

**A Phase 2, Randomised, Double-Blind,
Placebo-Controlled Study to Evaluate the Efficacy, Safety,
Tolerability, and Pharmacokinetics of Different Doses of
MEDI0382 in Overweight and Obese Subjects with Type 2
Diabetes Mellitus**

Sponsor Protocol Number: D5670C00011

Application Number: EudraCT number 2017-002025-38

Investigational Product: MEDI0382

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

Medical Monitor:

[REDACTED]
[REDACTED] MedImmune
[REDACTED]

Contract Research Organization: Covance Clinical and Periapproval Services GmbH,
Carl-Wery-Straße 42, 81739 Munich, Germany

Protocol History, Date: Original Protocol, 30May2017
Protocol Amendment 1, 25Jul2017
Protocol Amendment 2, 17Oct2017

This document contains trade secrets and commercial information that is privileged or confidential and may not be disclosed without prior authorisation from MedImmune.

PROTOCOL SYNOPSIS

TITLE	
A Phase 2, Randomised, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy, Safety, Tolerability, and Pharmacokinetics of Different Doses of MEDI0382 in Overweight and Obese Subjects with Type 2 Diabetes Mellitus	
HYPOTHESES	
Primary Hypothesis:	
Administration of MEDI0382 once daily titrated up to a dose level of 300 µg will result in superior blood glucose control and weight loss versus placebo after 49 days of treatment in overweight and obese subjects with type 2 diabetes mellitus (T2DM)	
Secondary Hypotheses:	
<ul style="list-style-type: none"> Administration of MEDI0382 once daily titrated up to a dose level of 300 µg across 49 days will be safe and well tolerated in overweight and obese subjects with T2DM Administration of MEDI0382 once daily titrated up to a dose level of 300 µg from 50 µg will have a predictable pharmacokinetic (PK) profile Administration of MEDI0382 once daily at a dose level of 50 µg will result in superior blood glucose control versus placebo after 7 days of treatment in overweight and obese subjects with T2DM 	
OBJECTIVES AND ENDPOINTS	
Objectives	Endpoints
Primary	
To assess the effects of MEDI0382 titrated up to a dose level of 300 µg on glucose control and body weight versus placebo after 49 days of treatment (Cohort 1 only)	<ul style="list-style-type: none"> Percentage change in glucose area under the curve (AUC) as measured by a standardised mixed-meal tolerance test (MMTT) from baseline (Day -1) to the end of 49 days of treatment Percentage change in body weight from baseline (Day 1) to the end of 49 days of treatment
Secondary	
To assess the effects of MEDI0382 titrated up to a dose level of 300 µg on additional measures of glucose control and body weight versus placebo after 49 days of treatment (Cohort 1 only)	<ul style="list-style-type: none"> Change in glycated haemoglobin (HbA1c) from baseline (Day -1) to the end of 49 days of treatment Change in fasting plasma glucose (Day -1) from baseline to the end of 49 days of treatment Change in body weight (kg) from baseline (Day 1) to the end of 49 days of treatment Proportion of subjects achieving > 5% body weight loss from baseline (Day 1) after 49 days of treatment
To characterise the safety profile and tolerability of MEDI0382 titrated up to a dose level of 300 µg during dosing and follow-up (Cohorts 1 and 2)	<ul style="list-style-type: none"> Measures of safety and tolerability (24-hour heart rate and blood pressure, other vital signs, electrocardiogram [ECG], laboratory test results, adverse events [AEs])

<p>To characterise the PK profile and immunogenicity of 50 and 300 µg of MEDI0382 (Cohorts 1 and 2)</p>	<ul style="list-style-type: none"> • PK endpoints for 50 µg MEDI0382 after 1, 7, and 14 days of treatment and 300 µg MEDI0382 after 1 and 28 days of treatment; AUC over a dosing duration, maximum observed concentration (C_{max}), time to C_{max} (T_{max}), terminal half-life ($T_{1/2}$), trough plasma concentration (C_{trough}), and accumulation ratio ($C_{min} [R_0]$) • Development of anti-drug antibodies (ADA) and titre (if confirmed positive)
<p>To characterise the effect of 50 µg of MEDI0382 on glucose lowering versus placebo after 7 days (Cohorts 1 and 2)</p>	<ul style="list-style-type: none"> • Percentage change in glucose AUC as measured by a standardised MMTT from baseline (Day -1) to the end of 7 days of treatment
<p>Exploratory</p>	
<p>[REDACTED]</p>	<p>[REDACTED]</p>
<p>To assess gastrointestinal (GI) tolerability across different titration schedules (Cohorts 1 and 2)</p>	<ul style="list-style-type: none"> • Percentage of subjects with GI AEs at each dose level • Percentage of subjects with nausea and vomiting from baseline (Day 1) over 7 days of treatment
<p>To assess the effect of MEDI0382 on glucose lowering during different meals and times of the day as measured by continuous glucose monitoring (CGM) (Cohort 1 only)</p>	<ul style="list-style-type: none"> • Change in glucose AUC_{24h} from baseline (Day -1) to the end of dosing at each dose level (Days 7, 14, 21, 28, and 49) • Change in coefficient of variation (ratio of standard deviation: mean) over 24 hours from baseline (Day -1) to the end of dosing at each dose level (Days 7, 14, 21, 28, and 49) • Change in coefficient of variation (ratio of standard deviation: mean) over 7 days at each dose level (Days 1 to 7, Days 8 to 14, Days 15 to 21, and Days 22 to 28) • Change in percentage of time in hyperglycaemia (defined as > 7.8 mmol/l (> 140 mg/dl) and hypoglycaemia (defined as < 3.0 mmol/l (< 54 mg/dl) from baseline (Day-1) over 24 hours to the end of dosing at each dose level (Days 7, 14, 21, 28, and 49) • Change in percentage of time in hyperglycaemia; (defined as > 7.8 mmol/l or (> 140 mg/dl) and hypoglycaemia (defined as < 3.0 mmol/l or < 54 mg/dl) over 7 days at each dose level (Days 1 to 7, Days 8 to 14, Days 15 to 21, and Days 22 to 28) • Change in glucose AUC_{120min} during a standardised meal in the morning from baseline (Day -1) and at the end of 49 days of treatment • Change in glucose AUC_{120min} during a standardised meal in the evening from baseline (Day -1) and at the end of 49 days of treatment

<p>To characterise the effect of MEDI0382 on glucose lowering and weight versus placebo after 7, 14, and 49 days (Cohort 2 only)</p>	<ul style="list-style-type: none"> • Percentage change in glucose AUC as measured by a standardised MMTT from baseline (Day -1) after 14 and 49 days • Change in fasting plasma glucose from baseline (Day -1) to the end of 7, 14, and 49 days of treatment • Percentage and absolute change in body weight from baseline (Day 1) to the end of 7, 14, and 49 days of treatment • Change in HbA1c from baseline (Day -1 to the end of 49 days of treatment
<p>[REDACTED]</p>	<p>[REDACTED]</p>
<p>To assess the effect of MEDI0382 on ketone bodies, amino acids, and free fatty acid (FFA) levels over 49 days of treatment (Cohort 1 only)</p>	<ul style="list-style-type: none"> • Change in plasma beta-hydroxybutyrate from baseline (Day -1) while fasted and at 4 hours postdose after 49 days • Change in FFA levels from baseline (Day -1) after 49 days of treatment • Change in amino acid levels from baseline (Day -1) after 49 days of treatment
<p>To assess the effect of MEDI0382 on uric acid [REDACTED]</p>	<ul style="list-style-type: none"> • Change in uric acid levels from baseline (Day -1) after 49 days of treatment • [REDACTED]

STUDY DESIGN

This is a randomised, double-blind, placebo-controlled study to evaluate the efficacy, safety, tolerability, and PK profile of 50 and 300 µg of MEDI0382 in overweight and obese subjects with T2DM. It is planned to randomise up to 63 subjects across multiple study sites.

The study is divided into 2 cohorts that will be recruited in parallel; for both cohorts, subjects will be consented, screened for suitability, and randomised within 60 days if eligible. Cohort 1 will evaluate the efficacy, safety, tolerability, and PK of MEDI0382 when up-titrated in weekly intervals from 50 to 300 µg and administered over 49 days. Cohort 2 will explore an alternative 2-week titration schedule, and will provide additional information on the PK profile and glucose-lowering efficacy of 50 µg MEDI0382, [REDACTED]

Cohort 1

Subjects will undergo blood tests for safety between Day -7 and Day -3 if the screening visit was more than 7 days before dosing begins on Day 1. On Day -2, subjects will be admitted to the clinical unit for 2 nights and will undergo further initial safety assessments and training in subcutaneous (SC) injection administration. At this time an ambulatory blood pressure monitoring (ABPM) device will be fitted on Day -2 and worn for 24 hours; simultaneously a CGM sensor will be fitted on the contralateral arm and the subject will be given training for CGM use, and subjects will be expected to wear CGM sensors continuously until the end of dosing. On Day -1, eligibility criteria will be verified and subjects will undergo 2 MMTT assessments (MMTT type A; with blood sampling in the morning and MMTT type C; without blood sampling in the evening). Subjects can be randomised at any time after confirming eligibility from Day -1 to Day 1 (predose) to receive either MEDI0382 or placebo. On Day 1, dosing will commence following predose safety measures including vital signs, blood tests for safety, an ECG, and measurement of weight. Since the dose of 50 µg will require a dilution by site staff prior to administration, subjects will have the option to remain as an inpatient or alternatively attend the clinical unit every day for dosing during the first week, and during this time will undergo supervision to self-administer the investigational product. On Day 7, safety

assessments will be performed and the MMTT will be repeated, and where relevant, subjects will be discharged home.

Subjects will then return to the clinical unit at weekly intervals until a maintenance dose of 300 µg is achieved. On Day 22, subjects will be readmitted to the clinical unit for an overnight stay to undergo PK sampling and ABPM for 24 hours. Subjects will be discharged on Day 23 and will thereafter attend for weekly visits for safety assessments and ABPM device fitting. At the end of dosing, subjects will be readmitted to the clinical unit for a final overnight stay and MMTTs type A and C will be repeated alongside safety assessments, ABPM, weight measurement, and blood tests. A 7- to 14 day post-last dose follow-up visit and final follow-up visit approximately 28 days after the last dose will be performed for safety assessments and this will include a final ABPM recording.

Cohort 2

Study procedures for Cohort 2 will be similar to Cohort 1 at baseline, although subjects will not undergo ABPM assessments, nor wear a CGM monitor in this cohort. [REDACTED]

[REDACTED] On Day -2 subjects will undergo baseline safety assessments, and undergo their first MMTT (MMTT Type A) on Day -1. Dosing will commence on Day 1. Since the dose of 50 µg will require a dilution by site staff prior to administration, subjects will be given the option to either remain as an inpatient, or attend the clinical unit every day during the first 2 weeks of dosing, but will be required to stay overnight for a total of 5 nights across this period (on Days -2, -1, 1, 7, and 14); thereafter, subjects will attend the unit for dose up-titration. During this time subjects will self-administer investigational product under supervision. [REDACTED] and MMTTs will be repeated at different points across the study as described in the schedule. At the end of dosing on Day 49, subjects will be admitted for a final overnight stay; a repeat MMTT will be performed, alongside measurement of weight, [REDACTED] and safety assessments. A 7-to 14-day post-last dose follow-up visit and final follow-up visit approximately 28 days after the last dose will be performed for safety assessments [REDACTED]

Up to 63 subjects are planned to be enrolled across the study, 44 to receive MEDI0382 and 19 to receive placebo.

TARGET SUBJECT POPULATION

Male or female subjects aged ≥ 18 years of age, with body mass index ≥ 27 and ≤ 40 kg/m², a diagnosis of T2DM, and an HbA1c of 6.5% to 8.5%. Females of childbearing potential must not be pregnant and lactating females will be excluded. Females of childbearing potential should be using appropriate contraception.

INVESTIGATIONAL PRODUCT, DOSAGE, AND MODE OF ADMINISTRATION

Cohort 1

MEDI0382 or matched placebo once daily in the morning via SC injection

MEDI0382 50 µg for 7 days, followed by 100 µg for 7 days, followed by 200 µg for 7 days, and 300 µg SC once daily for 28 days (n = 26)

Matched placebo SC once daily for 49 days (n = 13)

Cohort 2

MEDI0382 or matched placebo once daily in the morning via SC injection

MEDI0382 50 µg for 14 days, followed by 100 µg for 14 days, followed by 200 µg for 14 days, and 300 µg SC once daily for 7 days (n = 18)

Matched placebo SC once daily for 49 days (n = 6)

STATISTICAL ANALYSIS PLAN

Sample size:

For Cohort 1, 26 subjects in the MEDI0382 arm and 13 subjects in the placebo arm will provide 97% power to detect a 28% glucose AUC change-from-baseline difference between MEDI0382 300 µg and placebo, assuming a standard deviation of 20%. It will also provide 85% power to detect a 2.3% difference of percentage change of body weight from baseline versus placebo, assuming a standard deviation of 2.2%.

Under the conservative assumption that the two endpoints are independent, the overall power that hypotheses for both endpoints are met is over 80%. From the 2 cohorts, the combined 44 subjects in the MEDI0382 arms and 19 subjects in the placebo arms can also provide 80% power to detect a 12% glucose AUC change-from-baseline difference between MEDI0382 50 µg and placebo at Day 7.

Statistical analyses:

The efficacy analysis will be based on the Intent-to-treat population. The coprimary efficacy endpoints of percentage glucose AUC change and percentage weight change from baseline to 49 days will be compared between the MEDI0382 and placebo arms using an analysis of covariance (ANCOVA) model, adjusting for treatment and measurement at baseline. A similar ANCOVA model will also be used for other continuous endpoints. For the other proportion-related endpoints, a logistic regression model will be used with fixed effects of treatment and baseline measurement.

Safety analyses:

The safety analyses will be based on the As-treated population. Safety data, such as vital signs, clinical laboratory data, ECG, and physical examination findings will be descriptively summarised at each time point by treatment period.



Pharmacokinetic analysis and immunogenicity:


Pharmacokinetic parameters such as MEDI0382 C_{max} and area under the concentration-time curve from 0 to infinity ($AUC_{(0-inf)}$) will be evaluated from plasma concentration-time data for MEDI0382 at 50 and 300 µg. Descriptive statistics including mean, standard deviations, median, minimum, and maximum will be generated for all PK parameters for MEDI0382 at each dose level separately. Samples confirmed positive for ADA will be tested and analysed for antibody titre and reported. ADA incidence rate and titre will be tabulated for each treatment.

Interim analysis: An interim analysis of PK data only will be performed following last subject last dose.

TABLE OF CONTENTS

PROTOCOL SYNOPSIS	2
LIST OF ABBREVIATIONS	12
1 INTRODUCTION	14
1.1 Disease Background.....	14
1.2 MEDI0382 Background	14
1.3 Summary of Nonclinical Experience	14
1.4 Summary of Clinical Experience	15
1.5 Rationale for Conducting the Study.....	15
1.6 Benefit-risk and Ethical Assessment.....	16
1.7 Research Hypotheses	16
1.7.1 Primary Hypothesis.....	16
1.7.2 Secondary Hypotheses	16
2 OBJECTIVES AND ENDPOINTS	17
2.1 Primary Objective and Associated Endpoints	17
2.2 Secondary Objectives and Associated Endpoints.....	17
2.3 Exploratory Objectives.....	18
3 STUDY DESIGN.....	19
3.1 Description of the Study.....	19
3.1.1 Overview	19
3.1.2 Treatment Regimen.....	23
3.1.3 Dose Escalation	23
3.1.4 Management of Study Medication Related Toxicities.....	23
3.1.4.1 Tolerability	23
3.1.4.2 Hypoglycaemia	23
3.1.4.3 Hyperglycaemia	24
3.2 Study Design and Dose Rationale	24
3.2.1 Dose Rationale.....	24
3.2.2 Rationale for Study Population	26
3.2.2.1 Recruitment of Subjects with T2DM and a Body Mass Index 27 to 40 kg/m ²	26
3.2.2.2 Selection of Subjects with Stable HbA1c in the Range of 6.5% to 8.5% (Inclusive) on Metformin	26
3.2.3 Rationale for Endpoints	27
3.2.3.1 Primary Endpoints.....	27
3.2.3.2 Secondary Endpoints.....	27
3.2.3.3 Exploratory Endpoints.....	28
4 MATERIALS AND METHODS.....	30

4.1	Subjects.....	30
4.1.1	Number of Subjects	30
4.1.2	Inclusion Criteria	30
4.1.3	Exclusion Criteria	30
4.1.4	Subject Enrollment and Randomisation.....	32
4.1.5	Withdrawal from the Study	33
4.1.6	Discontinuation of Investigational Product.....	33
4.1.7	Replacement of Subjects	34
4.1.8	Withdrawal of Informed Consent for Data and Biological Samples	34
4.2	Schedule of Study Procedures	35
4.2.1	Enrollment/Screening Period	35
4.2.2	Randomised Treatment Period	37
4.2.3	Follow-up Period	49
4.2.3.1	Early Discontinuation Visit or Unscheduled Study Visit... ..	50
4.3	Description of Study Procedures	50
4.3.1	Efficacy.....	50
4.3.1.1	Mixed-meal Tolerance Tests	50
4.3.1.2	Weight.....	52
4.3.2	Safety Assessments.....	52
4.3.2.1	Medical History and Physical Examination	52
4.3.2.2	Assessment of the Injection Site.....	53
4.3.2.3	Electrocardiograms	53
4.3.2.4	Vital Signs	53
4.3.3	Clinical Laboratory Tests.....	54
4.3.3.1	Glucometer Measured Capillary Blood Glucose Readings	56
4.3.4	Pharmacokinetic Evaluation and Methods.....	56
4.3.5	Immunogenicity Evaluation and Methods	56
4.3.6	Pharmacodynamic Evaluation and Methods.....	57
		
4.3.6.2	Training for Application and Wearing of CGM Sensor.....	58
4.3.6.3	Training for Application and Wearing of ABPM Device ..	59
4.3.7	Biomarker Analysis	59
		
4.3.7.2	Storage, Re-use, and Destruction of Pharmacodynamic Samples	59
4.3.8	Estimate of Volume of Blood to Be Collected.....	59
4.4	Study Suspension or Termination.....	60
4.5	Investigational Products	60

4.5.1	Identity of Investigational Products.....	60
4.5.1.1	Investigational Product Dose Preparation	61
4.5.1.2	Investigational Product Inspection.....	62
4.5.1.3	Dose Preparation Steps.....	62
4.5.1.4	Treatment Administration	63
4.5.1.5	Monitoring of Dose Administration.....	64
4.5.1.6	Reporting Product Complaints	64
4.5.2	Additional Study Medications.....	65
4.5.3	Labeling.....	65
4.5.4	Storage.....	65
4.5.5	Treatment Compliance.....	65
4.5.6	Accountability.....	65
4.6	Treatment Assignment and Blinding	65
4.6.1	Methods for Assigning Treatment Groups.....	65
4.6.1.1	Cohort 1.....	65
4.6.1.2	Cohort 2.....	66
4.6.2	Methods for Ensuring Blinding.....	66
4.6.3	Methods for Unblinding.....	66
4.6.3.1	Unblinding in the Event of a Medical Emergency.....	66
4.6.3.2	Unblinding for Interim Analysis Purposes	66
4.7	Restrictions During the Study and Concomitant Treatment(s)	67
4.7.1	Permitted Concomitant Medications	67
4.7.2	Prohibited Concomitant Medications	67
4.8	Statistical Evaluation.....	68
4.8.1	General Considerations	68
4.8.1.1	Analysis Populations.....	68
		
4.8.3	Efficacy.....	69
4.8.3.1	Primary Efficacy Analysis.....	69
4.8.3.2	Secondary Efficacy Analyses	69
4.8.3.3	Exploratory Analyses.....	69
4.8.4	Safety.....	69
4.8.4.1	Analysis of Clinical Laboratory Parameters.....	70
4.8.5	Analysis of Immunogenicity/Pharmacokinetics.....	70
4.8.6	Interim Analysis	70
5	ASSESSMENT OF SAFETY.....	71
5.1	Definition of Adverse Events	71
5.2	Definition of Serious Adverse Events.....	71

5.3	Definition of Adverse Events of Special Interest	72
5.3.1	Hepatic Function Abnormalities.....	72
5.4	Recording of Adverse Events	72
5.4.1	Time Period for Collection of Adverse Events	73
5.4.2	Follow-up of Unresolved Adverse Events	73
5.5	Reporting of Serious Adverse Events	73
5.6	Other Events Requiring Immediate Reporting	74
5.6.1	Overdose.....	74
5.6.2	Hepatic Function Abnormality	74
5.6.3	Pregnancy	75
5.6.3.1	Maternal Exposure	75
6	STUDY AND DATA MANAGEMENT	75
6.1	Training of Study Site Personnel.....	75
6.2	Monitoring of the Study	76
6.2.1	Source Data	76
6.2.2	Study Agreements.....	76
6.2.3	Archiving of Study Documents.....	77
6.3	Study Timetable and End of Study	77
6.4	Data Management	77
6.5	Medical Monitor Coverage.....	77
7	ETHICAL AND REGULATORY REQUIREMENTS	78
7.1	Subject Data Protection.....	78
7.2	Ethics and Regulatory Review.....	78
7.3	Informed Consent.....	79
7.4	Changes to the Protocol and Informed Consent Form.....	79
7.5	Audits and Inspections	80
8	REFERENCES	81
9	CHANGES TO THE PROTOCOL.....	83
9.1	Protocol Amendment 2, 17Oct2017	83
9.2	Protocol Amendment 1, 25Jul2017.....	84
10	APPENDICES	86
10.1	Appendix 1 - Signatures.....	86
10.2	Appendix 2 – Contraception Guidance	88
10.3	Appendix 3 - Additional Safety Guidance	89
10.4	Appendix 4 - National Institute of Allergy and Infectious Diseases and Food Allergy and Anaphylaxis Network Guidance for Anaphylaxis Diagnosis	92
10.5	Appendix 5 - Actions Required in Cases of Increases in Liver Biochemistry and Evaluation of Hy’s law	93

10.7 Appendix 7 Biological Samples 101

LIST OF IN-TEXT TABLES

Table 2.1-1 Primary Objective and Associated Endpoints..... 17
Table 2.2-1 Secondary Objectives and Associated Endpoints..... 17
Table 2.3-1 Exploratory Objectives and Associated Endpoints 18
Table 3.2.1-1 Proposed Study Doses and Predicted Safety Margins Based on Rat and
Cynomolgus Monkey Data 26
Table 4.2.1-1 Schedule of Screening Procedures 35
Table 4.2.2-1 Schedule of Treatment Period Study Procedures: Cohort 1 38
Table 4.2.2-2 Schedule of Treatment Period Study Procedures: Cohort 2 44
Table 4.2.3-1 Schedule of Follow-up Procedures..... 49
Table 4.5.1-1 Identification of Investigational Products..... 61
Table 4.5.1.3-1 MEDI0382 and Placebo Dose Preparation 62
Table 9.1-1 Summary of Revisions to the Protocol 83
Table 9.2-1 Summary of Revisions to the Protocol 84
Table 10.2-1 Highly Effective Methods of Contraception..... 88

LIST OF IN-TEXT FIGURES

Figure 3.1.1-1 Study Flow Diagram..... 22

LIST OF ABBREVIATIONS

Abbreviation or Specialised Term	Definition
ABPM	ambulatory blood pressure monitoring
AE	adverse event
AESI	adverse event of special interest
ADA	anti-drug antibodies
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
C _{max}	maximum observed concentration
CGM	continuous glucose monitoring
█	█
ECG	electrocardiogram
EDC	electronic data capture
eCRF	electronic case report form
FFA	free fatty acid
GCP	Good Clinical Practice
█	█
GI	gastrointestinal
GLP-1	glucagon-like peptide-1
GMP	Good Manufacturing Practice
GFR	glomerular filtration rate
HbA1c	glycated haemoglobin
HBsAg	hepatitis B surface antigen
HIV	human immunodeficiency virus
IB	investigator brochure
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
ITT	intent-to-treat
IWRS	interactive voice response system
IXRS	interactive voice/web response system
MedDRA	Medical Dictionary for Regulatory Activities
MMTT	mixed-meal tolerance test
MDRD	Modification of Diet in Renal Disease

Abbreviation or Specialised Term	Definition
NOAEL	no-observed-adverse-effect level
PD	pharmacodynamics
PK	pharmacokinetics
SAE	serious adverse event
SC	subcutaneous
SID	subject identification
T _{1/2}	half-life
T2DM	type 2 diabetes mellitus
ULN	upper limit of normal
w/v	weight per volume

1 INTRODUCTION

1.1 Disease Background

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

1.2 MEDI0382 Background

MEDI0382 is a synthetic peptide with both glucagon-like peptide-1 (GLP-1) and glucagon receptor co-agonist activity which is under development for the treatment of T2DM and obesity. GLP-1 receptor agonists are established treatments for T2DM that improve glycaemic control, [REDACTED] and depress appetite leading to modest, but often non-sustained weight loss (typically 3% versus baseline at one year). Glucagon has similar effects to GLP-1 on [REDACTED] appetite, and has also been shown to promote increased energy expenditure (Lynch et al, 2014; Habegger et al, 2013). Oxyntomodulin, a naturally occurring peptide with GLP-1 and glucagon receptor co-agonist activity, has been shown to promote weight loss through effects on appetite and energy expenditure (Wynne et al, 2006) and co-infusion of GLP-1 and glucagon has synergistic effects on reducing food intake and promoting weight loss in human subjects (Bagger et al, 2015).

1.3 Summary of Nonclinical Experience

Refer to the current MEDI0382 Investigator's Brochure (IB) for a complete summary of nonclinical information. Consistent with other GLP-1 receptor agonists, MEDI0382 exposure resulted in the anticipated pharmacologic effects on body weight (reduced gain or loss), food consumption (sporadic reductions), [REDACTED]

[REDACTED]



1.4 Summary of Clinical Experience

In prior clinical experience (Cohort 4 of Study D5670C00002), treatment with MEDI0382 up to 200 µg from a start dose of 100 µg for 41 days with 2 titration steps of 4 days duration was associated with a mean reduction from baseline in body weight of 4.1% (90% confidence interval [CI] -4.9, -3.4) in MEDI0382-treated subjects versus 1.8% (90% CI -2.5, -1.0) in placebo, $p < 0.001$, and a mean reduction from baseline in glucose AUC_{MMT,4h} of 32.8% (90% CI -37.0, -28.6) vs 10.2% (90% CI -14.1, -6.2) in placebo, $p \leq 0.0001$. MEDI0382 was shown to have an acceptable safety profile. There were no unexpected safety signals and no increases in systolic or diastolic BP across the study. In Cohort 4, dosing over 41 days was associated with increased gastrointestinal (GI) adverse events (AEs) with 40 AEs of vomiting observed in 8 (32%) of subjects; however, the number of events diminished in frequency with dose up-titration ($n = 19$ at 100 µg, $n = 10$ at 150 µg, and $n = 11$ at 200 µg).

Extrapolating from these results it is anticipated that MEDI0382 will achieve GLP-1 receptor agonist-like glucose control, but with the potential for disease-modifying weight loss of greater than 10% of body weight over one year.

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

1.5 Rationale for Conducting the Study

This is a Phase 2a study designed to: 1) assess the efficacy, safety, tolerability, and the pharmacokinetic (PK) profile of MEDI0382 titrated up to a dose level of 300 µg from 50 µg across 49 days; 2) characterise the PK profile and blood glucose-lowering efficacy of 50 µg of MEDI0382 as this dose level has not been previously studied, and 3) to explore different dosing and titration schedules in order to determine if it is possible to minimise GI AEs associated with MEDI0382 treatment. The results of this study will provide additional information about the safety, tolerability, PK profile, and exposure-response following extended dosing at the 300 µg dose level.

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 (GCP), and applicable regulatory requirements.

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

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

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

1.7 Research Hypotheses

1.7.1 Primary Hypothesis

Administration of MEDI0382 once daily titrated up to a dose level of 300 µg will result in superior blood glucose control and weight loss versus placebo after 49 days of treatment in overweight and obese subjects with T2DM.

1.7.2 Secondary Hypotheses

- Administration of MEDI0382 once daily titrated up to a dose level of 300 µg across 49 days will have an acceptable safety profile and be well tolerated in overweight and obese subjects with T2DM
- Administration of MEDI0382 once daily titrated up to a dose level of 300 µg from 50 µg will have a predictable PK profile
- Administration of MEDI0382 once daily at a dose level of 50 µg will result in superior blood glucose control versus placebo after 7 days of treatment in overweight and obese subjects with T2DM

2 OBJECTIVES AND ENDPOINTS

2.1 Primary Objective and Associated Endpoints

Table 2.1-1 Primary Objective and Associated Endpoints

Type	Objective	Endpoint
Efficacy	To assess the effects of MEDI0382 titrated up to a dose level of 300 µg on glucose control and body weight versus placebo after 49 days of treatment (Cohort 1 only)	<ul style="list-style-type: none"> Percentage change in glucose AUC as measured by a standardised MMTT from baseline (Day -1) to the end of 49 days of treatment Percentage change in body weight from baseline (Day 1) to the end of 49 days of treatment

AUC = area under the concentration-time curve; MMTT = mixed-meal tolerance test

2.2 Secondary Objectives and Associated Endpoints

Table 2.2-1 Secondary Objectives and Associated Endpoints

Type	Objective	Endpoint
Efficacy	To assess the effects of MEDI0382 titrated up to a dose level of 300 µg on additional measures of glucose control and body weight versus placebo after 49 days of treatment (Cohort 1 only)	<ul style="list-style-type: none"> Change in HbA1c from baseline (Day - 1) to the end of 49 days of treatment Change in fasting plasma glucose (Day -1) from baseline to the end of 49 days of treatment Change in body weight (kg) from baseline (Day 1) to the end of 49 days of treatment Proportion of subjects achieving > 5% body weight loss from baseline (Day 1) after 49 days of treatment
Safety	To characterise the safety profile and tolerability of MEDI0382 titrated up to a dose level of 300 µg during dosing and follow-up (Cohorts 1 and 2)	Measures of safety and tolerability (24-hour heart rate and blood pressure, other vital signs, ECG, laboratory test results, and AEs)
PK, Immunogenicity	To characterise the PK profile and immunogenicity of 50 and 300µg of MEDI0382 (Cohorts 1 and 2)	<ul style="list-style-type: none"> PK endpoints for 50 µg MEDI0382 after 1, 7, and 14 days of treatment and 300 µg MEDI0382 after 1 and 28 days of treatment; AUC over a dosing duration, C_{max}, T_{max}, T_{1/2}, trough plasma concentration (C_{trough}), and accumulation ratio (C_{min} [R₀]) Development of anti-drug antibodies and titre (if confirmed positive)
Efficacy	To characterise the effect of 50 µg of MEDI0382 on glucose lowering versus placebo after 7 days (Cohorts 1 and 2)	Percentage change in glucose AUC as measured by a standardised MMTT from baseline (Day -1) to the end of 7 days of treatment

Table 2.2-1 Secondary Objectives and Associated Endpoints

Type	Objective	Endpoint
------	-----------	----------

AE = adverse event; AUC = area under the concentration-time curve; C_{max} = maximum observed concentration; C_{min} [R_0] = accumulation ratio; C_{trough} = trough plasma concentration;
ECG = electrocardiogram; HbA1c = glycated haemoglobin; MMTT = mixed-meal tolerance test;
PK = pharmacokinetic; $T_{1/2}$ = terminal half-life.

2.3 Exploratory Objectives

Table 2.3-1 Exploratory Objectives and Associated Endpoints

Type	Objective	Endpoint
Safety	To assess gastrointestinal tolerability across different titration schedules (Cohorts 1 and 2)	<ul style="list-style-type: none"> Percentage of subjects with gastrointestinal AEs at each dose level Percentage of subjects with nausea and vomiting from baseline (Day 1) over 7 days of treatment
PD	To assess the effect of MEDI0382 on glucose lowering during different meals and times of the day as measured by continuous glucose monitoring (CGM) (Cohort 1 only)	<ul style="list-style-type: none"> Change in percentage of time in hyperglycaemia (defined as > 7.8 mmol/l or > 140 mg/dl) and hypoglycaemia (defined as < 3 mmol/l or < 54 mg/dl) from baseline (Day -1) over 24 hours to the end of dosing at each dose level (Days 7, 14, 21, 28, and 49) Change in percentage of time in hyperglycaemia (defined as > 7.8 mmol/l or > 140 mg/dl) and hypoglycaemia (defined as < 3 mmol/l or < 54 mg/dl) over 7 days at each dose level (Days 1 to 7, Days 8 to 14, Days 15 to 21, and Days 22 to 28) Change in glucose AUC_{120min} during a standardised meal in the morning from baseline (Day -1) and at the end of 49 days of treatment Change in glucose AUC_{120min} during a standardised meal in the evening from baseline (Day -1) and at the end of 49 days of treatment
Efficacy	To characterise the effect of MEDI0382 on glucose lowering and weight versus placebo after 7, 14 and 49 days (Cohort 2 only)	<ul style="list-style-type: none"> Percentage change in glucose AUC as measured by a standardised MMTT from baseline (Day -1) after 14 and 49 days Change in fasting plasma glucose from baseline (Day -1) to the end of 7, 14, and 49 days of treatment Percentage and absolute change in body weight from baseline (Day 1) to the end of 7, 14, and 49 days of treatment Change in HbA1c from baseline (Day -1) to the end of 49 days of treatment

Table 2.3-1 Exploratory Objectives and Associated Endpoints

Type	Objective	Endpoint
PD	To assess the effect of MEDI0382 on ketone bodies, amino acids, and free fatty acid (FFA) levels over 49 days of treatment (Cohort 1 only)	<ul style="list-style-type: none"> Change in plasma beta-hydroxybutyrate from baseline (Day -1) while fasted and at 4 hours postdose after 49 days Change in FFA levels from baseline (Day -1) after 49 days of treatment Change in amino acid levels from baseline (Day -1) after 49 days of treatment
PD	To assess the effect of MEDI0382 on uric acid	<ul style="list-style-type: none"> Change in uric acid levels from baseline (Day -1) after 49 days of treatment

AE = adverse event; AUC = area under the concentration–time curve; CGM = continuous glucose monitoring; FFA = free fatty acids; GLP-1 = glucagon-like peptide-1; HbA1c = glycated haemoglobin; MMTT = mixed-meal tolerance test; PD = pharmacodynamics; T_{lag} = lag phase; T_{1/2} = half -life

3 STUDY DESIGN

3.1 Description of the Study

3.1.1 Overview

This is a randomised, double-blind, placebo-controlled study to evaluate the efficacy, safety, tolerability, and PK profile of 50 and 300 µg of MEDI0382 in overweight and obese subjects with T2DM. Up to 63 subjects are planned to be enrolled across multiple study sites.

The study is divided into 2 cohorts that will be recruited in parallel; for both cohorts, subjects will be consented, screened for suitability, and randomised within 60 days if eligible. A total of 39 subjects will be randomised to Cohort 1, and 24 subjects will be randomised to Cohort 2. Cohort 1 will evaluate the efficacy, safety, tolerability, and PK of MEDI0382 when titrated up in weekly intervals from 50 to 300 µg and administered over 49 days. Cohort 2 will explore an alternative 2-week titration schedule, and will provide additional information on the PK profile and glucose-lowering efficacy of 50 µg MEDI0382

Cohort 1

Subjects will undergo safety blood tests at any time from Day -7 to Day -3 if the screening visit is more than 7 days before Day 1. On Day -2, subjects will be admitted to the clinical unit for 2 nights and will undergo further initial safety assessments and training in SC injection administration; normal saline will be used for SC injection administration training. At this time an ambulatory blood pressure monitoring (ABPM) device will be fitted on Day -2 and worn for 24 hours; simultaneously a continuous glucose monitoring (CGM) device will be fitted on the contralateral arm and the subject will be given training for CGM use (Figure 3.1.1-1). Subjects will be expected to wear the CGM continuously until the end of dosing. On Day -1, eligibility criteria will be verified and subjects will undergo 2 mixed-meal tolerance test (MMTT) assessments (Meal type A; with serial blood sampling in the morning, and meal type C without serial blood sampling on the evening of that day). Subjects can be randomised after confirming eligibility at any time from Day -1 to Day 1 (predose) to receive either MEDI0382 or placebo. On Day 1, dosing will commence following predose safety measures including vital signs, blood tests for safety, glycated haemoglobin (HbA1c) and exploratory biomarkers, an ECG, and measurement of weight. Since the dose of 50 µg will require a dilution by site staff prior to administration, subjects will have the option to remain as an inpatient or alternatively attend the clinical unit every day for dosing during the first week; during this time subjects will undergo supervision to self-administer the investigational product. On Day 7, safety assessments will be performed and the MMTT meal type B, with serial blood sampling, will be repeated; where relevant, subjects will be discharged home (refer to Section 4.3.1.1 for description of MMTT meal types).

Subjects will then return to the clinical unit at weekly intervals until a maintenance dose of 300 µg is achieved. On Day 22, subjects will be readmitted to the clinical unit for an overnight stay to undergo PK sampling and ABPM for 24 hours. Subjects will be discharged on Day 23 and will thereafter attend for weekly visits for safety assessments and ABPM application. At the end of dosing, subjects will be readmitted to the clinical unit for a final overnight stay, and an MMTT (Type A) will be repeated alongside safety assessments, ABPM, measurement of weight, and blood tests. A second MMTT (Type C) without serial blood sampling will be performed on the evening of Day 49 and an HbA1c and exploratory biomarkers will be repeated. A 7- to 14-day post-last dose follow-up visit and final follow-up visit approximately 28 days after the last dose will be performed for safety assessments, and a final ABPM recording will be made at this time.

Cohort 2

Study procedures for Cohort 2 will be similar to Cohort 1 at baseline, although subjects will not undergo ABPM assessments nor wear a CGM monitor in this cohort. [REDACTED]

[REDACTED]
[REDACTED]
[REDACTED] Safety bloods will be performed at anytime from Day -7 to Day -3 if the screening visit was more than 7 days before Day 1 (Figure 3.1.1-1). Subjects may be confined to rest for the duration of the breath test period. On admission to the clinical unit on Day -2, subjects will undergo further baseline safety assessments and undergo their first MMTT (Type A) with serial blood sampling on Day -1. Dosing will commence on Day 1. Since the dose of 50 µg will require a dilution by site staff prior to administration, subjects will be given the option to either remain as an inpatient, or attend the clinical unit every day during the first 2 weeks of dosing, but will be required to stay overnight for a total of 5 nights across this period (on Days -2, -1, 1, 7, and 14); thereafter, subjects will attend the unit for dose up-titration. During this time subjects will self-administer investigational product under supervision. [REDACTED] and MMTTs (Type B) with serial blood sampling will be repeated at different points across the study as described in the schedule. At the end of dosing on Day 49, subjects will be admitted for a final overnight stay; a repeat MMTT (Type A) will be performed, alongside measurement of weight and safety assessments. [REDACTED]

[REDACTED] A 7- to 14-day post-last dose follow-up visit and final follow-up visit approximately 28 days after the last dose will be performed for safety assessments [REDACTED]
[REDACTED]

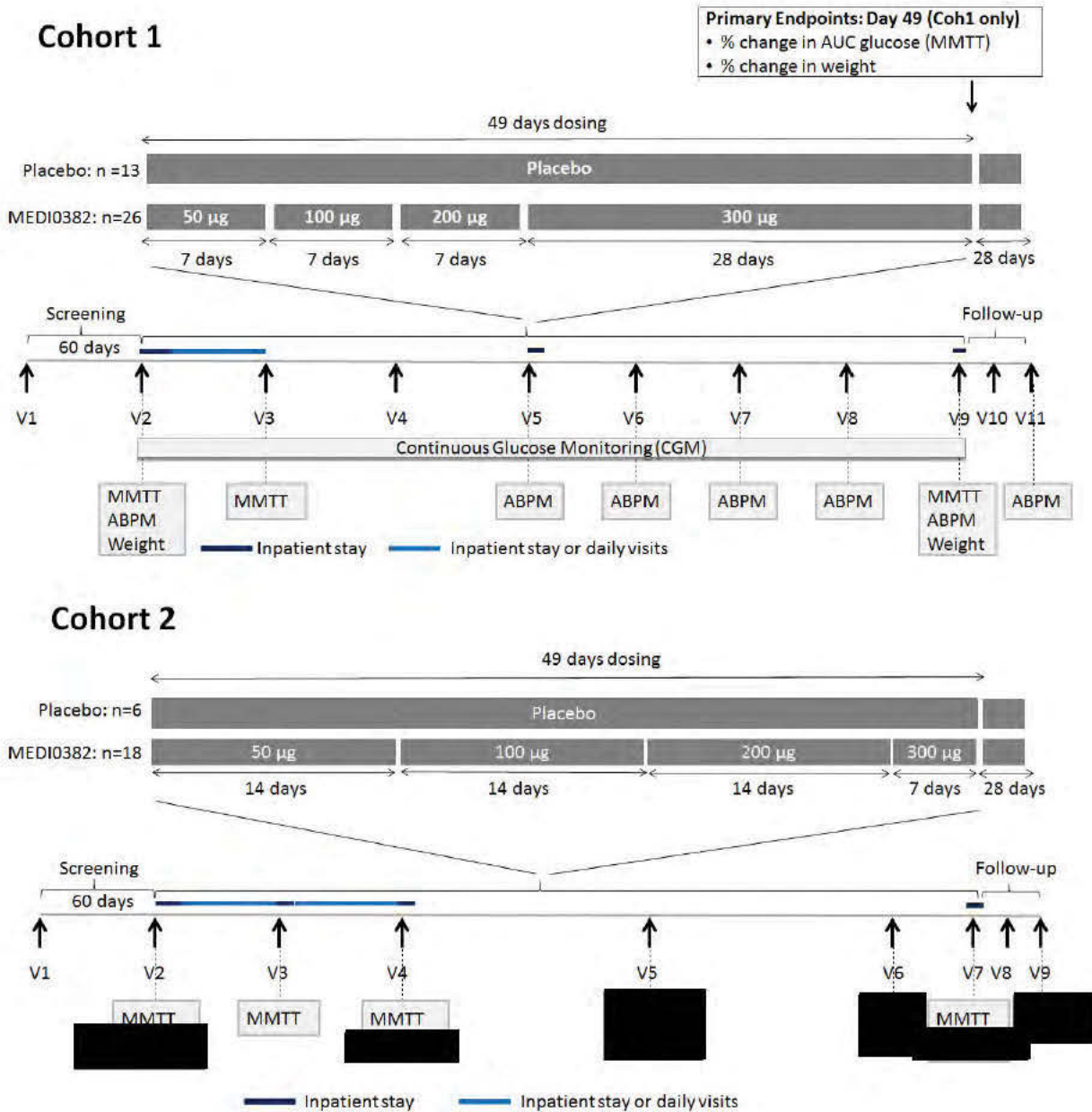


Figure 3.1.1-1 Study Flow Diagram

ABPM = 24-hour ambulatory blood pressure (and heart rate) monitoring; AUC = area under the concentration-time curve; CGM = continuous glucose monitoring; Coh = cohort; [REDACTED]
 MMTT = mixed-meal tolerance test; n = number of subjects; V = visit

Assessments detailed in the schematics illustrate that those assessments will occur at that particular visit (unless specified otherwise), but they will not necessarily occur on the same day.

There is also a post-last dose visit 7 to 14 days after the last dose (Visit 10 for Cohort 1 and Visit 8 for Cohort 2), and there is a final follow-up visit (Visit 11 for Cohort 1 and Visit 9 for Cohort 2) approximately 28 days after the last dose for both cohorts.

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

3.1.2 Treatment Regimen

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

Cohort 1

- MEDI0382 50 µg for 7 days, followed by 100 µg for 7 days, followed by 200 µg for 7 days, and 300 µg SC once daily for 28 days (n = 26)
- Matched placebo SC once daily for 49 days (n = 13)

Cohort 2

- MEDI0382 50 µg for 14 days, followed by 100 µg for 14 days, followed by 200 µg for 14 days, and 300 µg SC once daily for 7 days (n = 18)
- Matched placebo SC once daily for 49 days (n = 6)

3.1.3 Dose Escalation

Doses will escalate from the initial dose of 50 µg to 300 µg in 1-week intervals for Cohort 1 and in 2-week intervals for Cohort 2 (Section 3.1.2).

3.1.4 Management of Study Medication Related Toxicities

3.1.4.1 Tolerability

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

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 (Skyder et al, 2017) has not been experienced in prior studies with MEDI0382 up to a dose of 300 µg alongside metformin

treatment and is therefore unlikely to occur in this study. All subjects (both Cohorts 1 and 2) will be provided with a diary and a glucometer and will be advised to check their capillary blood glucose level if they have symptoms of hypoglycaemia (hunger, dizziness, shaking, sweating, or irritability) or feel unwell and will be expected to record the level in their diary. Local protocols for treatment and follow-up of any hypoglycaemic episode should be followed. Any blood glucose level of < 3.0 mmol/L (54 mg/dL) is considered as clinically important hypoglycaemia and should be reported by investigators as an AE. 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), capillary blood glucose readings (eg, 3 readings > 260 mg/dL [14.4 mmol/L] within one week) or CGM readings (eg, $> 30\%$ of readings above 260 mg/dL [14.4 mmol/L]), the investigator should perform additional fasting blood glucose levels as necessary to further investigate. If 2 or more laboratory plasma fasting glucose levels of > 260 mg/dL [14.4 mmol/L] more than 3 days apart are detected, the investigator should consider rescue therapy following discussion with the medical monitor.

3.2 Study Design and Dose Rationale

3.2.1 Dose Rationale

PK information collected in previous single and multiple dose clinical studies (Studies D5670C00001 and D5670C00002) suggest that MEDI0382 has a linear profile in the dose range 5 to 300 μ g with a half-life of approximately 8 to 13 hours, which allows minimal accumulation after repeat daily administration and achievement of steady state between 4 and 7 days. Moreover, the absorption profile in the low-dose range tested suggests that doses lower than 100 μ g may have a different bioavailability to doses greater than 100 μ g.

Based on PK/pharmacodynamics (PD) modelling conducted using available clinical data and from a literature review of GLP-1 and glucagon modulators, the maximal clinically efficacious dose for glucose control of MEDI0382 was predicted to be in the range of 200 to 300 μ g/day; in addition early clinical data from a prior single-ascending-dose study (Study D5670C00001) identified potentially efficacious doses in a range lower than 100 μ g. However, there is no information available on efficacy with repeat dosing at dose levels below 100 μ g. The initial dose for Cohorts 1 and 2 of this study is therefore proposed to be 50 μ g and the maximum dose to be administered in this study will not exceed 300 μ g/day. As

described above, the principle of dose up-titration to improve tolerability with higher doses is well established with short-acting GLP-1 analogues ([Victoza, 2014](#)).

The study is designed to provide efficacy information on glucose control and weight loss at 300 µg administered daily for 28 days to allow comparison with previous clinical data collected at 200 µg at a similar administration duration. It will also explore a prolonged dose titration schedule for repeated doses of MEDI0382 to characterise the safety/tolerability profile and PK/PD profile of MEDI0382 at a relevant pharmacological range to facilitate rational design of future studies. Moreover, it is designed to establish the efficacy of repeated dosing of 50 µg MEDI0382 on glucose control.

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]

[REDACTED]

3.2.2 Rationale for Study Population

3.2.2.1 Recruitment of Subjects with T2DM and a Body Mass Index 27 to 40 kg/m²

MEDI0382 is a GLP-1 and glucagon receptor co-agonist which promotes glucose lowering and weight loss and is targeted at subjects with T2DM.

Male and female subjects with T2DM who are overweight or obese are likely to benefit most from losing weight. While subjects with a body mass index (BMI) > 40 kg/m² may be offered bariatric surgery, those with a BMI in the range of 27 to 40 kg/m² rely upon conservative or medical management for weight reduction. The entry criteria with respect to T2DM and BMI of 27 to 40 kg/m² both maximise recruitment potential and provide efficacy, safety, and tolerability data in the likely intended clinical population. There is no requirement for a given number of subjects in each gender to be enrolled.

3.2.2.2 Selection of Subjects with Stable HbA1c in the Range of 6.5% to 8.5% (Inclusive) on Metformin

The study population to be recruited is similar to that studied in the prior study (Study D5670C00002) with respect to HbA1c and existing diabetes treatment to enable benchmarking of results between the 2 studies, as subjects with a later stage of T2DM or who have failed multiple oral therapies may have a different glycaemic response to MEDI0382.

3.2.3 Rationale for Endpoints

3.2.3.1 Primary Endpoints

Coprimary endpoints of glucose AUC and weight loss are required to evaluate the efficacy of the 300 µg dose level over a longer duration of dosing than has been studied before at this dose level.

3.2.3.2 Secondary Endpoints

Additional Measures of Glucose Lowering and Weight Loss

In order to better characterise the glucose-lowering efficacy of MEDI0382 up to 300 µg across 49 days of dosing, additional markers of glucose control including HbA1c and fasting glucose level will be measured, alongside exploratory measures of glucose control generated by CGM. Absolute change in weight will also be measured and the proportion of subjects achieving clinically significant weight loss (> 5% of body weight) will be recorded.

In evaluating the 50 µg dose of MEDI0382, this study will determine if repeat administration of 50 µg is more effective than placebo with respect to glucose lowering at 7 days through measurement of glucose AUC during a standardised MMTT. Results from the prior multiple-ascending-dose study (Study D5670C00002) of MEDI0382 on glucose AUC reduction have shown a reduction of 41.8% after 7 days at 100 µg, 36.7% after 11 days at 150 µg following up-titration from 100 µg, and 39.6% after 15 days at 200 µg following up-titration from 100 µg and 150 µg. Results from this previous study will be used as a benchmark to further evaluate the results.

Safety and Tolerability

In prior studies (Study D5670C00002), 300 µg of MEDI0382 has been administered to 23 obese and overweight subjects with T2DM for 7 days after 2 up-titration steps, and was shown to have an acceptable tolerability and safety profile over this period of dosing. During treatment, there was no significant increase in systolic or diastolic BP, but a significant increase in heart rate of 6.6 beats per minute (90% CI 4.1, 9.1) was recorded after 7 days of dosing (Cohorts 5 and 6 pooled data; n = 19). In the cohorts that received MEDI0382 up-titrated to 300 µg, nausea and vomiting were observed in a maximum of 41.7% (Cohort 6) and 27.3% (Cohort 5) of subjects, respectively. Safety and tolerability with greater exposure at the 300 µg dose level will be measured with safety laboratory tests, ABPM recording of heart rate and BP and other vital signs, and recording of AEs.

Pharmacokinetic Profile and Immunogenicity

Plasma concentrations of MEDI0382 at 50 and 300 µg will be used to evaluate the PK profile (C_{max} , time to maximum concentration [T_{max}], AUC_{tau} , and $C_{min}[R_0]$ [accumulation ratio]). In addition, C_{trough} at other dose levels will be evaluated to establish steady state achievement.

Anti-drug antibodies (ADA) incidence rate and titre will be tabulated for each treatment to monitor immunogenicity. Tiered analyses will be performed to include screening, confirmatory and titre assay components; samples confirmed positive for ADA will be tested and analysed for antibody titre and reported and may be utilised for further characterisation of the ADA response.

3.2.3.3 Exploratory Endpoints

GLP-1 analogues are established to cause increased GI side-effects which are most pronounced in the early phases of treatment (Meier, 2012). The mechanisms underlying these symptoms are multifactorial and related to PK and effects on [REDACTED] and vomiting centers of the brain (area postrema) (Orskov et al, 1996). An added dimension of complexity here is that tolerance to the effects of GLP-1 receptor agonism on [REDACTED] may develop with short-term treatment (Nauck et al, 2011). In attempts to improve GI tolerability in this drug class, both dose up-titration (Victoza, 2014) and lengthening of titration intervals from between 1 to 4 weeks have been utilised (Exenatide, 2016). In a prior Phase 1/2 study (Study D5670C00002), subjects dosed with MEDI0382 titrated in 4-day intervals from 100 µg up to 200 µg across 41 days reported mild to moderate nausea (13/25, 52%) and vomiting (8/25, 32%); however, the number of nausea and vomiting events diminished in frequency with dose up-titration (n = 19 at 100 µg, n = 10 at 150 µg, and n = 11 at 200 µg) and in most cases, events were noted to occur within 3 days of a dose up-titration step. In Cohorts 5 and 6 of Study D5670C00002, a comparison of different dose up-titration steps was made: 100 µg → 150 µg → 200 µg → 300 µg (Cohort 5; n = 11) versus 100 µg → 200 µg → 300 µg (Cohort 6; n = 12) with 5-day up-titration steps in between. The percentage of subjects reporting nausea was lower with an intermediate 150 µg dose up-titration step between 100 and 200 µg (27% vs 42%); however, the percentage of subjects with vomiting was in fact higher in this group (27% vs 8%). These results and the prior clinical experience with GLP-1 analogues imply that further modulation of the titration schedule may help to minimise GI side-effects experienced with MEDI0382. To investigate different titration schedules, Cohort 1 of this study will test a lower starting dose of MEDI0382 (50 µg) than has been previously tested in overweight and obese subjects with T2DM, and with longer up-titration steps (7 days). Cohort 2 will run in parallel with Cohort 1

and will test up-titration of MEDI0382 every 2 weeks in order to assess if this further minimises GI AEs.

[REDACTED]

CGM is a minimally invasive device applied to the skin in the upper arm that provides a measure of interstitial glucose levels every 15 minutes. In this study, results of CGM will be used to calculate the average glucose level over 24-hour and 7-day periods, to observe glucose excursions during different meals and at different times of the day, and to determine the percentage of time subjects have abnormally high or low blood glucose levels. To further supplement this investigation, standardised meals (in some cases as part of an MMTT) will be given in the morning and evening to view the difference in post-prandial glucose excursion at different times in the day. [REDACTED]

[REDACTED]

It is postulated that the glucagon receptor agonist component of MEDI0382 may lead to an increase in fatty acid oxidation in the liver (Keller and Shulman, 1979). Ketone bodies are the byproduct of fatty acid oxidation and may be increased if there is an up-regulation of fatty acid oxidation. Concurrent measurement of free fatty acids (FFAs) and amino acids will determine if there is increased consumption of these ketogenic substrates during treatment with MEDI0382.

[REDACTED] uric acid (Gagliardi et al, 2009) are markers of cardiovascular risk; measurements before and after MEDI0382 treatment will be interpreted in the context of change in weight and lipids to gain an early insight on the impact of MEDI0382 on cardiovascular risk.

4 MATERIALS AND METHODS

4.1 Subjects

4.1.1 Number of Subjects

Enrollment of up to 63 subjects across multiple study sites is planned, 39 subjects in Cohort 1 (26 subjects to receive MEDI0382 and 13 to receive matched placebo) and 24 subjects in Cohort 2 (18 subjects to receive MEDI0382 and 6 subjects to receive matched placebo).

4.1.2 Inclusion Criteria

Subjects must meet all of the following criteria:

1. Male and female subjects aged ≥ 18 years at screening
2. Provision of signed and dated written informed consent (██████████ nongenetic research) prior to any study specific procedures
3. BMI between 27 and 40 kg/m² (inclusive) at screening
4. HbA1c range of 6.5% to 8.5% (inclusive) at screening*
5. Diagnosed with T2DM with glucose control managed with metformin monotherapy where no significant dose change (increase or decrease ≥ 500 mg/day) has occurred in the 3 months prior to screening
6. Subjects prescribed oral dual therapy with a dipeptidyl peptidase-4 inhibitor, sulphonylurea, glitinide, or a sodium-glucose co-transporter 2 inhibitor in addition to metformin at screening may be eligible to enter the study following a 4-week washout period
7. Female subjects of childbearing potential must have a negative pregnancy test at screening and randomisation, and must not be lactating
8. Females of childbearing potential who are sexually active with a nonsterilised male partner must use 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 through to the end of the study. It is strongly recommended for the male partner of a female subject to also use male condom plus spermicide throughout this period. Cessation of contraception after this point should be discussed with a responsible physician. Periodic abstinence, the rhythm method, and the withdrawal method are not acceptable methods of contraception.

*Note: Subjects may be retested for the HbA1c entry criterion only once.

4.1.3 Exclusion Criteria

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

1. History of, or any existing condition that, in the opinion of the investigator, would interfere with evaluation of the investigational product, put the subject at risk, influence the subject's ability to participate or affect the interpretation of the results of the study and/or any subject unable or unwilling to follow study procedures
2. Any subject who has received another investigational product as part of a clinical study or a GLP-1 analogue-containing preparation within the last 30 days or 5 half-lives of the drug (whichever is longer) at the time of screening
3. Any subject who has received any of the following medications within the specified timeframe prior to the start of the study (Visit 2) (see Section 4.7.2 for further details):
 - Herbal preparations or drugs licensed for control of body weight or appetite (eg, orlistat, bupropion-naltrexone, phentermine-topiramate, phentermine, lorcaserin)
 - Aspirin (acetylsalicylic acid) at a dose greater than 150 mg once daily
 - Paracetamol (acetaminophen) or paracetamol-containing preparations at a total daily dose of greater than 3000 mg
 - Ascorbic acid (vitamin C) supplements at a total daily dose of greater than 1000 mg
 - [REDACTED]
4. Concurrent participation in another study of any kind and repeat randomisation in this study is prohibited
5. Severe allergy/hypersensitivity to any of the proposed study treatments, excipients, or ingredients of standardised meals
6. Symptoms of acutely decompensated blood glucose control (eg, thirst, polyuria, weight loss), a history of type 1 diabetes mellitus or diabetic ketoacidosis, or if the subject has been treated with daily SC insulin within 90 days prior to screening
7. Significant inflammatory bowel disease, gastroparesis, or other severe disease or surgery affecting the upper GI tract (including weight-reducing surgery and procedures) which [REDACTED] could affect the interpretation of safety and tolerability data
8. Significant hepatic disease (except for non-alcoholic steatohepatitis or non-alcoholic fatty liver disease without portal hypertension or cirrhosis) and/or subjects with any of the following results at screening:
 - Aspartate transaminase (AST) $\geq 3 \times$ upper limit of normal (ULN)
 - Alanine transaminase (ALT) $\geq 3 \times$ ULN
 - Total bilirubin $\geq 2 \times$ ULN
9. Impaired renal function defined as estimated glomerular filtration rate (GFR) < 60 mL/minute/1.73 m² at screening (GFR estimated according to Modification of Diet in Renal Disease [MDRD] using the isotope dilution mass spectrometry [IDMS]-traceable MDRD Study Equation [SI units])
10. Poorly controlled hypertension defined as:
 - Systolic BP > 160 mm Hg
 - Diastolic BP ≥ 95 mm Hg

after 10 minutes of seated rest and confirmed by repeated measurement at screening. Subjects who fail BP screening criteria may be considered for 24-hour ABPM at the discretion of the investigator. Subjects who maintain a mean 24-hour systolic BP \leq 160 or diastolic BP $<$ 95 mm Hg with a preserved nocturnal dip of $>$ 15% will be considered eligible.

11. 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
12. Severe congestive heart failure (New York Heart Association Class III or IV)
13. Basal calcitonin level $>$ 50 ng/L at screening or history/family history of medullary thyroid carcinoma or multiple endocrine neoplasia
14. Haemoglobinopathy, haemolytic anemia, or chronic anaemia (haemoglobin concentration $<$ 11.5 g/dL [115 g/L] for males, $<$ 10.5 g/dL [105 g/L] for females) at screening or any other condition known to interfere with interpretation of HbA1c measurement
15. 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
16. Any positive results for serum hepatitis B surface antigen (HBsAg), hepatitis C antibody, and human immunodeficiency virus (HIV) antibody
17. History of substance dependence, alcohol abuse, or excessive alcohol intake (defined as an average weekly intake of $>$ 21 alcoholic drinks for men or $>$ 10 alcoholic drinks for women) within 3 years prior to screening, and/or a positive screen for drugs of abuse or alcohol at screening or on admission to the study unit. 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.
18. Involvement of any AstraZeneca, MedImmune, contract research organization, or study site employee or their close relatives
19. History of acute or chronic pancreatitis or other diseases of the pancreas

4.1.4 Subject Enrollment and Randomisation

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

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 should not, under any circumstances, be enrolled or receive investigational product. There can be no exceptions to this rule. Subjects who are enrolled, but subsequently found not to meet all the eligibility criteria must not be randomised or initiated on treatment, and must be withdrawn from the study.

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

4.1.5 Withdrawal from the Study

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

4.1.6 Discontinuation of Investigational Product

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

- Withdrawal of consent from further treatment with investigational product or lost to follow-up
- An AE that, in the opinion of the investigator or the sponsor, contraindicates further dosing
- Subject is determined to have met one or more of the exclusion criteria or failed to meet all of the inclusion criteria for study participation at study entry and continuing investigational product, in the decision of the investigator, might constitute a safety risk
- Subject noncompliance that, in the opinion of the investigator or sponsor, warrants withdrawal (eg, refusal to adhere to scheduled visits).
- Pregnancy in a female subject

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

4.1.7 Replacement of Subjects

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

4.1.8 Withdrawal of Informed Consent for Data and Biological Samples

Biological Samples Obtained for the Main Study

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

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

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

4.2 Schedule of Study Procedures

4.2.1 Enrollment/Screening Period

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

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

Table 4.2.1-1 Schedule of Screening Procedures

Study Period	Screening
Visit Number	V1
Procedure/Study Day	Day -60 to Day -2
Written informed consent/assignment of SID number	X
[REDACTED]	■
[REDACTED]	■

Table 4.2.1-1 Schedule of Screening Procedures

Study Period	Screening
Visit Number	V1
Procedure/Study Day	Day -60 to Day -2
Medical history, including smoking and alcohol history	X
Physical examination (full) including structured neurological examination ^a	X
Verify eligibility criteria	X
Weight, height, and BMI calculation	X
Demographics	X
12-lead ECG ^b	X
Vital signs (BP ^c , heart rate, body temperature, RR)	X
Collect blood for:	
LFTs, CR, and eGFR calculation only	X
Haematology (FBC)	X
HbA1c	X
Calcitonin	X
HIV-1 and -2 antibodies; hepatitis B and C serology	X
Collect urine for:	
Urinalysis	X
Drug and alcohol screen	X
Urine or serum pregnancy test if applicable	X
CGM device demonstration ^d	X
SC injection self-administration training ^e	X
Concomitant medications	X

BMI = body mass index; BP = blood pressure; CGM = continuous glucose monitoring; CR = creatinine; 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 transaminase [AST], alkaline phosphatase [ALP], and total bilirubin); RR = respiration rate; SC = subcutaneous; SID = subject identification; V = visit

^a examination is required.

^b A single digital ECG recording should be performed after the subject has rested in the supine position for 10 minutes.

^c Blood pressure should be measured once at heart level in the nondominant arm where possible, after the subject has rested in either a seated or supine position for at least 10 minutes.

^d Cohort 1 only; subjects should be shown the device and given an explanation as to how it is worn; allocation to Cohort 2 may be preferable for subjects who would rather not use a CGM device during the study.

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

4.2.2 Randomised Treatment Period

Table 4.2.2-1 and Table 4.2.2-2 show all procedures to be conducted during the treatment period for Cohort 1 and Cohort 2, respectively. Assessments should be performed in the order shown in the table.

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

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

Study Period	Inpatient		Inpatient or daily visits	Outpatient		Inpatient		Outpatient		Inpatient		Outpatient							
	-2	-1		1	2-6	7	15	22	23	29	36	43	49	50					
Study Day																		7 to 14 Days Post Last Dose	
Visit Number																			V10
Procedure																			
Verify eligibility criteria ^a																			
Admit to clinical unit ^b	X											X							
Discharge from clinical unit ^c													X						X
Outpatient visit to clinic ^c			(X)	(X)						X	X			X	X				X
Medical and disease history	X																		
Pregnancy test (if applicable) ^d	X									X									
Targeted physical examination	X									X		X		X	X				
Vital signs (BP, heart rate, body temperature, RR) ^e	X		X							X		X	X	X	X				X
ABPM ^f	X											X		X	X				
ECG ^g										X		X		X	X				X
Body weight ^h										X		X		X	X				X
SC injection training using normal saline	X	X	X																
Randomisation ⁱ			X																
Subjects required to fast overnight for 10 hours ^j	X	X		X(D6)								X(D21)						X(D48 & 49)	
IP administration ^k (SC)			X	X						X	X	X		X	X				
Up-titration ^l					X	X				X	X	X							

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

Study Period	Inpatient		Inpatient or daily visits	Outpatient		Inpatient		Outpatient		Inpatient		Outpatient		
	-2	-1		1	2-6	7	15	22	23	29	36	43	49	50
Study Day														
Visit Number	V2		V3	V4	V5	V6	V7	V8	V9	V10				
Collect blood for:														
Haematology panel (predose as applicable) ^m	X (Day -7 to -3)		X		X	X	X	X	X	X	X	X	X	X
Serum chemistry panel (predose as applicable) ^m	X (Day -7 to -3)		X		X	X	X	X	X	X	X	X	X	X
Lipase and amylase			X					X				X		
Calcitonin											X			
Fasting lipid profile		X			X						X			
Fasting HbA1c		X			X						X			
PK for MEDI0382 ⁿ		X			X	X	X	X	X	X	X	X	X	X
ADA ^o			X						X					
[REDACTED]														
[REDACTED]														
Capillary blood ketone and beta hydroxybutyrate ^q		X			X							X		
Free fatty acids (predose)		X										X		
[REDACTED]														

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

Study Period	Inpatient		Inpatient or daily visits	Outpatient			Inpatient		Outpatient			Outpatient 7 to 14 Days Post Last Dose
	-2	-1		1	2-6	7	15	22	23	29	36	
Visit Number	V2			V3	V4	V5	V6	V7	V8	V9	V10	
[REDACTED]					■							
Fasting amino acids (predose)		X								X		
[REDACTED]		■								■		
Fasting uric acid		X								X		
[REDACTED]		■								■		
MMTT Type B - blood samples for glucose only ¹					X							
Collect urine for:												
Urinalysis (dipstick; predose as applicable)		X			X							X
Drug and alcohol screen	X											
MMTT Type C (no blood sampling) ^s		X										X
CGM device training	X	X	X									
CGM ^t	←	-----To be worn continuously throughout until Day 50-----→										
CGM sensor application/change ^u	X				X			X			X	
Glucometer and diary provision ^v	←	-----Subjects will be expected to check capillary blood glucose levels if they are unwell or have symptoms of hypoglycaemia-----→										
AEs/SAEs	←	-----For the duration of the study-----→										
Concomitant medications	←	-----For the duration of the study-----→										

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

Study Period	Inpatient		Inpatient or daily visits		Outpatient		Inpatient		Outpatient		Inpatient		Outpatient	
	-2	-1	1	2-6	7	15	22	23	29	36	43	49	50	7 to 14 Days Post Last Dose
Study Day														
Visit Number	V2		V3	V4	V5	V6	V7	V8	V9	V10				

ADA = anti-drug antibody; AE = adverse event; APBM = ambulatory blood pressure monitoring; BP = blood pressure; CGM = continuous glucose monitoring; D = day; ECG = electrocardiogram; GLP-1 = glucagon-like peptide-1; HbA1c = glycated haemoglobin; IP = investigational product; min = minutes; MMTT = mixed-meal tolerance test; PD = pharmacodynamic(s); PK = pharmacokinetic(s); RR = respiration rate; SAE = serious adverse event; SC = subcutaneous; V = Visit.

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

- a The eligibility check should be based on all clinical measurements and blood tests taken during the screening visit (V1) with the exception of eGFR, liver function tests, blood pressure, urinary illicit drug, alcohol and pregnancy tests, which should be rechecked on Day -2. A targeted physical examination and repeat medical history should also be undertaken to ensure the subject is well enough to commence dosing.
- b The diet of subjects should not be restricted in any way during the study (including during inpatient stay) unless fasting or a standardised meal is specified.
- c Subjects who prefer to attend for daily visits during the first week will be discharged home on Day 1 after all assessments are complete. (X) indicates that subjects can be inpatients or outpatients at these visits.
- d A serum or urine pregnancy test should be conducted on any female subject of childbearing potential as detailed in the schedule. Pregnancy tests do not need to be conducted in women who are surgically sterile (ie, bilateral tubal ligation, bilateral oophorectomy, or complete hysterectomy) or are postmenopausal (defined as at least 1 year since last menses and having an elevated follicle stimulating hormone laboratory value which is in the postmenopausal range in previous laboratory test results).
- e Vital Signs Schedule (blood pressure, heart rate, respiratory rate, and temperature): on days where ABPM is due to be checked a predose set of vital signs should be performed prior to application of the ABPM cuff. Blood pressure should be measured once at heart level in the nondominant arm where possible, opposite to the arm where the CGM device is applied, after the subject has rested in either a seated or supine position for at least 10 minutes. 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.
 - o Day -2; vital signs to be taken prior to fitting the ABPM device; postural (standing and supine) blood pressures should be performed at this time.
 - o Day 1; vital signs to be taken; predose (-15 min), 15, 30, and 60 minutes (\pm 5 min) and 2 hours (\pm 10 min) postdose

- o Day 7, 15; 23 no specific time point
 - o Day 22, 29, 36, and 43; vital signs to be taken prior to fitting ABPM device
 - o Day 49: vital signs to be taken prior to fitting the ABPM device; postural (standing and supine) blood pressures should be performed at this time.
- f Subjects will be fitted with the ABPM device while at the clinical unit, which may involve practice inflations. The ABPM device should be applied on the opposite arm to the arm where the CGM device is applied. The subject will then wear the monitor/cuff for approximately 24 hours (including overnight at home) and will remove the device at home at the end of the 24-hour period. Subjects will return the device to the clinic.
- g A single digital ECG recording should be performed predose after the subject has rested for 10 minutes in the supine position on Day 1, 7, 22, and 49. No specific time point for other visits.
- h Body weight should be measured in the morning prior to breakfast (predose on Day 1); the subject should take off their shoes and remove bulky clothing. Calibrated scales should be used.
- i Randomisation may occur any time from Day -1 to Day 1 predosing.
- j Subjects are required to fast overnight on the night of Day -2, -1, 6, 21, 48, and 49. Refer to footnote (s) for additional fasting requirements on Day -2 and Day 49 during the day.
- k Subjects are required to dose at the clinic on Day 1 – 7 as dilution of dose is required by site staff. Subjects are also required to dose at the clinic on study day visits when predose assessments are required. See Section 4.5.1.3 for further information.
- l On Day 7, the subject will receive a final 50-µg dose, and should be provided with 7 days of IP supply to dose at the 100-µg dose level and advised to commence this dose level on Day 8 while they are at home. On Day 15, subjects will be given a 200-µg dose during their study visit, and should be provided with 6 days IP supply for dosing at the 200-µg dose level while at home. Subjects should be given the first 300-µg dose on Day 22 and continue this dose level for the remainder of the study.
- m Predose not applicable on Days 7, 29, 36, and 43. An additional blood test for safety (to be taken at any time between Day -3 and Day -7) is not required if the screening visit occurs within 7 days of dosing (Day 1); if the screening visit is more than 7 days prior to dosing on Day 1, then additional safety blood tests should be taken (as described in Section 4.3.3).
- n PK Sampling Schedule for MED10382:
Day -1; No specific time point
Day 1; Predose
Day 7 and Day 15; Predose
Day 22; Predose, 1, 2 (± 15 min); 4, 6, 8, and 12 (± 30 min) hours postdose
Day 23: Predose
Day 29; 36; 43 Predose
Day 49; Predose, 1, 2 (± 15 min); 4, 6, 8, and 12 (± 30 min) hours postdose
Day 50; Predose

^o ADA Sampling Schedule: Day 1 predose; Day 29 predose; Day 50 predose; and 28 days after administration of the last dose in the study

■ [REDACTED]

^q Capillary blood ketone (point-of-care testing) and serum beta-hydroxybutyrate will be measured at baseline after at least 10 hours fasting on Day -1 and predose and 4 hours postdose on Day 22, and Day 49 with fasting for at least 10 hours the night before.

^r MMTT Type A and B Schedule: Following a minimum 10-hour fast overnight and 2.5 hours after taking the IP, a blood sample for glucose (Type B) or glucose metabolism panel [REDACTED] will be taken immediately prior (within 15 minutes) to the subject drinking one entire can of Ensure Plus as a standardised meal (ie, “0 minutes”). Blood samples for glucose metabolism panel will additionally be drawn at 15, 30, 45, 60, 90, 120, 180, and 240 minutes (\pm 5 min) after consumption of the standardised meal.

^s MMTT Type C Schedule: the subject should be fasted from 1400 hours (\pm 15 min) and receive water only from this time until 2000 hours. A standardised liquid meal (one entire can of Ensure Plus) should be administered to the subject at 1800 hours. The subject should ensure that they are wearing their CGM device before, during, and after the test. No additional blood tests are required to be taken during this period, and the subject will be permitted to eat and drink freely from 2000 hours onwards.

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

^u CGM sensor application should occur at approximately 1200 hours on Day -2; thereafter, existing CGM sensors should be removed and a new sensor applied at 1200 hours \pm 20 minutes on Days 7 and at any time on Day 36. On Day 22, the old sensor should be removed and a new sensor applied predose and ideally should be the first study procedure performed at that visit. If the sensor fails, or needs to be replaced, it should be re-applied as soon as possible. The CGM sensor should be removed after 0800 hours on Day 50. Whenever a new CGM sensor is applied, at least 1 hour afterwards, the site staff should place the monitor in close proximity with the sensor to transfer data and ensure that the sensor and monitor are functioning adequately.

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

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

Study Period	Inpatient		Inpatient or daily visits	Inpatient		Inpatient or daily visits	Inpatient		Inpatient or daily visits	Outpatient		Outpatient	
	-2	-1		1	2-6		7	8		9-13	14		15
Visit Number	V2		V3		V4		V5		V6		V7		V8
Procedure													
Verify eligibility criteria ^a		X											
Admit to clinical unit ^b	X				X							X	
Discharge from clinical unit ^c				(X) (D2)		(X)			X				X
Outpatient visit to clinic ^c				(X)						X			X
Medical and disease history	X												
Pregnancy test (if applicable) ^d	X								X			X	
Targeted physical examination	X				X				X		X	X	
Vital signs (BP, heart rate, body temperature, RR) ^e	X		X		X	X		X	X	X	X	X	X
ECG ^f			X		X				X		X	X	
Body weight ^g			X								X	X	
SC injection training	X	X	X										
Randomisation ^h		X											
Subject required to fast overnight for 10 hours ⁱ	X (D-3 and D-2)	X		X (D6)			X (D13)	X		X (D28)	X (D42)	X (D48 and D49)	
IP administration ^j			X	X	X	X							
Up-titration ^k									X	X	X		
Collect blood for:									X	X	X		

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

Study Period	Inpatient		Inpatient or daily visits		Inpatient		Inpatient or daily visits		Inpatient		Outpatient		Inpatient		Outpatient	
	-2	-1	1	2-6	7	8	9-13	14	15	29	43	49	50	7 to 14 Days Post Last Dose		
Study Day																
Haematology panel (predose as applicable) ¹	X (Day -7 to -3)	X	X		X				X	X		X			X	
Serum chemistry panel (predose as applicable) ¹	X (Day -7 to -3)	X	X		X				X	X		X			X	
Lipase and amylase					X				X			X				
Fasting lipid profile					X				X			X				
Calcitonin																
HbA1c		X			X				X			X				
PK for MEDI0382 ^m		X	X	X (D2)	X	X			X	X	X	X	X			
MMTT Type B :blood samples for glucose only ⁿ					X				X							
ADA ^o		X														

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

Study Period	Inpatient		Inpatient or daily visits		Inpatient or daily visits		Inpatient		Outpatient		Outpatient		
	-2	-1	1	2-6	7	8	9-13	14	15	29	43	49	50
Study Day													
Collect urine for;													
Urinalysis (dipstick; predose as applicable)	X		X					X				X	
Drug and alcohol screen	X												
[REDACTED]													
[REDACTED]													
Glucometer and diary provision and capillary blood glucose monitoring ^s	←---Subjects will only be expected to check capillary blood glucose levels if they are unwell or have symptoms of hypoglycaemia--->												
AEs/SAEs	←-----For the duration of the study----->												
Concomitant medications	←-----For the duration of the study----->												

ADA = anti-drug antibody; AE = adverse event; BP = blood pressure; CGM = continuous glucose monitoring; D = day; ECG = electrocardiogram; eCRF = electronic case report form; [REDACTED] GLP-1 = glucagon-like peptide-1; HbA1c = glycated haemoglobin; IP = investigational product; LFT = liver function tests; min = minutes; MMIT = mixed-meal tolerance test; PD = pharmacodynamic(s); PK = pharmacokinetic(s); RR = respiration rate; SAE = serious adverse event; SC = subcutaneous; V = Visit

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

- ^a The eligibility check should be based on all clinical measurements and blood tests taken during the screening visit (V1) with the exception of eGFR, liver function tests, blood pressure, urinary illicit drug, alcohol and pregnancy tests, which should be rechecked on Day -2. A targeted physical examination and repeat medical history should also be undertaken to ensure the subject is well enough to commence dosing.
- ^b The diet of subjects should not be restricted in any way during the study (including during inpatient stay) unless fasting or a standardised meal is specified.

-
- c Subjects who prefer to attend for daily visits will be discharged home on Day 2 and will be readmitted for overnight stays on Day 7 and Day 14.
- d A pregnancy test should be conducted on any female subject of childbearing potential as detailed in the schedule. Pregnancy tests do not need to be conducted in women who are surgically sterile (ie, bilateral tubal ligation, bilateral oophorectomy, or complete hysterectomy) or are postmenopausal (defined as at least 1 year since last menses and having an elevated follicle stimulating hormone laboratory value which is in the postmenopausal range in previous laboratory test results).
- e Vital Signs Schedule (blood pressure, heart rate, respiratory rate, and temperature): On Days 1, 7, and 14 vital signs are to be recorded predose (-15 min) and at 15, 30, 60, 90 (\pm 5 min) minutes and 2 hours postdose (\pm 10 min), and predose (-15 min) at all other times. Vital signs should be performed after the subject has rested in either a seated or supine position for at least 10 minutes prior to the measurement. For time points where ECG recording precedes vital sign measurement, the 10-minute rest in the supine position prior to the ECG suffices for the rest prior to vital sign measurement.
- f A single digital ECG recording should be performed predose after the subject has rested in the supine position for 10 minutes.
- g Body weight should be measured in the morning prior to breakfast (predose on Day 1); the subject should take off their shoes and remove bulky clothing. Calibrated scales should be used.
- h Randomisation may occur on either Day -1 to Day 1 predosing.
- i Subjects are required to fast overnight on the night of Day -3 [REDACTED] -2, -1, 6, 13, 14, 28, 42, 48, and 49.
- j Subjects are required to dose at the clinic on Day 1 – 14 as dilution of dose is required by site staff. Subjects are also required to dose at the clinic on study day visits when predose assessments are required.
- k On Day 14, the subject will receive a final 50 μ g dose; on Day 15 subjects will receive a 100- μ g dose of IP, and should be discharged home with adequate supply of IP for a further 13 days of dosing at the 100- μ g dose level. On Day 29, subjects should receive a 200- μ g dose during their study visit, and again be discharged with 13 days supply of IP for dosing at the 200- μ g dose level. On Day 43, subjects should receive a 300- μ g dose during their study visit and continue this dose until the end of the study.
- l Predose not applicable on Days 7, 15, 29, and 43. An additional blood test for safety (to be taken at any time between Day -3 and Day -7) is not required if the screening visit occurs within 7 days of dosing (Day 1); if the screening visit is more than 7 days prior to dosing on Day 1 then additional safety blood tests should be taken (as described in Section 4.3.3).
- m PK Sampling Schedule for MED10382:
Day -1: No specific time point
Day 1: Predose, 1, 2 (\pm 15 min); 4, 6, 8, and 12 (\pm 30 min) hours postdose
Day 2: Predose
Day 7: Predose, 1, 2 (\pm 15 min); 4, 6, 8, and 12 (\pm 30 min) hours postdose
Day 8: Predose (\pm 15 min)
Day 14: Predose, 1, 2 (\pm 15 min); 4, 6, 8, and 12 (\pm 30 min) hours postdose
Day 15, 29, 43, 49, 50; Predose
- n MMTT Schedule (Type A and Type B): Following a minimum 10-hour fast overnight and 2.5 hours after taking the IP, a blood sample for glucose (Type B) or a glucose metabolism panel [REDACTED] will be taken immediately (within 15 minutes) prior to the subject drinking 1 entire can of Ensure Plus as a standardised meal (ie, “0 minutes”). Blood samples for glucose metabolism panel will

additionally be drawn at 5, 10, 15, 30, 45, 60, 90, 120, 180, and 240 minutes (\pm 5 minutes) after consumption of the standardised meal. The same procedure and schedule applied to MMITT with glucose only measurements.

- o ADA Sampling Schedule: Day 1 predose; Day 29 predose; Day 50 predose; and 28 days after administration of the last dose in the study.

p [REDACTED]

- q Subjects should fast for > 10 hours the night before; in the morning, 2.5 hours postdose (except for the baseline measurement), a baseline blood test for glucose and insulin should be taken alongside a baseline measurement of expired CO₂ just prior to administration of the C¹³-octanoate in conjunction with a standardised solid meal. Subjects will be expected to consume the meal within less than 5 minutes and may be required to be on bed rest until the final breath sample is taken. Collection of expired CO₂ should occur as described in the detailed methods section (Section 4.3.6.1). Where indicated, concurrent blood sampling of glucose and insulin should be performed at t = 0 (baseline), t = 30 min, t = 60 min, t = 120 min and t = 240 min (\pm 5 min) after taking the standardised meal.

r [REDACTED]

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



4.2.3 Follow-up Period

Table 4.2.3-1 shows all procedures to be conducted during the follow-up period.

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

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

Table 4.2.3-1 Schedule of Follow-up Procedures

Study Period	Follow-up Period
Visit Number	Final
Procedure/Study Day	28 days post last dose (\pm 3 days)
Targeted physical examination	X
Weight	X
ECG	X
Vital signs (BP, heart rate, body temperature, RR) ^a	X
ABPM (Cohort 1 only)	X
	
Serum chemistry panel	X
Fasting lipid profile	X
Calcitonin ^c	X
Haematology	X
Urinalysis	X
HbA1c	X
Pregnancy test	X
MEDI0382 ADA ^d	X
Assessment of AEs/SAEs	X
Concomitant medications	X

ABPM = ambulatory blood pressure monitoring; AE = adverse event; ADA = anti-drug antibody; BP = blood pressure; ECG = electrocardiogram; HbA1c = glycated haemoglobin; min = minute; RR = respiration rate; SAE = serious adverse event; ULN = upper limit of normal

- ^a Blood pressure should be measured once at heart level in the nondominant arm where possible, after the subject has rested in either a seated or supine position for at least 10 minutes.
- ^b Subjects should fast for > 10 hours the night before; in the morning, a baseline blood test for glucose and insulin should be taken alongside a baseline measurement of expired CO₂ just prior to administration of C¹³- octanoate in conjunction with a standardised solid meal. Subjects will be expected to consume the meal within less than 5 minutes. Blood sampling of glucose and insulin should be performed at t = 0

Table 4.2.3-1 Schedule of Follow-up Procedures

Study Period	Follow-up Period
Visit Number	Final
Procedure/Study Day	28 days post last dose (± 3 days)

(baseline), t = 30 min, t = 60 min, t = 120 min and t = 240 min (± 5 min) after taking the standardised meal. Concurrent sampling of expired CO₂ should occur as described in the detailed methods section.

^c Only to be repeated if the calcitonin level was > ULN in the sample taken at the end of dosing

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

4.2.3.1 Early Discontinuation Visit or Unscheduled Study Visit

The following study procedures should be conducted for subjects who prematurely discontinue from the study or for subjects who require an unscheduled study visit.

Assessments may be performed in any order:

- Targeted physical examination
- ECG
- Vital signs
- Body weight
- PK for MEDI0382
- Blood tests: Chemistry and haematology panel
- ADA
- Assessment of AEs/serious adverse events (SAEs)
- Concomitant medications
- Pregnancy test (if applicable)

4.3 Description of Study Procedures

4.3.1 Efficacy

4.3.1.1 Mixed-meal Tolerance Tests

Following a minimum 10-hour fast the subject will undergo an MMTT which will involve the consumption of a standardised liquid meal (Ensure Plus, a nutritional supplement containing the components of fat, carbohydrate, and protein, which make up a standard MMTT) within 5 minutes, and timed serial blood samples will be obtained for measurement of glucose and parameters related to glucose metabolism through 240 minutes after

consumption of the standardised meal (with no additional food intake during this time). The MMTT procedures will be performed at the time points specified in the schedules of procedures by cohort.

For Cohort 1 blood will be drawn within 15 minutes before consuming the standardised liquid meal (ie, “0 minutes”), and at 15, 30, 45, 60, 90, 120, 180, and 240 minutes (± 5 minutes) after consumption. Blood sampling should occur as close as possible to the specified times for the MMTT. Sampling ± 5 minutes of the specified time will not be considered a protocol deviation but the exact time of sampling should be recorded.

For Cohort 2, blood will be drawn within 15 minutes before consuming the standardised liquid meal (ie, “0 minutes”), and at 5, 10, 15, 30, 45, 60, 90, 120, 180, and 240 minutes (± 5 minutes) after consumption.

For clarity, MMTTs have been subdivided into Types A, B, and C; according to the timing of the test, and differences in blood sampling schedules.

Ingestion of standardised liquid meals/Ensure as part of an MMTT Type A or B, where relevant, should occur after blood sampling for PK, 2.5 hours after investigational product administration and PD sampling should be arranged in accordance with this schedule.

Mixed-meal Tolerance Test Type A (Cohorts 1 and 2)

[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED] Glucose measurements from these pre- and post-MMTT samples will be used for the primary efficacy assessment and secondary endpoints including fasting glucose and AUC glucose 7 days at the 50 μ g dose level. All MMTT test results will be used to generate PD profiles.

Mixed-meal Tolerance Test Type B (Cohorts 1 and 2)

All timings and procedures are identical to MMTT Type A except for PD sampling which should be for collection of blood glucose samples only.

Mixed-meal Tolerance Test Type C – Cohort 1 only

For subjects in Cohort 1 a standardised liquid meal (Ensure Plus, a nutritional supplement containing the components of fat, carbohydrate, and protein) will be administered on Day -1

at 1800 and also Day 49 at 1800. The subject should consume the Ensure Plus within 5 minutes. The subject will be expected to fast from 1400 hours prior to the test, and to consume water only during this period up until 2000 hours. The subject should be wearing their CGM sensor before, after, and during the test. As the CGM sensor will record interstitial glucose levels, there is no need to perform concurrent blood sampling during this test. From 2000 hours onwards the subject may eat and drink normally. If the subject is required to fast for the next day assessments, fasting should commence from mid-night.

4.3.1.2 Weight

Weight will be measured at the time points specified in the schedules of procedures by cohort(s), after the subject has toileted and removed bulky clothing including shoes. Whenever possible, the same (properly calibrated) scale should be used for each measurement for any given subject.

4.3.2 Safety Assessments

4.3.2.1 Medical History and Physical Examination

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

Physical examinations will be performed by a physician or qualified designee and will include examination of the following body systems: immunologic/allergy; head, ears, eyes, nose, throat; respiratory; cardiovascular; 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.

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

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

4.3.2.2 Assessment of the Injection Site

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

4.3.2.3 Electrocardiograms

At the visits specified in [Table 4.2.1-1](#), [Table 4.2.2-1](#), and [Table 4.2.2-2](#), ECGs will be obtained after 10 minutes supine rest. Only a single ECG will be required at the specified time points. Only the overall evaluation will be recorded in the eCRF.

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

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

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

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

4.3.2.4 Vital Signs

Vital sign measurements (BP, heart 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 procedures for each cohort (for time points where ECG recording precedes vital sign measurement, the 10-minute rest in the supine position prior to the ECG suffices for the rest prior to vital sign measurement). Route of body temperature measurement will be according to local protocols. Where indicated at Days -2 and 49, postural BPs (standing and supine) should be performed.

4.3.3 Clinical Laboratory Tests

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

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

The following clinical laboratory tests will be performed (refer to time points in the schedules of procedures by cohorts):

Serum Chemistry Panel for Safety To Be Taken At Any Time From Day -7 to Day -3 Only

- eGFR
- Potassium
- Sodium
- AST
- ALT
- Alkaline phosphatase (ALP)
- Total bilirubin
- Creatinine
- Blood urea
- Albumin

Hematology Panel for Safety To Be Taken at Any Time From Day -7 to Day -3 Only

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

Serum Chemistry Panel

- Calcium
- Chloride
- Potassium
- Sodium
- Bicarbonate*
- AST
- ALT
- Alkaline phosphatase (ALP)
- Total bilirubin
- Creatinine
- Blood urea
- Albumin
- Magnesium

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.

* may be measured via serum chemistry sample of blood gas analyser per local procedures.

Hematology Panel

- 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* (screening and Day -2 for both cohorts)
- Ketones

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

*Illicit drug panel will test for the following drugs; Amphetamines, barbituates, benzodiazepines, cocaine, opiates (morphine, heroin), methamphetamine, cannabinoids (marijuana), methodone, phencyclidine, methylenedioxy-methamphetamine (ecstasy), propoxyphene, 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.

Other Tests

- Calcitonin
- Alcohol screening test (breath or urine based test)
- Pancreatic amylase, lipase
- [REDACTED]
- Uric acid
- [REDACTED]
- HbA1c
- Anti-drug antibodies

- Serum or urine pregnancy test (females with childbearing potential only)
- HBsAg, hepatitis C antibody (screening only)
- HIV-1, -2 antibodies (screening only)

- Glucose only MMTT (MMTT Type B): Timed glucose

- Fasting lipid profile: high-density lipoprotein, low-density lipoprotein, triglycerides, FFA, and beta-hydroxybutyrate
- Capillary blood ketone levels (point-of-care testing)
- Amino acids

4.3.3.1 Glucometer Measured Capillary Blood Glucose Readings

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

4.3.4 Pharmacokinetic Evaluation and Methods

Blood will be collected to evaluate PK of MEDI0382 in plasma (Table 4.2.2-1 and Table 4.2.2-2 for collection time points). Sampling within the specified window around the specified time will not be considered a protocol deviation but the exact time of sampling should be recorded. The PK of MEDI0382 in plasma will be measured utilising a validated immunoassay method. PK samples should be taken at the specified times and prior to administration of investigational product where indicated, and before meals/other assessments.

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

4.3.5 Immunogenicity Evaluation and Methods

Blood samples will be collected to evaluate ADA responses to MEDI0382 (Table 4.2.2-1 and Table 4.2.2-2 for collection time points). Anti-drug antibody sampling will occur at the time points specified in the schedules of procedures by cohort(s). A screening assay will be used to determine ADA-positive samples. This will be in the form of a traditional ligand-binding

“bridging” assay using electrochemiluminescence. Any positive samples will be tested in a confirmatory assay whereby the specificity of the ADA response will be confirmed as either positive or negative with respect to MEDI0382. Cross-reactivity of ADA-positive samples to GLP-1 and glucagon may also be assessed in the confirmatory assay. Titre evaluation will be performed on samples that are confirmed positive for ADA. [REDACTED] positive ADA result, [REDACTED]
[REDACTED]
[REDACTED]

At the end of study visit, if a subject’s sample is confirmed ADA positive, the subject will be asked to return to provide another sample in approximately 3 months to evaluate whether or not ADAs persist. If the sample taken in 3 months is ADA positive, the subject will be asked to return to provide a sample in another 3 months (ie, 6 months after the end of study visit). If the sample is ADA positive at 6 months, the investigator and the medical monitor will discuss what further action will be taken. Serum samples collected for ADA should be stored for 2 years after marketing approval, and they may be utilised for further characterisation of the antibody response. See Section 10.7 for further details.

4.3.6 Pharmacodynamic Evaluation and Methods

[REDACTED] [REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]

[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]



4.3.6.2 Training for Application and Wearing of CGM Sensor

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

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

4.3.6.3 Training for Application and Wearing of ABPM Device

Subjects will be given training at their local study site about how to set up and apply the ABPM device. In brief, an appropriate size cuff encircling 80% to 100% of the arm will be selected and the device will be fitted to the nondominant arm of the subject, with the bladder placed over the artery and an initial test reading performed. The subjects will be advised that for the first reading the device will inflate to a pressure of 180 mm Hg, and thereafter the device will adapt to inflate to a pressure just above the last recorded BP. The subject will be advised to undergo normal daily activities while wearing the cuff, and he/she will be advised to avoid any strenuous form of activity, bathing, or showering while wearing the cuff. The subject will be advised to remain still during a measurement with the arm relaxed at heart level. The subject will also be given advice on how to wear the device during the day and at night while sleeping, and what to expect in terms of frequency of readings during the day (every 15 minutes) and overnight (every 30 minutes). During ABPM, systolic BP, diastolic BP, heart rate pressure, heart rate, and mean arterial pressure readings will be recorded over a period of 24 hours.

[REDACTED]

[REDACTED]

4.3.7.2 Storage, Re-use, and Destruction of Pharmacodynamic Samples

Samples will be stored for a maximum of 15 years from the date of the Last Subject's Last Visit, after which they will be destroyed. The results of any investigation will be reported either in the clinical study report itself or as an addendum, or separately in a scientific report or publication.

4.3.8 Estimate of Volume of Blood to Be Collected

The estimated volume of blood to be collected from each subject over the entire course of their participation in the study is 342 mL for Cohort 1 and 439 mL for Cohort 2. 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 terminate this study at any time. The reasons for temporarily suspending or terminating the study may include but are not limited to the following:

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

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

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

4.5 Investigational Products

4.5.1 Identity of Investigational Products

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

Table 4.5.1-1 Identification of Investigational Products

Investigational Product	Manufacturer	Concentration and Formulation as Supplied
MEDI0382	MedImmune	2 mg/mL liquid formulation
Matched placebo	MedImmune	Solution
Normal saline	NA	9 g/L NaCl solution

NA = not applicable; NaCl = sodium chloride

Note: Diluent (solution manufactured by MedImmune) will be provided to sites for use in the event that a dose level requires dilution. The diluent solution is the same as the matched placebo, and diluent and matched placebo are provided in the same vials. Matched placebo will be used for dilution for the 50 µg doses only.

[REDACTED]

[REDACTED]

Investigational product will be supplied to the site in blinded kits each containing 1 vial. Each kit has a unique number that is printed on all labels within the kit (ie, the outer carton label and the label of the vial within the carton). When supplying the investigational product for at-home dosing, the 1-vial kits will be supplied in an additional take-home carton.

4.5.1.1 Investigational Product Dose Preparation

In-clinic Investigational Product Handling

Investigational product should be stored at 2°C to 8°C in the original container. Investigational products do not contain preservatives and any unused portion must be discarded. Preparation of syringes for dose administration is to be performed aseptically. Total in-use storage time from needle puncture of the investigational product vial to start of administration should not exceed 4 hours. If storage time exceeds these limits, a new dose must be prepared from new vials.

At-home Investigational Product Handling

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

The subject is to remove from the refrigerator only the 1-vial kit required for their daily dose. All other kits are to be kept in the outer carton in the refrigerator until required. The subject is to avoid the risk of freezing the investigational product by carefully placing the investigational product within their refrigerator, and should not use investigational product if it has been frozen. The subject is not to administer investigational product if the time outside of the refrigerator has exceeded 24 hours; if storage time exceeds this limit, a new dose must be prepared from a new vial. After use, the subject is to retain the vial during the at-home self-administration period for return to the site (along with any unused vials) for accountability at the weekly visit. The subject should be instructed not to re-use the vial (vials are single-use only) after administration of a single dose. Investigational product should be protected from heat and light. The needle should always be removed and safely discarded after each use.

4.5.1.2 Investigational Product Inspection

Each vial selected for dose preparation should be inspected. MEDI0382 is supplied as a liquid solution at a concentration of 2 mg/mL.

If there are any defects noted with the investigational product, the investigator and site Monitor should be notified immediately. Refer to the Product Complaint section for further instructions (Section 4.5.1.6).

4.5.1.3 Dose Preparation Steps

The final delivery volume and concentration for each dose level and the syringe sizes to be used for preparation are described in Table 4.5.1.3-1.

Table 4.5.1.3-1 MEDI0382 and Placebo Dose Preparation

Dose Level	Formulation Stock Concentration (mg/mL)	Volume of Injection (mL)	Number of Units ^b	Syringe Size
50 µg or placebo	0.2	0.25 ^a	NA	1 mL
100 µg or placebo	2.0	0.05	5	0.3 mL
200 µg or placebo	2.0	0.1	10	0.3 mL
300 µg or placebo	2.0	0.15	15	0.3 mL

^a For the 50 µg dose, the stock concentration will be achieved by dilution in the clinic.

^b The 0.3-mL syringe is marked in “units” where each unit = 0.01 mL and 0.15 mL = 15 units.

No incompatibilities between MEDI0382 and plastics passing compatibility tests (ie, polyolefin or polyvinylchloride syringes) have been observed.

1. Investigational product is supplied in 3-mL glass vials at a nominal concentration of 2 mg/mL.
2. Determine from [Table 4.5.1.3-1](#) the correct dose level and injection volume.
3. For doses of 50 ug a 10-fold diluted stock concentration of 0.2 mg/mL will be prepared by site staff at the clinical unit, prior to administration.
4. To make a 10-fold diluted MEDI0382, it is recommended to take 0.1 mL of MEDI0382 investigational product using a needle and 1-mL syringe, add it into a sterile empty vial, followed by addition of 0.9 mL of diluent into the same vial using a needle and 1-mL syringe. The vial should be mixed by swirling gently to make a homogenous final admixture. Do not shake. The diluted dose should be administered using a 1-mL syringe.

The 100- μ g, 200- μ g, and 300- μ g doses do not require a dilution step and should be administered using a 0.3-mL syringe. For the 50 μ g dose, dilution steps will need to be carried out by site staff at the clinical unit.

At-home Dose Preparation Steps

No dilution steps for preparation of investigational product will be performed by the subject at home; all dilution steps will be performed at the study site. The 50- μ g dose is always administered in the clinic.

4.5.1.4 Treatment Administration

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

In-clinic Treatment Administration

The first day of dosing is considered Day 1. On the day of each dose, investigational product will be administered according to the schedule of procedures. On study days where fasting is required for an additional assessment, the investigational product should be taken 2.5 hours prior to any MMTT [REDACTED]. Investigational product will be administered by SC injection in the lower abdomen utilising either a 0.3-mL or a 1-mL insulin syringe according to the dose level. Refer to the Investigational product manual.

At-home Treatment Administration

Investigational product should be removed from the refrigerator for at least 15 minutes for temperature equilibration.

A once-daily dose is to be self-administered by SC injection using a 0.3-mL insulin syringe as soon as practicable upon waking each morning prior to breakfast. The investigational product is packaged in a carton with sufficient vial kits. Each vial contains 1 mL of liquid product with adequate overfill. The carton must be stored in the refrigerator. Refer to the home dosing instructions.

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

4.5.1.5 Monitoring of Dose Administration

As with any exogenous peptide delivered subcutaneously, allergic reactions to dose administration are possible. In prior experience with MEDI0382 there has been one injection site reaction and no anaphylactoid reactions. During visits to the clinical unit, the site of administration will be checked for signs of injection site reaction as required (Section 4.3.2.2).

4.5.1.6 Reporting Product Complaints

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

MedImmune contact information for reporting product complaints:

Email: productcomplaints@medimmune.com

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

Fax: +1-301-398-8800

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

4.5.2 Additional Study Medications

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

4.5.3 Labeling

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

4.5.4 Storage

Store investigational product at the clinical site at 2°C to 8°C. Investigational product taken home by the subject must be stored in a refrigerator and must not exceed 25°C.

4.5.5 Treatment Compliance

Investigational product is administered by study site personnel, who will monitor compliance.

4.5.6 Accountability

The investigator's or site's designated investigational product manager is required to maintain accurate investigational product accountability records. Upon completion of the study, copies of investigational product accountability records will be returned to MedImmune. All unused investigational product will be returned to a MedImmune-authorized depot or disposed of upon authorization by MedImmune.

4.6 Treatment Assignment and Blinding

4.6.1 Methods for Assigning Treatment Groups

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

4.6.1.1 Cohort 1

Subjects will be randomised using a ratio of 2:1 to one of 2 treatment arms to receive either MEDI0382 titrated up to 300 µg or placebo. Sufficient subjects will be invited to participate

in the study such that a maximum of 26 will complete dosing in the active arm and 13 will complete dosing in the placebo arm.

4.6.1.2 Cohort 2

Subjects will be randomised using a ratio of 3:1 to receive either MEDI0382 titrated up to 300 µg or placebo respectively. Sufficient subjects will be invited to participate in the study such that a maximum of 18 will complete dosing in the active arm and 6 will complete dosing in the placebo arm.

4.6.2 Methods for Ensuring Blinding

This is a double-blind study in which MEDI0382 and placebo are identically labeled and indistinguishable in appearance. As such, 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). (See Section 4.6.3.2 for unblinding related to the interim analysis.) In the event that treatment allocation for a subject becomes known to the investigator or other study staff involved in the management of study subjects, the sponsor must be notified *immediately*.

4.6.3 Methods for Unblinding

4.6.3.1 Unblinding in the Event of a Medical Emergency

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

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.

4.6.3.2 Unblinding for Interim Analysis Purposes

An interim analysis is planned for this study after the last subject has received their last dose as described in Section 4.8.6. Only the study team pharmacokineticist will be unblinded and only descriptive PK analyses will be performed. The unblinded pharmacokineticist will stop

day-to-day work on the study and other pre-selected personnel will take over these roles for the remainder of the trial.

4.7 Restrictions During the Study and Concomitant Treatment(s)

The investigator must be informed as soon as possible about any medication taken from the time of screening until the end of the study (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, antiemetics, 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 including over-the-counter medications, herbal supplements, vitamin, etc 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.

Subjects should not be initiated on any new medications to control blood glucose levels during the dosing and follow-up period unless it is deemed necessary by the investigator for safety and following discussion with the medical monitor. Refer to Section 3.1.4.3 for further details.

- 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 study (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 study (Visit 2)

- Concurrent use of aspirin (acetylsalicylic acid) at a dose greater than 150 mg once daily and within the last 72 hours prior to the start of the study (Visit 2)
- Concurrent use of paracetamol (acetaminophen) at a total daily dose greater than 3000 mg once daily and within the last 72 hours prior to the start of the study (Visit 2)
- Concurrent use of ascorbic acid (vitamin C) at a total daily dose of > 1000 mg and within the last 72 hours prior to the start of the study (Visit 2)
- Concurrent use of opiates, domperidone, metoclopramide, or other drugs [REDACTED] within 2 weeks prior to the start of the study (Visit 2) [REDACTED]
- Concurrent use of medications (other than metformin) for control of blood glucose within 4 weeks prior to the start of the study (Visit 2) unless it is deemed necessary by the investigator for safety reasons.

4.8 Statistical Evaluation

4.8.1 General Considerations

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

4.8.1.1 Analysis Populations

Efficacy Analysis Set

The Intent-to-treat (ITT) population includes all subjects who receive at least one dose of any investigational product and will be analysed according to their randomised treatment group.

Safety Analysis Set

The As-treated population includes all subjects who receive at least one dose of any investigational product and will be analysed according to the treatment they actually receive.

PK Analysis Set

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

[REDACTED]

4.8.3 Efficacy

4.8.3.1 Primary Efficacy Analysis

The efficacy analysis will be based on the ITT population. The coprimary efficacy endpoints of percentage glucose AUC change and percentage weight change from baseline to 49 days (Section 2.1) will be compared between MEDI0382 and placebo arms, using an analysis of covariance (ANCOVA) model, adjusting for treatment and measurement at baseline.

4.8.3.2 Secondary Efficacy Analyses

For analyses of the secondary endpoints (Section 2.2), an ANCOVA model similar to the primary efficacy analysis will be used for continuous endpoints. For proportion-related endpoints, a logistic regression model will be used with fixed effects of treatment and baseline measurement. For the secondary endpoint evaluating glucose AUC reduction at the 50 µg dose level, only glucose readings taken at 0, 15, 30, 45, 60, 90, 120, 180, and 240 minutes will be used in this analysis.

4.8.3.3 Exploratory Analyses

For analyses of the exploratory endpoints (Section 2.3), an ANCOVA model similar to the primary efficacy analysis will be used for continuous endpoints. For proportion-related endpoints, a logistic regression model will be used with fixed effects of treatment and baseline measurement.

4.8.4 Safety

AEs and SAEs will be coded by the most updated version of Medical Dictionary for Regulatory Activities (MedDRA), and the type, incidence, severity, and relationship to study investigational product will be summarised by MedDRA System Organ Class and Preferred

Term and by treatment. AEs leading to discontinuation, AEs leading to death, and deaths will also be summarised and will be marked in the listings or will be in a separate listing. Specific AEs will be counted once for each subject for calculating percentages. In addition, if the same AE occurs multiple times within a particular subject, the highest severity and level of relationship observed will be reported. Subject-level data listings of all AEs will be presented.

4.8.4.1 Analysis of Clinical Laboratory Parameters

Other safety data, such as vital signs, clinical laboratory data, ECG, and physical examination findings, will be descriptively summarised at each time point by treatment. Mean ambulatory BP and heart rate measurements recorded over 24 hours at different time points will be analysed using an ANCOVA model, adjusting for treatment and measurement at baseline. ADA incidence rate and titre will be tabulated for each treatment.

4.8.5 Analysis of Immunogenicity/Pharmacokinetics

Pharmacokinetic parameters such as MEDI0382 C_{max} , T_{max} , AUC, and $T_{1/2}$ will be estimated if data allow, from plasma concentration time data for MEDI0382 at the 50 and 300 μg dose level separately.

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

The incidence and impact of ADA to MEDI0382 will be evaluated. The number and percentage of subjects with confirmed positive serum antibodies to MEDI0382 will be reported by dose level. Data on titres and cross-reactivity to GLP-1 and glucagon (where applicable) will be listed. If warranted by the data, the association of ADA positive with observed PK data may be explored.

4.8.6 Interim Analysis

An interim database lock for analysis of PK data only will be performed just after last subject last dose. Only the study team pharmacokineticist will be unblinded at this stage and will use the data to perform descriptive PK analyses. All other analyses will take place after final database lock.

5 ASSESSMENT OF SAFETY

5.1 Definition of Adverse Events

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

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

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

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

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

5.2 Definition of Serious Adverse Events

An SAE is any AE that:

- Results in death
- Is immediately life-threatening
- Requires inpatient hospitalisation or prolongation of existing hospitalisation
- 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 jeopardise 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 hospitalisations; or development of drug dependency or drug abuse.

5.3 Definition of Adverse Events of Special Interest

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

All AESIs should be recorded in the eCRF within 24 hours. In addition, AESIs that are also SAEs should be reported to the appropriate sponsor representative within 24 hours. Instructions to the site on how to record (in the eCRF) and report an AESI are provided in Section 5.3.1 and Section 10.5, respectively. The AESIs for this study are defined below.

5.3.1 Hepatic Function Abnormalities

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

5.4 Recording of Adverse Events

Adverse events will be recorded on the eCRF using a recognised medical term or diagnosis that accurately reflects the event. Adverse events will be assessed by the investigator for severity, relationship to the investigational product, possible aetiologies, and whether the event meets criteria of an SAE and therefore requires immediate notification to the sponsor

(Section 5.5). See Section 5.2 for the definition of SAEs and 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 in the eCRF.

5.4.1 Time Period for Collection of Adverse Events

All AEs will be collected from the time of admission to the clinical unit (Day -2 for Cohort 1 and Day -2 [REDACTED] for Cohort 2) throughout the treatment period and including the follow-up period (7 to 14 days after the last dose of investigational product; Visit 10 for Cohort 1 [Table 4.2.2-1] and Visit 8 [Table 4.2.2-2] for Cohort 2). Additionally, all SAEs will be collected from time of signature of informed consent throughout the treatment period and including the follow-up period as described above.

5.4.2 Follow-up of Unresolved Adverse Events

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

5.5 Reporting of Serious Adverse Events

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

If any SAE occurs during the course of the study, the investigator or other site personnel will inform the appropriate sponsor representative(s) within 1 day; ie, immediately but no later than 24 hours of when he or she becomes aware of the event.

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

For fatal or life-threatening AEs where important or relevant information is missing, active follow-up is undertaken immediately. Investigators or other site personnel will inform sponsor representatives of any follow-up information on a previously reported SAE within

1 calendar day; ie, immediately but no later than 24 hours of when he or she becomes aware of the event.

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

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

5.6 Other Events Requiring Immediate Reporting

5.6.1 Overdose

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

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

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

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

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

5.6.2 Hepatic Function Abnormality

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

5.6.3 Pregnancy

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

5.6.3.1 Maternal Exposure

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

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

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

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

The same timelines apply when outcome information is available.

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

6 STUDY AND DATA MANAGEMENT

6.1 Training of Study Site Personnel

Before the first subject is entered into the study, a MedImmune representative will review and discuss the requirements of the Clinical Study Protocol and related documents with the

investigational staff and also train them in any study-specific procedures and system(s) utilised.

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

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

6.2 Monitoring of the Study

During the study, 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 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 Clinical Study Protocol and the Clinical Study Agreement, the

terms of Clinical Study Protocol shall prevail with respect to the conduct of the study and the treatment of subjects and in all other respects, not relating to study conduct or treatment of subjects, the terms of the Clinical Study Agreement shall prevail.

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

6.2.3 Archiving of Study Documents

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

6.3 Study Timetable and End of Study

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

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

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

6.4 Data Management

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

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

The investigator ensures the accuracy, completeness, and timeliness of the data recorded and 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 (ICF) will incorporate (or, in some cases, be accompanied by a separate document incorporating) wording that describes how subject data will be collected, used, and distributed in compliance with relevant data protection and privacy legislation.

[REDACTED]

7.2 Ethics and Regulatory Review

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

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

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

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

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

Before the study is initiated, MedImmune will ensure that the national regulatory authority in each country has been notified and their approval has been obtained, as required.

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

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

7.3 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 ICF for use by all investigators in the clinical study. MedImmune must approve any modifications to the ICF 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 ICF 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 principal investigator(s). Before

implementation, amended protocols must be approved by relevant IEC (Section 7.2) and according to local requirements, the national regulatory authority approval. The IEC must also approve revisions to the ICF, advertising, and any other written information and/or materials resulting from the change to the protocol.

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

7.5 Audits and Inspections

Authorized representatives of MedImmune, a regulatory authority, or an 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, GCP, guidelines of the ICH, and any applicable regulatory requirements. The investigator will contact MedImmune immediately if contacted by a regulatory agency about an inspection at the site.

8 REFERENCES

Bagger et al, 2015

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

CDER, 2005

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

Exenatide, 2016

Exenatide SmPc. Saxenda Prescribing Information. 2016. Available from: URL: <http://www.novo-pi.com/saxenda.pdf>.

Gagliardi et al, 2009

Gagliardi AC, Miname MH, Santos RD. Uric acid: a marker of increased cardiovascular risk. *Atherosclerosis.* 2009 Jan;202(1):11-7.

Habegger et al, 2013

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

Keller and Shulman, 1979

Keller U, Shulman G. Effect of glucagon on hepatic fatty acid oxidation and ketogenesis in conscious dogs. *Am J Physiol.* 1979 Aug;237(2):E121-9.

[REDACTED]

Lynch et al, 2014

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

Meier, 2012

Meier JJ. GLP-1 receptor agonists for individualized treatment of type 2 diabetes mellitus. *Nat Rev Endocrinol.* 2012;8(12):728-42.

[REDACTED]

Orskov et al, 1996

Orskov C, Poulsen SS, Møller M, Holst JJ. Glucagon-like peptide I receptors in the subfornical organ and the area postrema are accessible to circulating glucagon-like peptide I. *Diabetes.* 1996 Jun;45(6):832-5.

Petersen et al, 2005

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

Skyder et al, 2017

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

Victoza, 2014

Victoza (liraglutide) 6 mg/mL for injection in pre-filled pen (Summary of Product Characteristics [SPC]). Last updated 2016 December 07; Novo Nordisk Limited, West Sussex, United Kingdom. Available from: URL:

http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/001026/WC500050017.pdf

Wynne et al, 2006

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

9 CHANGES TO THE PROTOCOL

9.1 Protocol Amendment 2, 17Oct2017

Text revisions resulting from this amendment are incorporated in the body of Protocol Amendment 2. Key changes to the protocol are summarized in the table below.

Table 9.1-1 Summary of Revisions to the Protocol

Key Details of Amendment	Reason for Amendment
Amendment 2 / 17Oct2017	
Table 4.2.2-1 (Schedule of Treatment Period Study Procedures: Cohort 1)	Footnote “u” amended to clarify that a new CGM can be applied at any time on Day 36, and that the CGM sensor should be removed after 0800 hours on Day 50.
Table 4.2.1-1 (Schedule of Screening Procedures), Table 4.2.2-1 (Schedule of Treatment Period Study Procedures: Cohort 1), Table 4.2.2-2 (Schedule of Treatment Period Study Procedures: Cohort 2), Table 4.2.3-1 (Schedule of Follow-up Procedures) and Section 4.3.2.4 (Vital Signs)	Table footnotes and text in Section 4.3.2.4 amended to clarify that vital signs can be taken after a subject has rested for 10 minutes in a seated or supine position.
Table 4.2.2-1 (Schedule of Treatment Period Study Procedures: Cohort 1) and Table 4.2.2-2 (Schedule of Treatment Period Study Procedures: Cohort 2)	Text added to clarify that the additional blood test for safety should be taken at any time between Day -7 and Day -3, if required.
Table 4.2.2-2 (Schedule of Treatment Period Study Procedures: Cohort 2)	The instruction to fast on the night of Day 7 was removed from footnote “i” to correct a previous oversight.
Table 4.2.3-1 (Schedule of Follow-up Procedures)	Text referring to a postdose sample in footnote “b” was removed to correct a previous oversight.
Section 4.2.3.1 (Early Discontinuation Visit or Unscheduled Study Visit)	Text was edited to allow flexibility around the order of assessments based on site feedback.
Section 4.3.1.1 (Mixed-meal Tolerance Tests)	The timeframe to consume a standardised liquid meal was changed from “15 minutes” to “5 minutes” to correct a previous oversight.
Section 5.4.1 (Time Period for Collection of Adverse Events)	The timeframe of SAE collection was updated for consistency with internal MedImmune processes.
Section 5.6.3.1 (Maternal Exposure)	Text was amended to state that women of childbearing potential in this study who are sexually active with a nonsterilized male partner are required to use 1 form of contraception. This change was made to correct a previous oversight and for consistency with the inclusion criteria.
Section 10.2 (Appendix 2-Contraception Guidance)	Text in bold added to the definition of postmenopausal to correct a previous oversight: “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.”

9.2 Protocol Amendment 1, 25Jul2017

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

Table 9.2-1 Summary of Revisions to the Protocol

Key Details of Amendment	Reason for Amendment
Amendment 1 / 25Jul2017	
Synopsis	Changes made to be consistent with the body of the protocol
[REDACTED]	[REDACTED]
Section 3.1.1 Overview, Section 4.3.3 Clinical Laboratory Tests	Subjects will undergo safety blood tests at any time from Day -7 to Day -3 if the screening visit is more than 7 days before Day 1 at the request of the ethics committee.
Section 3.1.4.3 Hyperglycemia	Additional guidance around management of hyperglycemia was added in response to feedback from the ethics committee.
Section 4.1.3 Exclusion criteria	Additional criterion #19 was added at the request of the ethics committee to exclude subjects with a history of acute or chronic pancreatitis or other diseases of the pancreas. Definition of hypertension was modified based on feedback from the ethics committee.
Section 4.1.3 Exclusion criteria, Table 4.2.1-1 Schedule of Screening Procedures, Table 4.2.2-1 Schedule of Treatment Period Study Procedures: Cohort 1, Section 4.3.3 Clinical Laboratory Tests	Additional criteria for alcohol abuse or excessive alcohol intake were added to the protocol in response to a request from the German Federal Institute for Drugs and Medical Devices (Bundesinstitut für Arzneimittel und Medizinprodukte [BfArM]).
Section 4.1.7 Replacement of Subjects	Stipulation that a maximum number of five subjects may be replaced in each cohort in response to a request from the BfArM.
Section 4.7.2 Prohibited Concomitant Medications	Additional restrictions around initiation of new medications to control blood glucose levels were included in response to a request from the BfArM.
Table 4.2.2-1 Schedule of Treatment Period Study Procedures: Cohort 1	Table footnote corrected to state that for MMTT Type C the subject should be fasted from 1400 hours. Correction of typographical error. Screening blood samples were added at the request of the ethics committee.
Table 4.2.2-2 Schedule of Treatment Period Study Procedures: Cohort 2	The table cells were corrected so that randomization occurs on Day-1 to Day 1 consistent with other

Table 9.2-1 Summary of Revisions to the Protocol

Key Details of Amendment	Reason for Amendment
	<p>sections of the protocol. The uptitration schedule was also corrected from Day 14 to Day 15.</p> <p>Footnote describing timings for MMTT Type A and Type B was corrected to be consistent with other sections of the protocol.</p> <p>Correction of typographical errors.</p> <p>Screening blood samples were added at the request of the ethics committee.</p>
Section 4.3.1.1 Mixed-meal Tolerance Tests	<p>Text describing the timing of consumption of Ensure Plus (within 15 minutes) was clarified to be consistent with other sections of the protocol.</p> <p>Correction of typographical error.</p>
Section 4.3.2.4 Vital Signs	<p>Corrected to state that vital signs measurements will be taken with the subject in a seated position.</p> <p>Correction of typographical error.</p>
Table 4.5.1.3-1 MEDI0382 and Placebo Dose Preparation	<p>The number of units for the 300 µg dose was corrected to 15.</p> <p>The example given for units calculation has been changed to be consistent with the table for clarity.</p> <p>Correction of typographical error.</p>
Section 4.5.1.4 Treatment Administration	<p>Clarification that investigational product will be administered by SC injection in the lower abdomen utilising either a 0.3-mL or a 1-mL insulin syringe according to the dose level.</p> <p>Correction of typographical error.</p>
Section 4.3.8 Blood Volumes	<p>Total blood volumes to be drawn in both cohorts have been reduced.</p>
Section 4.7.2 Prohibited Concomitant Medication	<p>Additional guidance around the allowed use of concomitant medications to control blood glucose were added at the request of the ethics committee.</p>
Section 4.8.2 Sample Size and Power Calculations	<p>The overall power for both primary endpoints was added at the request of the ethics committee.</p>
Table 10.2-1 Highly Effective Methods of Contraception	<p>The table has been modified to remove reference to oral contraceptives at the request of the ethics committee.</p>

10 APPENDICES

10.1 Appendix 1 - Signatures

Sponsor Signature(s)

A Phase 2, Randomised, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy, Safety, Tolerability, and Pharmacokinetics of Different Doses of MEDI0382 in Overweight and Obese Subjects with Type 2 Diabetes Mellitus

I agree to the terms of this protocol.

Signature and date: _____ Electronic signature attached _____

████████████████████

████████████████████

One MedImmune Way, Gaithersburg MD, 20878, USA

████████████████████

Signature of Principal Investigator

A Phase 2, Randomised, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy, Safety, Tolerability, and Pharmacokinetics of Different Doses of MEDI0382 in Overweight and Obese Subjects with Type 2 Diabetes Mellitus

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

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

Signature and date: _____

Name and title: _____

Address including postal code: _____

Telephone number: _____

Site/Center Number (if available) _____

This document contains confidential information, which should not be copied, referred to, released, or published without written approval from MedImmune or AstraZeneca. Investigators are cautioned that the information in this protocol may be subject to change and revision.

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 10.2-1](#).

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

Table 10.2-1 Highly Effective Methods of Contraception

<ul style="list-style-type: none">• 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 AE as it occurred or it is suspected that use or continued use of the product would result in the subject’s death. ‘Life-threatening’ does not mean that had an AE occurred in a more severe form it might have caused death (eg, hepatitis that resolved without hepatic failure).

Hospitalisation

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

Important Medical Event or Medical Intervention

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

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

Examples of such events are:

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

Assessment of Severity

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

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

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

Assessment of Relationship

Relationship to Investigational Product

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

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

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

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

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

Relationship to Protocol Procedures

The investigator is also required to provide an assessment of relationship of SAEs to protocol procedures on the SAE Report Form. This includes 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 Disease (NAID) and Food Allergy and Anaphylaxis Network (FAAN) define anaphylaxis as a serious allergic reaction that is rapid in onset and may cause death. They recognise 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, generalised 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), hypoxaemia)
 - b. Reduced BP or associated symptoms of end-organ dysfunction (eg, hypotonia [collapse], syncope, incontinence)
2. Two or more of the following that occur rapidly after exposure to a likely allergen for that patient (minutes to several hours):
 - a. Involvement of the skin-mucosal tissue (eg, generalised hives, itch-flush, swollen lips-tongue-uvula)
 - b. Respiratory compromise (eg, dyspnoea, wheeze-bronchospasm, stridor, reduced PEF, hypoxaemia)
 - 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

Introduction

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

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

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

The investigator is responsible for recording data pertaining to PHL/HL cases and for reporting adverse events (AE) and serious adverse events (SAE) according to the outcome of the review and assessment in line with standard safety reporting processes.

Definitions

Potential Hy's Law (PHL)

Aspartate aminotransferase or ALT $\geq 3 \times$ upper limit of normal (ULN) together with total bilirubin (TBL) $\geq 2 \times$ ULN at any point during the study following the start of investigational product irrespective of an increase in alkaline phosphatase (ALP).

Hy's Law (HL)

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

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

Identification of Potential Hy's Law Cases

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

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

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

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

Follow-up

Potential Hy's Law Criteria Are Not Met

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

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

Potential Hy's Law Criteria Are Met

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

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

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

Review and Assessment of Potential Hy's Law Cases

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

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

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

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

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

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

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

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

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

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

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

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[Redacted]

[Redacted]

[Redacted]

[Redacted]

[Redacted]

[Redacted]

[Redacted]

[Redacted]

[Redacted]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[Redacted text block]

[Redacted text block]

[Redacted text block]

[Redacted text block]

10.7 Appendix 7 Biological Samples

Storage, Re-use and Destruction of Biological Samples

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

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

Labelling and Shipment of Biological Samples

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

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

Chain of Custody of Biological Samples

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

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

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

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

Document Name:		d5670C00011-protocol-amendment-2	
Document Title:	d5670C00011-protocol-amendment-2		
Document ID:	Doc ID-003705066		
Version Label:	1.0 Approved CURRENT LATEST		
Server Date (dd-MMM-yyyy HH:mm 'GMT'Z)	SignedBy	Meaning of Signature	
17-Oct-2017 16:56 GMT+0100	██████████	Biostatistics Approval	
17-Oct-2017 17:05 GMT+0100	██████████	Research Approval	
17-Oct-2017 17:07 GMT+0100	██████████	Clinical Operations Approval	
17-Oct-2017 17:36 GMT+0100	██████████	Medical Monitor Approval	
18-Oct-2017 08:05 GMT+0100	██████████	Clinical Approval	

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