarised below have been incorporated in the body of Protocol Amendment 4.

Table 10 Summary of Revisions to the Protocol

Section of the Protocol Affected	Reason for Amendment
Protocol Synopsis (Objectives and Endpoints) and Section 2.3 (Exploratory Objectives and Endpoints)	Correction of typographic error: CO_2 consumption to production
Section 4.2.2 (Randomized Treatment Period, Table 6 Treatment Period Study Procedures)	Clarification: Change to time of DLW urine collection from 1 hour to 3 hours in footnote f Correction of typographic error: Removal of instruction relating to investigational product as not relevant at either time-point; footnote j.

9.3 Protocol Amendment 3, 20Aug2018

The changes to text summarised below have been incorporated in the body of Protocol Amendment 3.

Table 11 Summary of Revisions to the Protocol

Section of the Protocol Affected	Reason for Amendment
Protocol Synopsis (Objectives and Endpoints) and Section 2.2 (Secondary Objectives and Endpoints, Table 2, Secondary Objectives and Endpoints)	Typographic error: Corrected DLW assessment in text from Day 16 to 17.

Table 11 Summary of Revisions to the Protocol

Section of the Protocol Affected	Reason for Amendment
Section 1.6 (Benefit-risk and Ethical Assessment)	Typographic error: Removed reference to IB version to ensure this remains the most up to date version for the duration of the study in case of future IB updates.
Section 4.2.2 (Randomized Treatment Period, Table 6 Treatment Period Study Procedures)	• Typographic error: Inserted footnote "b" in table next to the abbreviated physical examination on Day 58 and added text to footnote "b" to state that the physical examination can occur at any time on Day 58 or 59. Table footnotes beginning with "b" reordered). • Typographic error: Corrected DLW assessment in table and footnote "f" from Day 16 to 17. • Typographic error: Activity monitor charging corrected in table from Day 17 to 16. • Typographical error: Corrected day of double-blind investigational product administration from Day 59 to 58 in table and footnote "v." • Typographical error: Corrected investigational product dispensing visit from Visit 7 to 8 in table. • Accidental omission: Added definition for "VAS = Visual Analog Scale" to list of abbreviations used in the table. • Typographical error: Corrected text in footnote "a" to include fasting on Day 59 and corrected the timing for subjects to be fasted for an additional 4 hours to Day 17 with cross-reference to footnote "s." • Accidental omission: Added C peptide to the metabolism panel in table footnote "j." • Clarification: Deleted portion of text in table footnote "m" to simplify/provide better consistency as details already provided in referenced section. • Clarification: Updated exercise times whilst inside the whole room calorimeter from "1000 ± 15 min and 1200 ± 15 min, 1400 ± 15 min and 1600 ± 15 min," to "1130 ± 15 min and 1430 ± 15 min, 1730 ± 15 min and 2030 ± 15 min," respectively, in table footnote "o." • Clarification: Amended table footnote "p" to remove sentence around pre- and post meal and to clarify that it is the VAS questionnaire that is to be repeated during the day.
Section 4.3.1 (Screening/Enrolment, Treatment, and Follow-up)	• Clarification: Added Day 15/16 to text to clarify timing of collection of urine for protein estimation. • Typographic error: Changed DLW assessment in text from Day 16 to 17.

Table 11 Summary of Revisions to the Protocol

Section of the Protocol Affected	Reason for Amendment
[redacted]	[redacted]
Section 4.6.2 (Methods to Ensure Blinding)	Clarification: Additional paragraph added to describe measures that will be taken to ensure the blind.

DLW = doubly labelled water; IB = Investigators Brochure; MMTT = mixed-meal tolerance test; VAS = Visual Analog Scale.

9.4 Protocol Amendment 2, 17Jul2018

The changes to text summarised below have been incorporated in the body of Protocol Amendment 2.

Table 12 Summary of Revisions to the Protocol

Section of the Protocol Affected	Reason for Amendment
Section 3.1.4.3 (Hyperglycaemia)	All changes were made at the request of the MHRA.
Section 4.1.3 (Exclusion Criteria)	
Section 4.2.1 (Enrolment/Screening Period) Table 5 (Schedule of Screening Procedures)	
Section 4.2.2 (Randomized Treatment Period) Table 6 Treatment Period Study Procedures	
Section 4.2.3 (Follow-up Period) Table 7 (Schedule of Follow-up Procedures)	
Section 4.2.4 (Early Discontinuation Visit or Unscheduled Study Visit)	
Section 4.3.5 (Clinical Laboratory Tests)	
Section 5.3.1 (Time Period for Collection of Adverse Events)	

MHRA = Medicines and Healthcare products Regulatory Agency.

9.5 Protocol Amendment 1, 23May2018

The changes to text summarised below have been incorporated in the body of Protocol Amendment 1.

Table 13 Summary of Revisions to the Protocol

Section of the Protocol Affected	Reason for Amendment
Section 3.2.2 (Rationale for Study Population), Section 4.1.2 (Inclusion Criteria), and Section 4.2.1 (Enrolment/Screening Period) Table 5 (Schedule of Screening Procedures)	Inclusion criterion 5 and additional text sections were revised to widen enrolment by allowing inclusion of subjects using SGLT2i.
Section 4.1.3 (Exclusion Criteria)	Text was added to exclusion criterion 13 to allow the study site flexibility in employing an alternative estimation of eGFR.
Section 4.1.4 (Subject Enrolment and Randomisation), Section 4.6.1 (Methods for Assigning Treatment Groups), Section 4.6.2 (Methods to Ensure Blinding), and Section 4.6.3.1 (Unblinding in the Event of a Medical Emergency)	Text describing manual randomisation procedures was amended to use an IXRS, as upon further consideration after authoring the original protocol, it was decided that it would be complex and time consuming for the study site to employ manual randomisation. Using an IXRS will help avoid manual randomisation errors.
Section 4.2.2 (Randomised Treatment Period) Table 6 (Treatment Period Study Procedures)	Added row for double-blind investigational product administration to clarify when investigational product will be administered. Two additional time points for in clinic administration of investigational product were added for Visit 4 as these were inadvertently not included in the original protocol. Footnote j was amended to correct a typographic error. Text was added to footnote u to clarify investigational product administration procedures. The letter w linking to footnote v was changed to v to correct a typographic error.
Section 4.2.2 (Randomized Treatment Period) Table 6 (Treatment Period Study Procedures) and Section 4.3.2.9 (Intravenous Glucose Tolerance Test)	Text was amended (including footnote g in Table 6) to correct and clarify the timing of samples for the IVGTT.
Section 4.2.3 (Follow-up Period) Table 7 (Schedule of Follow-up Procedures)	Revised footnotes to make consistent with Table 6.
Section 4.2.4 (Early Discontinuation Visit or Unscheduled Study Visit)	New section allowing for and describing procedures for early discontinuation or unscheduled study visits was added upon further consideration after authoring the original protocol, as some subjects could potentially withdraw from the study due to intensive study procedures or require additional visits.
Section 4.3.1 (Screening/Enrolment, Treatment, and Follow-up)	Text describing the administration of investigational product procedures was updated in accordance with the amendment described above for Table 6.
Section 4.3.10 (Estimate of Volume of Blood to Be Collected)	Blood volume estimations were updated in accordance with amendment in the IVGTT schedule described above for Table 6 and Section 4.3.2.9.

Table 13 Summary of Revisions to the Protocol

Section of the Protocol Affected	Reason for Amendment
Section 4.6.3.1 (Unblinding in the Event of a Medical Emergency)	Text describing discontinuation of investigational product in the event of unblinding of investigational product allocation was removed as this procedure was deemed unnecessary for this study.

eGFR = estimated glomerular filtration rate; IVGTT = intravenous glucose tolerance test; IXRS = interactive voice/web response system; SGLT2i = sodium-glucose co-transporter inhibitor(s).

10 APPENDICES

10.1 Appendix 1 – Signatures

Sponsor Signature(s)

An Exploratory Phase 2, Randomised, Double-blind, Placebo-controlled Study to Evaluate the Effect of MEDI0382 on Energy Balance in Overweight and Obese Subjects with Type 2 Diabetes Mellitus

I agree to the terms of this protocol and protocol amendment(s).

Signature and date: Electronic signature attached

Boaz Hirshberg, MD

Clinical Therapy Area Head

One MedImmune Way, Gaithersburg MD, 20878, USA

Telephone number: 1-301-398-0645

10.2 Appendix 2 - Contraception Guidance

For females of childbearing potential:

- Females of childbearing potential are defined as those who are not surgically sterile (ie, surgical sterilisation includes bilateral tubal ligation, bilateral oophorectomy, or complete hysterectomy) or those who are not postmenopausal (defined as at least 1 year since last menses and/or having an elevated follicle-stimulating hormone level in the postmenopausal range in previous laboratory test results).
- A highly effective method of contraception is defined as one that results in a low failure rate (ie, less than 1% per year) when used consistently and correctly. The acceptable methods of contraception are described in Table 14.
- 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 14 Highly Effective Methods of Contraception

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

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 an adverse event (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 oedema). Hospital admissions and/or surgical operations planned before or during a study are not considered AEs if the illness or disease existed before the subject was enrolled in the study, provided that it did not deteriorate in an unexpected way during the study.

Important Medical Event or Medical Intervention

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

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

Examples of such events are:

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

Assessment of Severity

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

Grade 1	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 or with physical or mental disabilities.
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, dyspnoea, wheeze-bronchospasm, stridor, reduced peak expiratory flow (PEF), hypoxemia)
   (b) Reduced blood pressure (BP) or associated symptoms of end-organ dysfunction (eg, hypotonia [collapse], syncope, incontinence)
2 Two or more of the following that occur rapidly after exposure to a likely allergen for that patient (minutes to several hours):
   (a) Involvement of the skin-mucosal tissue (eg, generalized hives, itch-flush, swollen lips-tongue-uvula)
   (b) Respiratory compromise (eg, dyspnoea, wheeze-bronchospasm, stridor, reduced 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 in order to identify and appropriately report potential Hy's law cases and Hy's Law cases. It is not intended to be a comprehensive guide to the management of elevated liver biochemistries.

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

All sources of laboratory data are appropriate for the determination of potential Hy's Law and Hy's Law events; this includes samples taken at scheduled study visits and other visits including all local laboratory evaluations even if collected outside of the study visits.

The investigator will also review AE data (for example, for AEs that may indicate elevations in liver biochemistry) for possible potential Hy's Law events.

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

10.5.2.1 Potential Hy's Law

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

10.5.2.2 Hy's Law

Aspartate transaminase (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.

10.5.3 Identification of Potential Hy's Law Cases

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

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

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

- Notify the sponsor study representative
- Determine whether the subject meets potential Hy's Law criteria (Section 10.5.2) by reviewing laboratory reports from all previous visits
- Promptly enter the laboratory data into the laboratory eCRF

10.5.4 Follow-up

10.5.4.1 Potential Hy's Law Criteria Are 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.

10.5.4.2 Potential Hy's Law Criteria Are Met

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

- Determine whether potential Hy's Law criteria were met at any study visit prior to starting study treatment (Section 10.5.2.1)
- Notify the sponsor study representative who will then inform the study team
- Within 1 day of potential Hy's Law criteria being met, the investigator will report the case as an SAE of Potential Hy's Law; serious criteria 'Important medical event' and causality assessment 'yes/related' according to clinical study protocol process for SAE reporting

The medical monitor contacts the investigator, to provide guidance, discuss and agree on an approach for the study subjects' follow-up (including any further laboratory testing) 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. Complete follow-up SAE Form as required.
- Investigate the etiology of the event and perform diagnostic investigations as discussed with the medical monitor.
- Complete the relevant eCRF Modules as information becomes available

10.5.5 Review and Assessment of Potential Hy's Law Cases

The instructions in this section should be followed for all cases where potential Hy's Law criteria are met.

As soon as possible after the biochemistry abnormality was initially detected, the medical monitor will contact the investigator in order to review available data and agree on whether there is an alternative explanation for meeting potential Hy's Law criteria other than DILI caused by the investigational product, to ensure timely analysis and reporting to health authorities per local requirements from the date potential Hy's Law criteria were met. The medical monitor and Global Safety Physician will also be involved in this review together with other subject matter experts as appropriate.

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

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

- If the alternative explanation is **not** an AE, record the alternative explanation on the appropriate eCRF
- If the alternative explanation is an AE/SAE, update the previously submitted potential Hy's Law SAE and AE CRFs accordingly with the new information (reassessing event term; causality and seriousness criteria) following the sponsor's standard processes

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

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

- Provide any further update to the previously submitted SAE of Potential Hy's Law (report term now 'Hy's Law case'), ensuring causality assessment is related to the investigational product and seriousness criteria are medically important, according to the clinical study protocol process for SAE reporting
- Continue follow-up and review according to agreed plan. Once the necessary supplementary information is obtained, repeat the review and assessment to determine whether Hy's Law criteria are still met. Update the previously submitted potential Hy's Law SAE report following clinical study protocol process for SAE reporting, according to the outcome of the review and amend the reported term if an alternative explanation for the liver biochemistry elevations is determined

10.5.6 Laboratory Tests

The list below represents the standard, comprehensive list of follow-up tests which are recommended but not mandatory when using a central laboratory. For studies using a local laboratory, the list may be modified based on clinical judgement. If required, for additional assistance on which tests could be used to evaluate other potential causes of liver dysfunction, consult with the Hepatic Safety Knowledge Group. Any test results need to be recorded.

Hy's Law Lab Kit for Central Laboratories

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

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

REFERENCES

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

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

10.6 Appendix 6 - Biological Samples

10.6.1 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 and muscle biopsy 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 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 and other residual samples will be stored for up to 2 years after marketing approval.

10.6.2 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.

10.6.3 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.

10.7 Appendix 7 – Genetic Research

Rationale and Objectives

Genetic variation may impact a subject's response to therapy, susceptibility to, and severity and progression of disease. Variable response to therapy may be due to genetic determinants that impact drug absorption, distribution, metabolism, and excretion; mechanism of action of

the drug; disease aetiology; and/or molecular subtype of the disease being treated. Therefore, where local regulations and IRB/IEC allow, blood samples will be collected for DNA analysis from consenting subjects.

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

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

Genetic research may consist of the analysis of the structure of the subject´s DNA, i.e. the entire genome.

The results of genetic analyses may be reported in the clinical study report (CSR) or in a separate study summary.

The sponsor will store the DNA samples in a secure storage space with adequate measures to protect confidentiality.

The samples will be retained while research on study treatment or study treatments of this class or indication continues but no longer than 15 years or other period as per local requirements

Genetic Research Plan and Procedures

Selection of Genetic Research Population and Study Selection Record

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

Inclusion Criteria

For inclusion in this genetic research, subjects must fulfil all of the inclusion criteria described in the main body of the Clinical Study Protocol **and** provide informed consent for the genetic sampling and analyses.

Exclusion Criteria

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

- Previous allogeneic bone marrow transplant
- Non-leukocyte depleted whole blood transfusion in 120 days of genetic sample collection

Discontinuation of Subjects from this Genetic Research

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

Withdrawal of consent for genetic research: Subjects may withdraw from this genetic research at any time, independent of any decision concerning participation in other aspects of the main study. Voluntary discontinuation will not prejudice further treatment. Procedures for discontinuation are outlined in Section 4.1.6 of the main Protocol.

Collection of Samples for Genetic Research

The blood samples for genetic research will be obtained from the subjects at Visit 2 provided that the subject has given explicit consent for this. Although deoxyribonucleic acid (DNA) variants are a stable parameter, early sample collection is preferred to avoid introducing bias through excluding subjects who may withdraw due to an AE, such subjects would be important to include in any genetic analysis. If for any reason the sample is not drawn at Visit 2, it may be taken at any visit until the last study visit. Only 1 sample should be collected per subject for genetic research during the study. Samples will be collected, labelled, stored and shipped as detailed in the Laboratory Manual.

Coding and Storage of DNA Samples

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

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

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

Ethical and Regulatory Requirements

The principles for ethical and regulatory requirements for the study, including this genetics research component, are outlined in Section 4.1.6 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.

In addition, 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 clinical study report 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.

10.8 Appendix 8 - Patient-Reported Outcome Questionnaires

10.8.1 Dutch Eating Questionnaire (DEBQ)

Example of Dutch Eating Questionnaire (DEBQ)

Volunteer Name: _____ **Date:** _____

Volunteer No. _____

Please place an **(✓)** in the box which applies best to each of the numbered statements. All of the results will be *strictly* confidential. Most of the questions directly relate to food or eating, although other types of questions have been included. Please answer each question carefully. Thank you.

1. If you have put on weight, do you eat less than you usually do?

❑ Never ❑ Seldom ❑ Sometimes ❑ Often ❑ Very Often ❑ Not Relevant

2. Do you try to eat less at mealtimes than you would like to eat?

❑ Never ❑ Seldom ❑ Sometimes ❑ Often ❑ Very Often

3. How often do you refuse food or drink offered because you are concerned about your weight?

❑ Never ❑ Seldom ❑ Sometimes ❑ Often ❑ Very Often

4. Do you watch exactly what you eat?

❑ Never ❑ Seldom ❑ Sometimes ❑ Often ❑ Very Often

5. Do you deliberately eat foods that are slimming?

❑ Never ❑ Seldom ❑ Sometimes ❑ Often ❑ Very Often

6. When you have eaten too much, do you eat less than usual the following days?

❑ Never ❑ Seldom ❑ Sometimes ❑ Often ❑ Very Often ❑ Not Relevant

7. Do you deliberately eat less in order not to become heavier?

❑ Never ❑ Seldom ❑ Sometimes ❑ Often ❑ Very Often

8. How often do you try not to eat between meals because you are watching your weight?

❑ Never ❑ Seldom ❑ Sometimes ❑ Often ❑ Very Often

9. How often in the evening do you try not to eat because you are watching your weight?

❑ Never ❑ Seldom ❑ Sometimes ❑ Often ❑ Very Often

10. Do you take into account your weight with what you eat?

❑ Never ❑ Seldom ❑ Sometimes ❑ Often ❑ Very Often

11. Do you have the desire to eat when you are irritated?

❑ Never ❑ Seldom ❑ Sometimes ❑ Often ❑ Very Often ❑ Not Relevant

12. Do you have a desire to eat when you have nothing to do?

❑ Never ❑ Seldom ❑ Sometimes ❑ Often ❑ Very Often ❑ Not Relevant

13. Do you have a desire to eat when you are depressed or discouraged?

❑ Never ❑ Seldom ❑ Sometimes ❑ Often ❑ Very Often ❑ Not Relevant

14. Do you have a desire to eat when you are feeling lonely?

❑ Never ❑ Seldom ❑ Sometimes ❑ Often ❑ Very Often ❑ Not Relevant

15. Do you have a desire to eat when somebody lets you down?

❑ Never ❑ Seldom ❑ Sometimes ❑ Often ❑ Very Often ❑ Not Relevant

16. Do you have a desire to eat when you are cross?

❑ Never ❑ Seldom ❑ Sometimes ❑ Often ❑ Very Often ❑ Not Relevant

17. Do you have a desire to eat when you are approaching something unpleasant to happen?

❑ Never ❑ Seldom ❑ Sometimes ❑ Often ❑ Very Often

18. Do you get the desire to eat when you are anxious, worried or tense?

❑ Never ❑ Seldom ❑ Sometimes ❑ Often ❑ Very Often

19. Do you have a desire to eat when things are going against you or when things have gone wrong?

❑ Never ❑ Seldom ❑ Sometimes ❑ Often ❑ Very Often

20. Do you have a desire to eat when you are frightened?

❑ Never ❑ Seldom ❑ Sometimes ❑ Often ❑ Very Often ❑ Not Relevant

21. Do you have a desire to eat when you are disappointed?

❑ Never ❑ Seldom ❑ Sometimes ❑ Often ❑ Very Often ❑ Not Relevant

22. Do you have a desire to eat when you are bore or restless?

❑ Never ❑ Seldom ❑ Sometimes ❑ Often ❑ Very Often ❑ Not Relevant

23. Do you have a desire to eat when you are emotionally upset?

❑ Never ❑ Seldom ❑ Sometimes ❑ Often ❑ Very Often ❑ Not Relevant

24. If food tastes good to you, do you eat more than usual?

❑ Never ❑ Seldom ❑ Sometimes ❑ Often ❑ Very Often

25. If food smells and looks good do you eat more than usual?

❑ Never ❑ Seldom ❑ Sometimes ❑ Often ❑ Very Often

26. If you see or smell something delicious, do you have the desire to eat it?

❑ Never ❑ Seldom ❑ Sometimes ❑ Often ❑ Very Often

27. If you have something delicious to eat, do you eat it straight away?

❑ Never ❑ Seldom ❑ Sometimes ❑ Often ❑ Very Often

28. If you walk past the baker do you have the desire to buy something delicious?

❑ Never ❑ Seldom ❑ Sometimes ❑ Often ❑ Very Often

29. If you walk past a snack bar or a café, do you have the desire to buy something delicious?

❑ Never ❑ Seldom ❑ Sometimes ❑ Often ❑ Very Often

30. If you see others eating, do you also have the desire to eat?

❑ Never ❑ Seldom ❑ Sometimes ❑ Often ❑ Very Often

31. Can you resist eating delicious foods?

❑ Never ❑ Seldom ❑ Sometimes ❑ Often ❑ Very Often

32. Do you eat more than usual, when you see others eating?

❑ Never ❑ Seldom ❑ Sometimes ❑ Often ❑ Very Often

33. When preparing a meal are you inclined to eat something?

❑ Never ❑ Seldom ❑ Sometimes ❑ Often ❑ Very Often

10.8.2 Appendix 8 - Visual Analogue Scale

Example of Visual Analogue Scale

HOW HUNGRY DO YOU FEEL RIGHT NOW?

NOT AT ALL EXTREMELY

HOW SICK DO YOU FEEL RIGHT NOW?

NOT AT ALL EXTREMELY

HOW PLEASANT WOULD IT BE TO EAT RIGHT NOW?

NOT AT ALL EXTREMELY

HOW MUCH DO YOU THINK YOU COULD EAT RIGHT NOW?

NOTHING A LARGE AMOUNT

10.9 References

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

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

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