Clinical Study Protocol	
Drug Substance	MEDI0382
Study Code	D5674C00001
Version	8.0
Date	12 June 2019

A Phase IIa, Randomised, Parallel, Double-Blind, Placebo-Controlled Study to Evaluate the Safety, Efficacy, and Pharmacokinetics of MEDI0382 in Japanese Preobese or Obese Subjects with Type 2 Diabetes Who Have Inadequate Glycemic Control with Diet and Exercise

Sponsor:

Astrazeneca K.K. 3-1, Ofuka-cho, Kita-ku, Osaka 530-0011, Japan

VERSION HISTORY

Version 1.0, 18 May 2018
Initial creation
Version 2.0, 18 June 2018
2.2 Background: Findings from Study D5670C00011 was added. 4.3 Justification for dose: Findings from completed clinical studies was added. 6.1.2 Medical devices: A typo was corrected. 6.5.2 Other concomitant treatment: Reporting process of adverse events due to self-injection was added. 6.5.3 Rescue medication: Monitoring process for significant vomiting was added. 8.1.4 Continuous glucose monitoring (CGM): Data handling and reporting process were clarified. 8.2.1 Clinical safety laboratory assessments: Duplications were corrected. 8.2.5.1 Ambulatory Blood Pressure Monitoring: Data handling and reporting process were clarified. 8.2.5.2 Daily Diaries: Any other events was added. 8.4.2.1 Maternal exposure: Reporting process was clarified. 8.4.4.3 Reporting of medical device incidents to sponsor: Reporting process was clarified. Appendix G: Created new.
Version 3.0, 17 July 2018
1.1 Schedule of Activities (SoA) Table2 Note i：A typo was corrected. 6.3.1 Methods for ensuring blinding：Blinding process was clarified. 6.5.3 Rescue medication Rescue process was clarified. Appendix G: Order was arranged. Appendix H: Order was arranged.
Version 4.0, 8 August 2018
1.1 Schedule of Activities (SoA) Table2：Withdrawal test was added and clarified. 1.1 Schedule of Activities (SoA) Table2: Note i Withdrawal test was clarified. 1.1 Schedule of Activities (SoA) Table2：Note o Created new. 1.2 Synopsis Study Period: Estimated date of last patient completed was extended. 6.3.1 Methods for ensuring blinding: Blinding process was clarified. 7.1.1 Procedures for discontinuation of study treatment: Discontinuation treatment was clarified.
Version 5.0, 4 September 2018
1.1 Schedule of Activities (SoA) Table1: Laboratory assessment was added. 1.1 Schedule of Activities (SoA) Table2: Change in measurement item from glycoalbumin to fructosamine. This change does not affect the efficacy evaluation and makes the measurement more convenient. 1.2 Synopsis: Change in measurement item from glycoalbumin to fructosamine. This change does not affect the efficacy evaluation and makes the measurement more convenient.

3 OBJECTIVES AND ENDPOINTS: Change in measurement item from glycoalbumin to fructosamine. This change does not affect the efficacy evaluation and makes the measurement more convenient. 4.2.2.2 Rationale for Secondary Endpoints: Change in measurement item from glycoalbumin to fructosamine. This change does not affect the efficacy evaluation and makes the measurement more convenient. 6.3.1 Methods for ensuring blinding: Change in measurement item from glycoalbumin to fructosamine. This change does not affect the efficacy evaluation and makes the measurement more convenient. Blinding process was clarified. 8 STUDY ASSESSMENTS AND PROCEDURES: Change the amount of blood and description was clarified. 8.1.3 HbA1c, Fasting plasma glucose and fructosamine : Change in measurement item from glycoalbumin to fructosamine. This change does not affect the efficacy evaluation and makes the measurement more convenient. 8.2.1 Clinical safety laboratory assessments:S-ketone to beta-hydroxybutyrate due to change of measurement item. Change in measurement item from glycoalbumin to fructosamine. This change does not affect the efficacy evaluation and makes the measurement more convenient. Laboratory assessment item was clarified. 8.7.1 Collection of samples: Description was clarified. Appendix H: Delete GA.
Version 6.0, 18 October 2018
1.2 Synopsis Objectives and Endpoints/Secondary Objectives/Endpoint/variable: Correction of typo in the evaluation schedule of CGM. 1.2 Synopsis Study Period: Estimated date of last patient completed was extended. 3 OBJECTIVES AND ENDPOINTS Table 5 Study objectives/Secondary Objective/Endpoint/Variable: Correction of typo in the evaluation schedule of CGM. 6.3.1 Methods for ensuring blinding: Description was clarified. 6.5.3 Rescue medication: Target period for rescue medication was clarified. 8 STUDY ASSESSMENTS AND PROCEDURES: Correction of the amount of blood draw. 8.7 Pharmacodynamics: Description was clarified.
Version 7.0, 17 May 2019
1.2 Synopsis Study Period: Estimated date of last patient completed was extended. 8 STUDY ASSESSMENTS AND PROCEDURES: Change the amount of blood. 8.6 Immunogenicity: Description of follow-up ADA data handling was added.
Version 8.0, 12 June 2019
8 STUDY ASSESSMENTS AND PROCEDURES: Correction of the amount of blood and description was clarified.

This Clinical Study Protocol has been subject to a peer review according to AstraZeneca Standard procedures. The Clinical Study Protocol is publicly registered and the results are disclosed and/or published according to the AstraZeneca Global Policy on Bioethics and in compliance with prevailing laws and regulations.

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1 PROTOCOL SUMMARY

1.1 Schedule of Activities (SoA)

Table 1 Schedule of Screening Procedures

Study Period	Screening
Visit Number	**V1**
Procedure/Study Day	**Day -14 to Day -2**
Written general informed consent/assignment of SID number (E code)	X
Optional informed consent for sample for future genetic research	X
Verify eligibility criteria	X
Demographics	X
Medical and disease history (including smoking and alcohol history)	X
Full physical examination (including structured neurological examination) [a]	X
Vital signs	X
12-lead digital ECG (also printed on paper)	X
Body height	X
Body weight	X
Calculate eGFR to confirm eligibility	X
Collect blood for:	
Pancreatic amylase, lipase, calcitonin, and TSH	X
Hepatitis B and C serology [b]	X
HbA1c	X
Serum chemistry panel	X
Hematology and coagulation panels	X
TG	X
Total Ig and subsets (Ig A/E/G/M)	X
Collect urine for:	
Urinalysis (dipstick)	X
Pregnancy test	X
Assessment of AEs/SAEs [c]	X
Concomitant medications	X
Check ability to self-administer investigational product [d]	X
CGM device demonstration	X
CGM measurement	Day -8 to Day -2 [e]

AE = adverse event; CGM = continuous glucose monitoring; ECG = electrocardiogram; eGFR = estimated glomerular filtration rate; HbA1c = glycated hemoglobin; Ig = immunoglobulin; SAE = serious adverse event; SID = subject identification; TSH = thyroid-stimulating hormone; V = visit.

a. Only the screening physical examination will be a full examination including a structured neurological examination. For all time points thereafter, only a targeted physical examination is required.
b. Serum hepatitis B surface antigen and hepatitis C antibody should be negative.
c. SAEs collected after informed consent signed and AEs after randomization will be assessed.
d. The subject's ability to self-administer investigational product will be verified using placebo or normal saline subcutaneous injections.
e. CGM should be started anytime from Day -14 to Day -8 and measured for at least 7 days. The CGM sensor should be removed at later time than the time that was applied.

Table 2 Schedule of Treatment Period Procedures

	Pre-dose	Treatment period							Follow-up
		Dose Level 1		Dose Level 2	Dose Level 3	Dose Level 4			
	V2	V3	V4-7	V8	V9	V10	V11	V12 / Withdrawal [o]	V13
Study Day	**-1**	**1**	**2-5**	**6**	**13**	**20**	**34**	**48**	**7-14 Days Post Last Dose**
Allowance	**-1**						**+1**		
Procedure									
Verify eligibility criteria	X								
Targeted physical examination		X		X	X	X	X	X	X
Body weight [a]		X		X	X	X	X	X	X
Randomization	X [b]	X [b]							
Collect blood for:									
Hematology panel (predose)		X		X		X	X	X	X
Serum chemistry panel (predose)		X		X		X	X	X	X
Pancreatic amylase and lipase (predose)		X						X	
Lactate (predose)		X		X		X	X	X	
HbA1c (predose)	X							X	
Fructosamine (predose)	X					X		X	
Fasting lipid profile (before breakfast and predose as applicable)	X							X	
Optional future genetic research [c]								X	(X)

Table 2 Schedule of Treatment Period Procedures

	Pre-dose	Treatment period							Follow-up
		Dose Level 1		Dose Level 2	Dose Level 3	Dose Level 4			
	V2	V3	V4-7	V8	V9	V10	V11	V12 / Withdrawal [o]	V13
Study Day	**-1**	**1**	**2-5**	**6**	**13**	**20**	**34**	**48**	**7-14 Days Post Last Dose**
Allowance	**-1**						**+1**		
Collect urine sample for:									
Urinalysis (dipstick)		X		X	X	X	X	X	X
Pregnancy test (only for premenopausal women)	X							X	X
ECG [d]	X	X		X	X	X		X	
Vital signs (BP, pulse, body temperature, RR) [e]	X	X	X	X	X	X	X	X	X
24-hour ABPM [f]	X					X		X	
Subject completes Daily Diary [g]	X	X	X	X	X	X	X	X	
Staff review Daily Diary with subject		X	X	X	X	X	X	X	
Train subject on self-administration	X	X	X	X					
Train subject on at-home dose preparation	X	X	X	X	X	X	X		
Staff train subject in Daily Diary completion	X	X		X					
IP administration by staff		X	X						
IP administration by subject				X	X	X	X	X	
IP dispense		X		X	X	X	X		

Table 2 Schedule of Treatment Period Procedures

	Pre-dose	Treatment period							Follow-up
		Dose Level 1		Dose Level 2	Dose Level 3	Dose Level 4			
	V2	V3	V4-7	V8	V9	V10	V11	V12 / Withdrawal [o]	V13
Study Day	**-1**	**1**	**2-5**	**6**	**13**	**20**	**34**	**48**	**7-14 Days Post Last Dose**
Allowance	**-1**						**+1**		
PK for MEDI0382 [h]		X	X	X	X	X	X	X	X
MMT [i]	X							X	
Blood samples for glucose and insulin [i]	X							X	
Blood samples for pro insulin and c peptide, GLP-1, and glucagon [i]	X							X	
CGM [j]		X (D1 to D5)		X (D6 to D12)	X (D13 to D19)			X (D41 to D47)	
CGM sensor application/change [k]		←	→	←	←		←	→	
ADA [l]		X			X	X		X	X
AEs/SAEs [m]	X	X	X	X	X	X	X	X	X
Injection site assessment [n]		X	X	X	X	X	X	X	
Concomitant medications	X	X	X	X	X	X	X	X	X

ABPM = ambulatory blood pressure monitoring; ADA = antidrug antibody; AE = adverse event; BP = blood pressure; CGM = continuous glucose monitoring; D = day; ECG = electrocardiogram; GLP-1 = glucagon-like peptide-1; HbA1c = glycated hemoglobin; IP = investigational product; min = minutes; MMT = mixed-meal test; PK = pharmacokinetic(s); RR = respiration rate; SAE = serious adverse event; V = Visit.

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

a. Body weight measurement should be taken in the morning before breakfast.

b. Randomization may occur on either Day -1 or Day 1 after all eligibility criteria were confirmed.
c. There is a consent form with check boxes available for the genetic future research sample and the non-genetic future research sample. Only sample(s) which the subject has consented to collect will be taken. Samples should be taken hat Visit 12 or Withdrawal visit.
d. Digital ECGs will be captured on Day -1; and pre-dose and 6 hours (± 15 min) post-dose on Days, 1, 6, 13, 20 and 48. All ECGs should be printed.
e. Vital Signs Schedule: On Day 1, vital signs are to be recorded predose, and at 30, 60 and 90 minutes, 2 and 4 hours postdose. From Visit 4 to 11, vital signs are to be recorded predose, Also, vital signs are to be taken at all PK time points.
f. ABPM device will be fitted at a convenient time on the day stated and worn for 24 hours, and subjects will receive training from study site staff on how to fit and wear the device during the day and whilst sleeping. On Visit 10, the ABPM device should be fitted as soon as possible after the subject arrives at the unit that morning
g. The subject should undergo a Ketostix® test daily on non-clinic-visit days during the at-home self-administration period; the subject will indicate whether the result is negative or positive in the Daily Diary, and be instructed to call the site if the result is positive.
h. PK Sampling Schedule for MEDI0382:
Pre-dose PK sample will be collected on Days 1 to 6, 13, 20, 34 and 48.
Follow-up: 7 to 14 days after administration of the last dose in the study.
PK sample at follow-up will be taken on the same day as that for ADA sampling.
i. MMT Schedule: Following a minimum 8-hour fast, blood samples for the tests indicated will be taken 15 minutes before the subject drinking 1 entire can of Ensure H as a standardised meal. On Day -1, and Day 48, after consumption of the standardised meal, blood samples will additionally be taken at 15, 30, 45, 60, 90, 120, 180, and 240 minutes (± 5 min) for glucose and insulin; 15, 45, 90, 180, and 240 minutes (± 5 min) for pro-insulin, c-peptide, GLP-1 and glucagon. If subject discontinues the investigational product, MMT should not be performed at the withdrawal visit.
j. CGM device to be fitted and worn continuously during the measurement period. The sensor should be applied to the arm, taking into account which side the subject sleeps on and also which side the ABPM device will be applied to. The sensor applied to the skin is for single use and may not be reattached once removed.
k. CGM sensors should be changed at each interval at the same time of day (± 20 minutes). For example, if the sensor is applied at 6:00 am on Day 1, it should also be applied at 6:00 am (± 20 minutes) predose on Day 6, Day 13 and Day 41. If the sensor fails, or needs to be replaced, it should be reapplied as soon as possible. The sensor can be replaced on Day 34 if the subject cannot visit on Day 41.
l. ADA Sampling Schedule: Day 1 (V3) predose; Day 13 (V9) predose; Day 20 (V10) predose; Day 48 (V12) predose; and 7 to 14 days after administration of the last dose in the study.
m. SAEs collected after informed consent signed and AEs after randomization will be assessed.
n. Injection Site Assessment Schedule: The injection site will be assessed by site staff at 4 hours postdose on Day 1 and the first day of each new dose level, and at 24 hours (prior to next dose) postdose on Day 1. The site staff will not be required to assess injection sites except for the above time points. Subjects will be instructed to contact the site if there is any abnormality observed at the injection site.
o For withdrawal subjects, assessment should be done after decision of the withdrawal.

Table 3 Example Schedule for Mixed Meal Test (MMT) on Day -1

Example Clock Time	MMT Blood sampling (time window ± 5 minutes)
(minimum 8-hour fast)	
9:15	15 minutes before Test Meal
9:30 [a] **Ensure H** (Ensure H to be consumed within 5 minutes, actual start time to be recorded in eCRF)	
9:45	15 minutes
10:00	30 minutes
10:15	45 minutes
10:30	60 minutes
11:00	90 minutes
11:30	120 minutes
12:30	180 minutes
13:30	240 minutes
13:45 **Go home (Mid-day Meal)**	

a. Ensure H should be taken between 9:00 and 9:30.

Table 4 Example Schedule for Pharmacokinetics (PK) sampling and MMT test on Day 48

Example Clock Time	Time Relative to Dosing	MEDI0382 PK sampling	MMT Blood sampling (time window ± 5 minutes)
(minimum 8-hour fast)			
6:45	Pre-dose	-15 minutes (± 10 min)	-
7:00 [a]	**Administer IP**		
9:00	2 hours postdose	-	-
9:15		-	15 minutes before Test Meal
9:30 **Ensure H** (Ensure H to be consumed within 5 minutes, actual start time to be recorded in eCRF)			
9:45		-	15 minutes
10:00		-	30 minutes
10:15		-	45 minutes
10:30		-	60 minutes
11:00	4 hours postdose	-	90 minutes
11:30		-	120 minutes
12:30		-	180 minutes
13:30	6.5 hours postdose	-	240 minutes
13:45	**Go home (Mid-day Meal)**		

a. IP should be administered between 6:30 and 7:30.

1.2 Synopsis

MEDI0382 is a synthetic peptide with glucagon-like peptide-1 (GLP-1) and glucagon receptor co-agonist activity. The combination of GLP-1 and glucagon activity is expected to cause significant weight loss and lead to improvement in glycemic control and lipid profiles.

This is a Phase 2a study designed to assess the safety and tolerability of MEDI0382 titrated up to a dose level of 300 µg from 50 µg across 48 days in Japanese subjects.

Protocol Title:

A Phase IIa, Randomised, Parallel, Double-Blind, Placebo-Controlled Study to Evaluate the Safety, Efficacy, and Pharmacokinetics of MEDI0382 in Japanese Preobese or Obese Subjects with Type 2 Diabetes Who Have Inadequate Glycemic Control with Diet and Exercise

Rationale:

Results of this study will provide information about the safety and tolerability, the blood glucose-lowering effect as well as body weight reduction of MEDI0382 titrated up to a dose level of 100, 200 or 300 µg and the pharmacokinetic (PK) profile.

Objectives and Endpoints

Primary objective:	Endpoint/variable:
To characterise the safety profile and tolerability of MEDI0382 titrated up to a dose level of 100, 200 or 300 µg during dosing and follow-up	Measures of safety and tolerability (24-hour heart rate and blood pressure, other vital signs, electrocardiogram [ECG], laboratory test results, and adverse event [AE]s)
To assess the effects of MEDI0382 titrated up to a dose level of 100, 200 and 300 µg on glucose control and body weight versus placebo after 48-day treatment	• Percentage change in glucose area under the curve (AUC) $_{0\text{-}4h}$ as measured by a standardised MMT from baseline to the end of 48-day treatment • Percentage change in body weight from baseline to the end of 48-day treatment
Secondary objective:	**Endpoint/variable:**
To assess the effects of MEDI0382 titrated up to a dose level of 100, 200 or 300 µg on additional measures of glucose control versus placebo after 48-day treatment	• Change in glycated hemoglobin (HbA1c) from baseline to the end of 48-day treatment • Change in fasting plasma glucose from baseline to the end of 48-day treatment • Change in fructosamine from baseline to the end of 48-day treatment
To assess the effect of MEDI0382 on glucose lowering during different meals and times of the day as measured by continuous glucose monitoring (CGM)	• 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 the last day of baseline CGM over 24 hours to the end of dosing at each dose level (Days 5, 12, 19, and 47) • Change in percentage of time in hyperglycaemia and hypoglycaemia at each dose level over 5 days for 50 µg and 7 days for other dose levels (Days 1 to 5, Days 6 to 12, Days 13 to 19, and Days 41 to 47)
To characterise the PK profile of 50, 100, 200 and 300 µg of MEDI0382	PK endpoints: Trough plasma concentration (C_{trough})
To characterise immunogenicity of 100, 200 and 300 µg of MEDI0382	Development of anti-drug antibodies and titre (if confirmed positive)
Exploratory Objective:	**Endpoint/variable:**
To assess the effect of MEDI0382 on pancreatic and incretin hormone profiles at baseline and during the MMT	• Change in insulin, GLP-1, and glucagon (AUC and levels) from baseline after 48-day treatment. • Change in pro-insulin, c-peptide levels, pro-insulin/c-peptide ratio from baseline after 48-day treatment.

Objectives and Endpoints

To assess the effects of MEDI0382 in insulin resistance and beta cell function.	• Change in percentage of Homeostatic model assessments (HOMA)-Beta and HOMA-R from baseline after 48-day treatment.

Overall design:

This is a Phase 2a study designed to assess the safety, tolerability, and efficacy of MEDI0382 titrated up to a dose level of 100, 200 or 300 µg from 50 µg across 48 days, compared with Placebo.

Study Period:

Estimated date of first patient enrolled: July 2018

Estimated date of last patient completed: Jan 2020

Number of Subjects:

- MEDI0382 100 µg group: n=15
- MEDI0382 200 µg group: n=15
- MEDI0382 300 µg group: n=15
- Placebo group: n=15

Treatments and treatment duration:

- MEDI0382 100 µg group: Start 50 µg/day for 5 days and dose up to 100 µg/day for 43 days
- MEDI0382 200 µg group: Start 50 µg/day for 5 days, dose up to 100 µg/day for 7 days and dose up to 200 µg/day for 36 days
- MEDI0382 300 µg group: Start 50 µg/day for 5 days, dose up to 100 µg/day for 7 days, dose up to 200 µg/day for 7 days and dose up to 300 µg/day for 29 days
- Placebo group: MEDI0382 matched placebo for 48 days

Statistical methods

Analysis Sets

The full analysis set (FAS) for the efficacy evaluation will be the primary analysis set and will include all randomized subjects who received at least one dose of Investigational Product (IP), and will be analysed according to their randomised treatment group.

The Safety analysis set, which includes all subjects receiving at least one dose of any study IP, will be analysed according to the treatment they actually received.

The PK set includes all subjects who received at least one dose of MEDI0382 and had at least one post-baseline MEDI0382 PK sample taken that is above the lower limit of quantification.

Sample size determination

Approximately 60 patients are to be randomized to Placebo, MEDI0382 100 μg, MEDI0382 200 μg, and MEDI0382 300 μg in a ratio 1:1:1:1.

Anticipating approximately 10% drop out during the 48-day treatment period, approximately 13 subjects are expected to be evaluable per treatment group.

Assuming standard deviation of percent change in MMT glucose $AUC_{(0-4h)}$ for 20%, approximately 13 patients per arm would provide more than 80% power to detect 23% difference in percent change of MMT glucose $AUC_{(0-4h)}$ for pairwise comparison between each of MEDI0382 dose group and Placebo each at two-sided alpha = 0.05, without formal multiplicity adjustment.

Assuming standard deviation of percent change from baseline in body weight for 2.5%, the same number of subjects would provide approximately 68% power to detect mean difference of 2.5% at two-sided alpha =0.05.

Statistical analysis methods

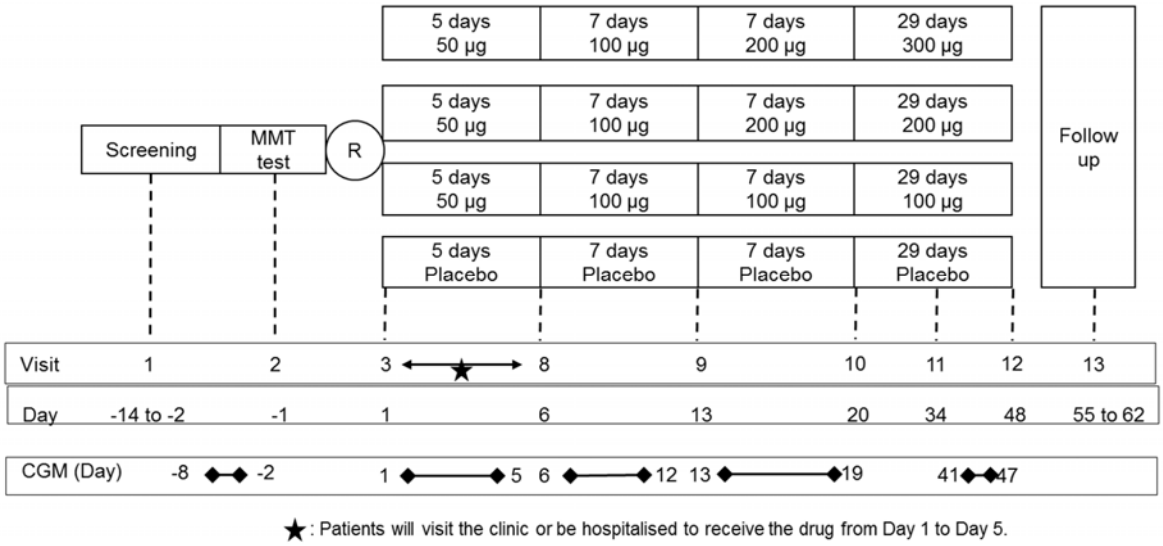
Safety data will be descriptively summarised with respect to AEs/serious adverse event (SAE)s, safety laboratory measurements, vital signs (including 24-hour ambulatory blood pressure monitoring [ABPM]) and ECGs, by treatment group.

Percent change from baseline in MMT Glucose $AUC_{(0-4h)}$ to Day 48 will be analysed with analysis of covariate (ANCOVA) model with treatment group as a factor and baseline as a covariate. Least-square mean and their 95% (CI for percent changes from baseline for each treatment group, as well as difference in Least-square mean, 95% CI and nominal p-values will be provided for pairwise comparison of each MEDI0382 dose vs. Placebo group. Percent change (and absolute change) from baseline in body weight will be analysed similarly. Analyses will be based on the FAS, which includes all randomised subjects who received at least one dose of IP. Secondary and exploratory variables will be descriptively summarised by treatment and analysed by ANCOVA or other appropriate models.

1.3 Schema

The general study design is summarised in Figure 1.

Figure 1 Study design



R=Randomisation, MMT=Mixed-Meal Test, CGM=Continuous Glucose Monitoring

2 INTRODUCTION

2.1 Study rationale

MEDI0382 is a synthetic peptide with both GLP-1 and glucagon receptor co-agonist activity. Combination of GLP-1 and glucagon activity is expected to improve glucose metabolism and lipid profiles, and result in significant weight loss. Currently MEDI0382 is under development for patients with type 2 diabetes mellites (T2DM).

This is a Phase 2a study designed to evaluate the safety and tolerability of MEDI0382 titrated up to a dose level of 100, 200 or 300 µg from 50 µg across 48 days in preobese/obese Japanese population with type 2 diabetes. Results of this study will also provide information about the blood glucose-lowering and weight loss effect of MEDI0382 as well as the PK profile. This study is designed based on the prior clinical experience with MEDI0382 in clinical studies D5670C00002 and D5670C00012.

According to the overseas study results and Japanese Phase 1 results as given above, the study D5674C00001 can be conducted with a reasonable expectation of safety and tolerability in Japanese T2DM patients. The design of this study has taken into account the known benefits and risks of GLP-1 receptor agonists and glucagon receptor agonists as well as the translatable effects observed in nonclinical studies of MEDI0382, such that benefit-risk balance for the Japanese preobese and obese patients with T2DM in this study is considered favourable.

2.2 Background

The rising prevalence of 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. 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 clinically meaningful weight loss. Average body mass index (BMI) in Japanese type 2 diabetes has been increasing gradually over past 10 years reaching BMI 24.7 in 2016 (The Japan Diabetes Society). In addition, accumulation of visceral fat causes insulin resistance even in Japanese type 2 diabetes patients with lower BMI. Therefore a medicine which improves both glycemic control and insulin resistance by reducing visceral fat is required in Japan.

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. GLP-1 receptor agonists are established treatments for T2DM which improve glycaemic control, delay gastric emptying and depress appetite leading to modest, weight loss (typically 4% to 5.4% placebo-subtracted weight loss at 1 year) (Astrup et al. 2012). Glucagon has similar effects to GLP-1 on gastric emptying and appetite, and has also been shown to promote increased energy expenditure (Lynch et al. 2014; Habegger et al. 2013). Oxyntomodulin, a naturally occurring peptide with GLP-1 and glucagon receptor co-agonist activity has been shown to promote weight loss through effects on appetite and energy expenditure (Wynne et al. 2006) and co-infusion of GLP-1 and glucagon has synergistic effects on reducing food intake and promoting weight loss in human subjects (Cegla et al. 2014).

As of the cut off date of J-IB version 1.0, a Phase 1/2 study (Study D5670C00002) was completed, and is in the reporting phase with data analysis ongoing. A Phase 1 study (Study D5670C00001) was completed. Three Phase 1 (Studies D5670C00003, D5670C00008, and D5670C00009) and 2 Phase 2 (Studies D5670C00004 and D5670C00011) studies are ongoing. One Phase 1（D5670C00012） and 3 Phase 2 (Studies D5671C00001, D5670C00007, and D5670C00013) studies are planned.

Study D5670C00001, a first-time-in-human, single-ascending-dose study assessing the safety, tolerability, and PK of MEDI0382 in healthy subjects, was completed, with 6 subjects each receiving 1 of 6 doses of MEDI0382 (5, 10, 30, 100, 150, or 300 µg) and 12 subjects receiving placebo. In this study, dose escalation proceeded from 5 to 300 µg as planned per the protocol; however, 300 µg was not tolerated as evidenced by events of significant vomiting, and the dose was de-escalated to 150 µg for the final cohort. A higher proportion of subjects in the MEDI0382 group (21/36 subjects, 58.3%) than in the placebo group (2/12 subjects, 16.7%) had at least one treatment emergent adverse event (TEAE), with vomiting, nausea, dizziness, and headache being the most frequent (incidence > 10% of subjects) in the MEDI0382 group; the majority of these TEAEs occurred at the highest two doses (150 and 300 µg). All of the TEAEs were mild or moderate in severity. There were no deaths and one subject (10 µg of

MEDI0382) had a treatment emergent serious adverse event (TESAE; atrioventricular block second degree); this was not deemed to be related to the investigational product.

After administration of increasing single subcutaneous (SC) doses (5, 10, 30, 100, 150, and 300 µg), MEDI0382 was in general moderately absorbed with median peak plasma concentration observed between 4.5 and 9 hours postdose. After this time, concentrations declined slowly between the peak and 48 hours postdose. The median terminal half-life ($t_{1/2}$) could not be estimated accurately in the lowest dose groups (5 and 10 µg) but was comparable in the other dose groups (30 to 300 µg) and was about 10 to 12 hours. No subject developed antidrug antibody (ADA) in this study.

A glucose lowering effect was seen in plasma glucose levels of subjects treated with MEDI0382 in Study D5670C00001. This effect was visible at low doses, especially around the first meal time.

Study D5670C00002, a Phase 1/2, multiple-ascending dose study assessing the efficacy, safety, and PK of MEDI0382 in overweight and obese subjects with T2DM was completed, and its Clinical Study Report (CSR) is available. Cohorts 1 through 3 (Part A of the study) established an up-titration schedule for MEDI0382 and an effective repeat dose of 200 µg. Subjects in Cohort 4 were dosed for an extended period (≥ 41 days) with 200 µg MEDI0382 (Part B of the study), following a period of up titration, to assess the effect of MEDI0382 on glucose control and body weight. Part C assessed the safety and tolerability of a 300 µg dose of MEDI0382, and explored 2 possible up-titration schedules from 100 to 300 µg from a tolerability, safety, and PK/pharmacodynamic (PD) perspective.

Overall, there were no deaths reported in the study, 2 subjects had a TESAE and 6 subjects had a TEAE that led to withdrawal from the study. The majority of subjects in all cohorts experienced at least 1 TEAE, with TEAEs in the Gastrointestinal Disorders System Organ Class being the most common. The majority of TEAEs were mild or moderate in severity.

Preliminary PK results collected from Study D5670C00002, suggest that MEDI0382, in the range of 100 to 300 µg, showed a linear PK after daily repeated SC administration, with $t_{1/2}$ of approximately 8 to 11 hours, which provided minimal accumulation after daily repeat dosing. Steady state was achieved, based on trough plasma concentration (C_{trough}) observation, between Days 4 and 7 at all doses tested. Plasma concentrations after 7 days at the highest dose (300 µg) seem to have been independent of the titration scheme adopted. Maximal plasma concentrations in the dose range tested and with the titration scheme adopted, ranged between 1.98 and 34.3 ng/mL.

The co-primary endpoints, the percent change from baseline to the end of treatment in MMT glucose area under the concentration time-curve from time zero to 4 hours (AUC_{0-4h}), and the change from baseline in body weight in kg to end of treatment, were assessed after ≥ 41 days

dosing of MEDI0382 up-titrated to 200 µg (Cohort 4). MEDI0382 treatment was associated with a mean change of -32.78% in MMT glucose AUC_{0-4h} (90% CI -36.98, -28.57) vs 10.16% (90% CI 14.10, -6.21) in placebo, $p < 0.0001$, and a mean change of 3.84 kg from baseline in body weight (90% CI - 4.55, -3.12) vs 1.70 kg (90% CI -2.40, -1.01) in placebo, $p = 0.0008$. MEDI0382 treatment was associated with numerically greater mean reductions in MMT glucose AUC_{0-4h} and body weight vs placebo in all cohorts. There were no unexpected safety signals and no increases in systolic or diastolic blood pressure (BP). With respect to heart rate, a trend towards a mean change from baseline in the order of 10 bpm that appeared to be consistent across Cohorts 1 to 3 was observed during office based measurements. In Cohort 4 an increase in heart rate of 11.7 bpm on Day 13 was observed and it reduced to 6.9 bpm on Day 41. Dosing was associated with increased gastrointestinal (GI) adverse events (AEs) with 40 vomiting related AEs observed in 8 (32%) subjects on MEDI0382 in Cohort 4, however the number of events diminished in frequency with dose up-titration. Tolerability was comparable to marketed GLP-1 receptor agonists. A Phase I, randomized, blinded (investigators and the subjects were blinded to the treatment assignment and the sponsor was unblinded to the treatment assignment) study (D5670C00012) to evaluate the safety, tolerability, PK, and immunogenicity of MEDI0382 administered as single SC doses to preobese/obese but otherwise healthy adult male and female subjects of Japanese and Chinese descent was finished (CSR preparation is ongoing). In Part A, 24 subjects of Japanese descent across 3 cohorts (8 subjects in each cohort) received single SC doses of 50 µg, 100 µg, and 150 µg of MEDI0382 or placebo in a 3:1 ratio. In Part B, approximately 8 subjects of Chinese descent received a single SC dose of 100 µg MEDI0382 or placebo in a 3:1 ratio. Increased GI adverse events (nausea, vomiting, etc.) were observed at the 150 µg dose level, which resulted in halting planned dose escalation to 200 µg. A higher proportion of subjects in the MEDI0382 group (6/24 subjects, 33.3%) than in the placebo group (1/6 subjects, 16.7%) had at least one TEAE, with vomiting, nausea, dizziness, and headache being the most frequent in the MEDI0382 group; the majority of these TEAEs occurred at the 150 µg dose level. All of the TEAEs were mild or moderate in severity. One subject (150 µg of MEDI0382) had atrioventricular block second degree; this was not deemed to be related to the investigational product. Increased heart rate was observed in 100 and 150 µg dose levels that follows the same pattern as reported previously, although a small number of patients experienced higher magnitude of changes in their heart rate from baseline in Study D5670C00002. In Study D5670C00011, in which dosing started from 50 µg and up-titrated to a maximum of 300 µg, there were no cases of arrhythmia reported. To date, there is no evidence to suggest the existence of a relationship between MEDI0382 dosing and clinically significant arrhythmia. Increase in heart rate was observed, consistent with what had been observed previously. No deaths or serious AEs were reported and no subject withdrew from the study due to AE. In conclusion, MEDI0382 was well tolerated in healthy male and female subjects of Japanese and Chinese descent. Overall, tolerability is comparable between studies D5670C00001 and

D5670C00012, and with up-titration from low dose to the final dose level, tolerable use of MEDI0382 is expected, which is supported by Study D5670C00002.

After administration of increasing single SC doses, from the preliminary data on 50 and 100 μg dose levels, MEDI0382 was in general moderately absorbed with median peak plasma concentration observed between 6 and 8 hours postdose. The median $t_{1/2}$ was about 10 hours. The available MEDI0382 plasma concentration data between Studies D5670C00001 and D5670C00012 are similar. No subject developed ADA in this study.

A detailed description of the chemistry, pharmacology, efficacy, and safety of MEDI0382 is provided in the Investigator's Brochure.

2.3 Benefit/risk 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 coagonist that promotes glucose lowering and weight loss and is targeted at subjects with T2DM. MEDI0382 has the potential to deliver improvements in glycemic control and lipid homeostasis, and it is predicted to be a useful therapy for T2DM. However, it should be noted that given the short treatment durations in Study D5674C00001 little, if any, direct benefit to the patient's underlying T2DM should be expected.

The study design aims to minimize potential risks to subjects participating in this study based on the proposed inclusion/exclusion criteria, safety monitoring, and up-titration dosing schedule. All subjects will be monitored throughout the study to ensure adequate glycemic control. Subjects will be given appropriate training in for SC injection administration as well as use of any devices. Refer to the current MEDI0382 IB for further information on the potential benefits of MEDI0382 and an assessment of the potential and known risks. Identified risks for Study D5674C00001 include nausea and vomiting.

3 OBJECTIVES AND ENDPOINTS

Table 5 Study objectives

Primary Objective:	Endpoint/Variable:
To characterise the safety profile and tolerability of MEDI0382 titrated up to a dose level of 100, 200 or 300 µg during dosing and follow-up	Measures of safety and tolerability (24-hour heart rate and blood pressure, other vital signs, ECG, laboratory test results, and AEs)
To assess the effects of MEDI0382 titrated up to a dose level of 100, 200 or 300 µg on glucose control and body weight versus placebo after 48 days of treatment	• Percentage change in glucose AUC_{0-4h} as measured by a standardised MMT from baseline to the end of 48-day treatment • Percentage change in body weight from baseline to the end of 48-day treatment
Secondary Objective:	**Endpoint/Variable:**
To assess the effects of MEDI0382 titrated up to a dose level of 100, 200 or 300 µg on additional measures of glucose control versus placebo after 48-day treatment	• Change in HbA1c from baseline to the end of 48-day treatment • Change in fasting plasma glucose from baseline to the end of 48-day treatment • Change in fructosamine from baseline to the end of 48-day treatment
To assess the effect of MEDI0382 on glucose lowering during different meals and times of the day as measured by CGM	• 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 the last day of baseline CGM over 24 hours to the end of dosing at each dose level (Days 5, 12, 19, and 47) • Change in percentage of time in hyperglycaemia and hypoglycaemia at each dose level over 5 days for 50 µg and 7 days for other dose levels (Days 1 to 5, Days 6 to 12, Days 13 to 19, and Days 41 to 47)
To characterise the PK profile of 50, 100, 200 and 300 µg of MEDI0382	PK endpoint: Trough plasma concentration (C_{trough})
To characterise immunogenicity of 100, 200 and 300 µg of MEDI0382	Development of anti-drug antibodies and titre (if confirmed positive)
Exploratory Objective:	**Endpoint/Variable:**
To assess the effect of MEDI0382 on pancreatic and incretin hormone profiles at baseline and during the MMT	• Change in insulin, GLP-1, and glucagon (AUC and levels) from baseline after 48-day treatment. • Change in pro-insulin, c-peptide levels, pro-insulin/c-peptide ratio from baseline after 48-day treatment.
To assess the effects of MEDI0382 in insulin resistance and beta cell function.	Change in percentage of HOMA-Beta and HOMA-R from baseline after 48-day treatment.

4 STUDY DESIGN

4.1 Overall design

This is a randomized, parallel-group, placebo-controlled, double-blind, multicenter Phase IIa study to evaluate the safety, efficacy, and pharmacokinetics of MEDI0382 in Japanese preobese and obese subjects with type 2 diabetes who have inadequate glycemic control with diet and exercise. Subject fulfilling all of the inclusion criteria and none of the exclusion criteria will be randomised in a 1:1:1:1 ratio to four treatment arms. For an overview of the study design see, Section 1.3. For details on treatments given during the study, see Section 6.1 Treatments Administered.

For details on what is included in the safety and efficacy endpoints, see Section 3: Objectives and Endpoints.

4.2 Scientific rationale for study design

This is a Phase IIa study designed to evaluate the dose range for MEDI0382 to explore the safety profile, as well as blood glucose control and weight loss effects of MEDI0382 in Japanese patients with T2DM. The design of this study has taken into account the known benefits and risks of GLP-1 receptor agonists and glucagon receptor agonists as well as the translatable effects observed in nonclinical studies of MEDI0382, such that benefit-risk balance for the Japanese preobese and obese patients with T2DM in this study is considered favourable. A treatment period of 48 days is required to properly evaluate the dose range and safety and tolerability in three different doses. Inclusion of placebo in the study allows appropriate basis of AEs, glycaemic control, and weight loss. Benefits related to participation in this trial include close follow-up of a subject's diabetes and treatment with anti-diabetes agents. Although one of possible treatments is placebo, appropriate rescue therapy for worsening glycaemic control will be implemented if required (see Section 6.5.3).

4.2.1 Rationale for Study Population

Recruitment of subjects with T2DM and a body mass index 24 to 40 kg/m^2

MEDI0382 is a GLP-1 and glucagon receptor co-agonist which relies upon glucose-dependent insulin release (the incretin effect) for glucose-lowering effect, and therefore targets subjects with T2DM.

Subjects with T2DM who are preobese or obese are likely to benefit most from losing weight. The entry criteria with respect to T2DM and BMI 24 - 40 kg/m^2 both will provide safety, tolerability, and expected efficacy data in the likely intended clinical population.

Recruitment of subjects with an HbA1c of 7.0% to 10.5%

Subjects with inadequate blood glucose control, defined as HbA1c between 7.0% and 10.5% will be enrolled to represent the likely clinical use setting. Only subjects who are treated with diet and excise will be enrolled; this will ensure that subjects with an early stage of T2DM are treated in this first Japanese study. Rescue therapy will be provided to ensure the safety of subjects during the trials. Subjects with acutely decompensated blood glucose control will not be enrolled.

4.2.2 Rationale for Endpoints

4.2.2.1 Rationale for Primary Endpoints

Safety and Tolerability

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

Measures of Glucose Lowering and Weight Loss

Co-primary endpoints of glucose AUC and weight loss are adequate to evaluate the efficacy of up to 300 µg dose level to assess the benefit of a GLP-1 and glucagon receptor co-agonist for 48 days. Percentage change in weight will also be measured.

4.2.2.2 Rationale for Secondary Endpoints

Additional Measures of Glucose Control

HbA1c and fasting plasma glucose (FPG) tests are used to monitor patient's diabetes control level. For the HbA1c test there are firm data that a chronically elevated HbA1c level predicts an increased risk for certain diabetic complications. Change from baseline through end of treatment in HbA1c should enable modelling for longer-term Phase 2b study design. Fructisamine changes more rapidly than HbA1c and represents blood glucose of one to two weeks. Therefore, fructisamine can monitor rapid changing blood glucose compared to HbA1c.

Glucose Lowering during different meals and times of the day as measured by CGM

CGM is obtained with 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 5-day periods or 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.

Pharmacokinetic Profile and Immunogenicity

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 µg with a half-life of approximately 8 to 13 hours in non-Japanese subjects, which allows minimal accumulation after repeated daily administration and achievement of steady state between 4 and 7 days. Preliminary PK results in Japanese subjects (Study D5670C00012) suggested that single dose PK profiles of MEDI0382 are comparable between Japanese and non-Japanese subjects. The goal for PK endpoint is to ensure that plasma levels of MEDI0382 in Japanese subjects achieve steady state during repeated daily administration in similar manner to that in non-Japanese subjects. Plasma concentrations of MEDI0382 from 50 µg up to 300 µg will be used to evaluate the PK profile (C_{trough}) at each dose level to establish steady state achievement.

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

4.2.2.3 Rationale for Exploratory Endpoints

Pancreatic and incretin hormone profiles

Changes in pancreatic and incretin hormone levels (active and total GLP-1, glucagon, C peptide, and insulin) will be measured during the MMT to stratify treatment response to MEDI0382.

Insulin resistance and beta cell function

Homeostatic model assessments (HOMA); HOMA-S, HOMA-β and HOMA-IR determined by fasting glucose, C-peptide, and insulin levels, will be used to assess the effect of MEDI0382 on insulin sensitivity, beta cell function, and insulin resistance respectively after 48 days of treatment, with improvements in these scores likely to correlate with delayed progression of T2DM.

4.3 Justification for dose

Based on PK/PD modelling conducted using available clinical literature data on GLP-1 and glucagon modulators, the clinically efficacious dose of MEDI0382 was predicted to be in the range of 300 to 2000 µg/day; however, in the Study D5670C00001 conducted overseas in healthy subjects, multiple episodes of vomiting was observed at the 300 µg dose administered as a single dose without up-titration. Given this observation, in the overseas Study D5670C00002 in patients with T2DM, a regimen of 100 µg once daily dosing for 7 days was employed, which demonstrated glucose lowering effect without gastrointestinal disorders. In addition, by initiating from 100 µg followed by step-wise dose increase, decreases of

gastrointestinal disorders were observed. The gastrointestinal disorders observed initially also did not increase as dose increased, and the tolerability and efficacy of up to 300 µg was confirmed. In Study D5670C00001 in healthy subjects and Study D5670C0002 in patients with T2DM performed overseas, linear and time-independent PK after single and multiple dosing was suggested. It was also suggested that the single dosing data allows accurate estimation of PK after multiple dosing. In Study D5670C00011 in patients with T2DM, starting from 50 µg followed by gradual increase up to 300 µg then changed to repeated dosing, the frequency of initial gastrointestinal disorders was more than halved while showing similar efficacy compared to Study D5670C00002. The principle of dose up-titration to achieve greater tolerability at higher than initial doses, as described above, is well established with daily GLP-1 agents (Victoza SPC, 2014).

In Study D5670C000012 in Japanese healthy subjects, after single dosing of MEDI0382 at 3 doses (50, 100 and 150 µg), 50 and 100 µg were tolerated, however, increase in gastrointestinal disorders compared to placebo group was confirmed for 150 µg dose. The severity of the observed gastrointestinal disorders, however, was Grade 1 in all the patients, showing similar tolerability as that in Study D567000001 in overseas healthy subjects. The preliminary PK analysis also presented dose-related exposure increase at 50 and 100 µg, and similar PK as that observed at a dose of 100 µg in Study D5670C00001. Given these results, we conclude that it is possible to estimate the safety and tolerability of repeated dosing in Japanese patients with T2DM from the result of Study D5670C00011 in non-Japanese patients with T2DM. In Study D5670C00011, Cohort 1 was designed to explore the 300 µg dose for 28 days as part of a 49-day dosing period. The up-titration schedule began at 50µg, to evaluate the tolerability profile, principally to see if starting at a lower dose improved the tolerability profile with respect to gastro-intestinal related adverse events. With the exception of 1 severe event, all nausea and vomiting TEAEs were transient, and mild (Grade 1) or moderate (Grade 2) in severity, which had resolved by the end of the study. One subject in the Cohort 1 MEDI0382 dose group had a vomiting TEAE that was severe (Grade 3) and that led to interruption of investigational product. This event was not serious and resolved the same day. In Cohort 1, MEDI0382 treatment group, nausea TEAEs were reported in 19.2% of subjects and vomiting TEAEs were reported in 11.5% of subjects; no nausea or vomiting were reported in placebo subjects. Higher frequency of nausea and vomiting was observed at the beginning of the up-titration period, which is following the similar pattern as seen in the Study D5670C00002 (Appendix G). Furthermore, Study D5670C00011 showed association of one-week titration with directional trend towards less nausea and vomiting, as well as dose initiation at 50 µg reduced the number of subjects experiencing nausea and vomiting comparing to the Study D5670C00002. Therefore, the initial dose of this study will be 50 µg followed by dose up-titration to 100 µg, 200 µg or 300 µg. It should be noted that the investigators should check the safety of each subject such as presence or absence of gastrointestinal disorders before dose up-titration.

Taken together, we believe that the dosage and administration in this study will allow evaluation of both the appropriate dose titration schedule for repeated doses of MEDI0382 and a maximal effective repeat-dose, while ensuring safety, in patients with T2DM.

4.4 End of study definition

The end of study is defined as the last expected visit/contact of the last subject undergoing the study.

See Appendix A 6 for guidelines for the dissemination of study results.

5 STUDY POPULATION

Prospective approval of protocol deviations to recruitment and enrolment criteria, also known as protocol waivers or exemptions, is not permitted.

Each subject should meet all of the inclusion criteria and none of the exclusion criteria for this study in order to be assigned/randomised to a study intervention. Under no circumstances can there be exceptions to this rule. Subjects who do not meet the entry requirements are screen failures, refer to Section 5.4.

In this protocol, “enrolled” subjects are defined as those who sign informed consent. “Randomized” subjects are defined as those who undergo randomization and receive a randomization number.

For procedures for withdrawal of incorrectly enrolled subjects see Section 7.3.

5.1 Inclusion criteria

Subjects are eligible to be included in the study only if all of the following inclusion criteria and none of the exclusion criteria apply:

Informed consent

1 Capable of giving signed informed consent which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol.

2 Provision of signed and dated, written informed consent form prior to any mandatory study specific procedures, sampling, and analyses.

The ICF process is described in Appendix A 3.

Age

3 Subjects must be 20 years of age or older at the time of signing the informed consent form.

Type of subject and disease characteristics

4 Individuals whose HbA1c range of 7.0% to 10.5% (inclusive) at screening.

5 Individuals who are diagnosed with T2DM

6 Individuals whose current condition at enrolment (Visit 1) is drug naïve defined as:

- Never received medical treatment for diabetes (insulin and/or other anti-diabetic agents [oral or injection])
  OR
- Received medical treatment for diabetes for less than 30 days since diagnosis. In addition, during the 30-day period prior to screening did not receive oral anti-diabetic agents for more than 3 consecutive or more than 7 non-consecutive days. Subjects also should not have a history of insulin therapy within 2 weeks of screening (with the exception of insulin therapy during a hospitalization for other causes or use in gestational diabetes)
  OR
- Previously received medical treatment for diabetes but have not been treated within 6 weeks of enrolment

Weight

7 BMI within the range of 24 – 40 kg/m^2 (inclusive) at screening

Sex

8 Male and/or female

Reproduction

9 For women of childbearing potential:

- Female subjects must be surgically sterile, or using an acceptable method of contraception (an acceptable method of contraception is defined as a barrier method in conjunction with a spermicide) for the duration of the study (from the time they sign consent) and for 4 weeks after the last dose of IP to prevent pregnancy. In addition, oral contraceptives, approved contraceptive implant, long-term injectable contraception, intrauterine device, or tubal ligation are allowed. Oral contraception alone is not acceptable; additional barrier methods in conjunction with spermicide must be used.
- Must have a negative serum or urine pregnancy test within 72 hours prior to the start of IP
- Must not be breastfeeding

Female subjects must be 1-year post-menopausal.

5.2 Exclusion criteria

Medical conditions

1 As judged by the investigator, history of, or any existing condition that would interfere with evaluation of the IP, put the subject at risk, influence the subject's ability to participate or affect the interpretation of the results of the study

2 Positive hepatitis C antibody, hepatitis B virus surface antigen or hepatitis C virus core antigen, at screening

3 Known to have tested positive for human immunodeficiency virus

4 Severe allergy/hypersensitivity to any of the proposed study treatments or excipients

5 Symptoms of acutely decompensated blood glucose control, a history of type 1 diabetes mellitus or diabetic ketoacidosis, or if the subject has been treated with daily SC insulin for a period longer than 2 weeks within 90 days prior to screening

6 Acute or chronic pancreatitis. Subjects with serum triglyceride concentrations above 1000 mg/dL (11 mmol/L) at screening as this can precipitate acute pancreatitis

7 Significant inflammatory bowel disease or other severe disease or surgery affecting the upper GI tract (including weight-reducing surgery and procedures) which may affect gastric emptying or could affect the interpretation of safety and tolerability data

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) ≥ 2.5 × upper limit of normal (ULN)
- Alanine transaminase (ALT) ≥ 2.5 × ULN
- Total bilirubin (TBL) ≥ 2 × ULN

9 Impaired renal function defined as estimated glomerular filtration rate≤ 60 mL/minute/1.73 m^2 at screening (glomerular filtration rate estimated according to the formula of Japanese Society of Nephrology)

10 Severely uncontrolled hypertension defined as systolic BP ≥ 180 mmHg and/or diastolic BP ≥ 110 mmHg on the average of two seated measurements after being at rest for at least 5 minutes

11 Unstable angina pectoris, myocardial infarction, transient ischaemic 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 IV)

13 Any clinically important abnormalities in rhythm, conduction or morphology of the resting ECG and any abnormalities in the 12-lead ECG that, as considered by the

investigator, may interfere with the interpretation of QTc interval changes, including abnormal ST-T-wave morphology or left ventricular hypertrophy.

14 Known history of drug or alcohol abuse within 3 months of screening

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

16 Haemoglobinopathy, haemolytic anaemia, or chronic anaemia (hemoglobin 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

17 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

18 History of psychosis or bipolar disorder. History of major depressive disorder within the past year with the subject being clinically unstable, or any history of suicide attempt or history of suicidal ideation within the past year.

Prior/concurrent clinical study experience

19 Participation in another clinical study with an investigational product administered in the last 30 days or 5 half-lives of the drug (whichever is longer) at the time of screening

Other exclusions

20 Involvement in the planning and/or conduct of the study (applies to both AstraZeneca staff and/or staff at the study site).

21 Judgment by the investigator that the subject should not participate in the study if the subject is unlikely to comply with study procedures, restrictions and requirements.

22 Previous randomisation in the present study.

23 For women only - currently pregnant (confirmed with positive pregnancy test) or breast-feeding.

24 Substance dependence likely to impact subject safety or compliance with study procedures

Subjects may be rescreened once, if in the opinion of the Investigator there is a reason to believe they may be eligible. Subjects should continue to meet all inclusion and none of the exclusion criteria to qualify for re-screening.

5.3 Lifestyle restrictions

Once screened and qualified for entry, subjects will be instructed as follows:

5.3.1 Meals and dietary restrictions

- Fast overnight for at least 8 hours prior to study site visits, i.e., no food or beverage except water.
-

5.3.2 Caffeine, alcohol, and tobacco

- Withhold alcohol, and refrain from intense exercise for 24 hours prior to each study site visit.

5.3.3 Activity

- The subjects should not take investigational products on the morning of the clinic visit.
- Any new prescription medications or over-the-counter preparations must be reported to study site staff. For restrictions on concomitant medications, see Section 5.1 and Section 5.2 (Inclusion and Exclusion Criteria) and Section 6.1.1 (Investigational Product).
- Do not donate blood for the duration of the study.

5.4 Screen failures

Screen failures are defined as subjects who signed the informed consent form to participate in the clinical study but are not subsequently randomly assigned to Study treatment in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure subjects to meet the Consolidated Standards of Reporting Trials publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAE.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened once. Rescreened subjects should be assigned the same subject number as for the initial screening. However, rescreening should be documented so that its effect on study results, if any, can be assessed.

These subjects should have the reason for study withdrawal recorded in the electronic case report form (eCRF).

6 STUDY TREATMENTS

Study treatment is defined as any investigational product(s) (including marketed product comparator and placebo) or medical device(s) intended to be administered to a study participant according to the study protocol. Study treatment in this study refers to MEDI0382 or placebo.

A once-daily dose is to be self-administered by SC injection as soon as practicable upon waking each morning prior to breakfast. If the subject forgets to administer the investigational product before the breakfast, s/he should self-administer his/her dose before the following meal (lunch or supper) on the same day. If the investigational product is not administered until the time after supper, the subject should skip the dose for the day and will self-administer from the next planned dose.

6.1 Treatments administered

6.1.1 Investigational products

Table 6 Identity of investigational product(s)

Investigational product	Dosage form and strength
1 vial MEDI0382 solution for injection 2 mg/mL	Solution for injection, 2 mg/mL, 1 mL per vial
pre-filled syringe MEDI0382 solution for injection 100 µg	0.5 mg/mL,1 mL long pre-filled syringe, 0.2 mL Fill, 100 µg per dose, 1 dose
pre-filled syringe MEDI0382 solution for injection 200 µg	0.5 mg/mL,1 mL long pre-filled syringe, 0.4 mL Fill, 200 µg per dose, 1 dose
pre-filled syringe MEDI0382 solution for injection 300 µg	0.5mg/mL,1 mL long pre-filled syringe, 0.6 mL Fill, 300 µg per dose, 1 dose
1 vial MEDI0382 solution for injection placebo A	Solution for injection, 2 mg/mL 1 mL
pre-filled syringe MEDI0382 solution for injection placebo B	Solution for injection, 1 mL long pre-filled syringe, 0.3 mL Fill, 1 dose

For the 50 µg, dilution steps will need to be carried out by site staff at the clinical unit.

The MEDI0382 50 µg and placebo A will be packed into kits, supplied as blinded kits each containing one vial. A unique identifying number will appear on both the vials and kit label.

The MEDI0382 100 µg, 200 µg, 300 µg and placebo B will be packed into kits enough for 1-week treatment, supplied as blinded kits each containing 8 pre-filled syringes. A unique identifying number will appear on both the syringes and kit label. Each container will be labelled in accordance with Good Manufacturing Practice (GMP) Annex 13 and per Japan's regulatory requirement.

6.1.2 Medical devices

The Medimmune manufactured medical device provided for use in this study is

- 1.0 mL pre-filled syringe

Other medical devices (not manufactured by or for AstraZeneca) provided for use in this study are

- Digital ECG
- CGM device
- 24-hour ABPM

For medical device incidences, see Appendix F.

Any medical device incidents, including those resulting from malfunctions of the device, must be detected, documented, and reported by the investigator throughout the study (see Section 8.4.4)

6.2 Preparation/handling/storage/accountability

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 at ≤ 8°C. The subject is to avoid the risk of freezing the investigational product by carefully placing the investigational product within their refrigerator, and they should not use investigational product if it has been frozen.

The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study treatment received and any discrepancies are reported and resolved before use of the study treatment.

Only subjects enrolled in the study may receive study treatment and only authorised site staff may supply or administer study treatment. All study treatments must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labelled storage conditions with access limited to the investigator and authorised site staff.

The investigator, institution, or the head of the medical institution (where applicable) is responsible for study treatment accountability, reconciliation, and record maintenance (i.e., receipt, reconciliation, and final disposition records).

For the first 5 days (Visit 3 to Visit 7), subjects will receive one dose/day of 50 µg or placebo A by SC injection at site. For doses of 50 µg a 10-fold diluted stock concentration of 0.2 mg/mL will be prepared by site staff at the clinical unit, prior to administration. 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. Then administer 0.25 mL/day. 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 same procedures are required to placebo A.

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 Visit 8 onward, subjects will receive the MEDI0382 100 µg, 200 µg, 300 µg or placebo B by SC injection. These IPs are pre-filled syringe, and subjects will receive one dose/day of the randomized drug for 43 days.

Further guidance and information for the final disposition of unused study treatment are provided in the 'Procedures for drug accountability' and 'Procedures for drug dissolution and usage'.

6.3 Measures to minimise bias: randomisation and blinding

All subjects will be assigned to randomised study treatment using an interactive voice/web response system (IVRS/IWRS). Before the study is initiated, the telephone number and call-in directions for the IVRS and/or the log-in information and directions for the IWRS will be provided to each site.

If a subject withdraws from the study, then his/her enrolment/randomisation code cannot be reused. Withdrawn subjects will not be replaced.

Blinded studies using IVRS/ IWRS	The IVRS/IWRS will provide to the Investigator(s) or pharmacists the kit identification number to be allocated to the patient at the dispensing visit. Routines for this will be described in the IVRS/IWRS user manual that will be provided to each centre. The randomisation code should not be broken except in medical emergencies when the appropriate management of the subject requires knowledge of the treatment randomisation. The Investigator documents and reports the action to AstraZeneca, without revealing the treatment given to subject to the AstraZeneca staff. AstraZeneca retains the right to break the code 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. Randomisation codes will not be broken for the planned analyses of data until all decisions on the evaluability of the data from each individual subject have been made and documented.

Blind Break (IVRS/IWRS)	The IVRS/IWRS will be programmed with blind-breaking instructions. The blind may be broken if, in the opinion of the investigator, it is in the subject's best interest for the investigator to know the study treatment assignment. The sponsor must be notified before the blind is broken unless identification of the study treatment is required for a medical emergency in which the knowledge of the specific blinded study treatment will affect the immediate management of the subject's condition (e.g., antidote available). In this case, the sponsor must be notified within 24 hours after breaking the blind. The date and reason that the blind was broken must be recorded in the source documentation and eCRF, as applicable. Study unblinding should not occur until database lock and all decisions on the evaluability of the data from each individual subject have been made and documented.

6.3.1 Methods for ensuring blinding

The study will be conducted in a double-blind fashion for MEDI0382 and placebo. Pre-filled syringes of MEDI0382 three different doses and placebo are visually distinct from one another. Clear, colourless solutions of MEDI0382 (0.5 mg/mL) will be supplied in 1 mL pre-filled syringes containing between 0.2 mL and 0.6 mL, depending on the dose. Buffer placebo will be supplied in 1 mL pre-filled syringe containing 0.3 mL. The different fill volumes and the relative position of the plunger rods will be visually distinct during administration. The IP kit cartons are identical in appearance which will be opened exclusively by subjects, just before taking the study drug (preferably at home). When administration occurs at the study site, subjects must open the kit and administer in absence of the site staff. The investigator should instruct subjects to ask only IP manager for any questions about study medication. The sponsor staff, the subjects, and the Investigators involved in the treatment of subjects or in the clinical evaluation of subjects will not be aware of the treatment received (ICH E9). IP will be handled by a designated individual (IP manager – pharmacist/study nurse) at the study site who will not be involved in the management or evaluation of study subjects. The tasks will/ may include dispensing of IP, collection of used IP boxes along with unused doses, drug accountability, instructing the subject on self-administration. This designated individual may also administer the IP during the subject's on-site visit, and answer the subject's questions related to the IP administration. IP managers should keep documents of drug accountability away from the site stuff who are involved in the management or evaluation of study subjects.

There may also be a designated site Monitor to verify drug accountability performed by designated IP manager.

The results for FPG, HbA1c, S-Glucose, fructosamine and the measurement result of efficacy evaluation (see Section 8.1)are blinded to the Investigator for all visits except Visits 1 and 2.

Body weight is not blinded measurement item. S-Glucose values are blinded to the Investigator site until the unblinding criteria for rescue therapy is met. Once the criteria is met, S-Glucose will be reported from the Central Laboratory to the site for an individual subject. Previous values will remain blinded and the site will only receive the values going forward from the point the criteria is met. The central laboratory will notify the Investigator to repeat S-Glucose without providing an explanation, and if the repeated S-Glucose value is at or above the defined level for the visit an instruction will be sent to the site by the Central Laboratory to start glycaemic rescue therapy in the subject.

6.4 Treatment compliance

Any change from the dosing schedule, does interruptions, dose reductions, dose discontinuations should be recorded in eCRF.

The Investigational Product Storage Manager is responsible for managing the IP from receipt by the study site until the destruction or return of all unused IP. The Investigator(s) is responsible for ensuring that the subject has returned all unused IP.

6.5 Concomitant therapy

Any medication or vaccine including over-the-counter or prescription medicines, vitamins, and/or herbal supplements that the subject is receiving at the time of enrolment or receives during the study must be recorded along with:

- Reason for use
- Dates of administration including start and end dates
- Dosage information including dose and frequency

6.5.1 Prohibited concomitant medication

Use of the following medications are restricted, generally speaking, from the time specified in the entry criteria until after the final follow-up visit:

- Use of other concomitant medications, including over-the-counter medications, herbal supplements, multivitamins, and vitamins containing selenium, that are thought to play a role in control of body weight or appetite, is prohibited from 1 week prior to Day 1 until after the final follow-up visit. Subjects must be instructed not to take any medications, including over-the-counter products, without first consulting with the investigator.
- Use of any anti-hyperglycaemic medication is prohibited (from the time of signing the informed consent form until after the final follow-up visit).
- Systemic corticosteroids are prohibited within 28 days prior to screening and throughout the study, except if needed to treat a generalized allergic reaction or anaphylaxis (Inhaled, intranasal, topical, and intra-articular corticosteroids are permitted). Systemic corticosteroid use should first be discussed with and permitted by the medical monitor.

- Compounds known to prolong the QTc interval are prohibited (from the time of signing the informed consent form until after the final follow-up visit).
- Refer to https://www.crediblemeds.org/healthcare-providers/.

6.5.2 Other concomitant treatment

Other medication than that those described above, which is considered necessary for the subject's safety and wellbeing, may be given at the discretion of the Investigator and recorded in the appropriate sections of the Case Report Form.

Investigators may prescribe concomitant medications or treatments deemed necessary to provide adequate supportive care except for those medications described in Section 6.5.1. Subjects may also continue to take their regular prescribed dose of statin during the study. Statins are allowed in all cohorts.

Subjects should receive full supportive care during the study in accordance with their institutional guidelines. In the event of nausea or vomiting subjects should be encouraged to reduce oral intake of food until symptoms pass. In the event that symptoms do not improve, subjects should be offered a centrally acting anti-emetic such as a 5 hydroxytryptamine-3 antagonist in the first instance, rather than a prokinetic agent such as domperidone or metoclopramide. Hormone replacement therapy and agents for benign prostatic hyperplasia are also permitted.

Appropriate measures should also be taken when a subject reports adverse event due to self injection.

6.5.3 Rescue medication

Subjects with inadequate glycemic control based on glycemic criteria as outlined in Table 7 should remain in the study and can receive rescue therapy with any anti-hyperglycemics excluding DPPIVi, SGLT2i, GLP-RA). Unless they still have glycemic control improved with the rescue therapy, the investigators may discuss with the AstraZeneca physician to decide to discontinue the treatment. From Visit 3 to Visit 12, if the results of S-Glucose at the visit show more than 270 mg/dL, the investigators should set up extra visit some other day in order to recheck the S-Glucose at the Central Laboratory. If the results of S-Glucose show more than 270 mg/dL consecutively at this second visit, the investigators can consider starting rescue treatment. See 6.3.1 for details of S-Glucose reports from the Central Laboratory. If significant vomiting (defined as 3 or more episodes in a day or two consecutive days despite change of food intake) occurs, adjust aqueous electrolytes balance while monitoring electrolytes and urea measured by the site, at the discretion of the investigators.

Table 7 Criteria for initiation of rescue therapy during the randomised treatment period

Period	Central Laboratory S-Glucose
From Visit 3 (Day 1) to Visit 12 (Day 48)	S-Glucose > 270 mg/dL (twice in a row)

7 DISCONTINUATION OF TREATMENT AND SUBJECT WITHDRAWAL

7.1 Discontinuation of study treatment

Subjects may be discontinued from investigational product (IP) in the following situations. Note that discontinuation from study treatment is NOT the same thing as a complete withdrawal from the study and reasonable effort should be made for the subject to remain in the study.

- Subject decision. The subject is at any time free to discontinue treatment, without prejudice to further treatment.
- Adverse Event
- Severe non-compliance with the Clinical Study Protocol
- Withdrawal of consent from further treatment with investigational product
- 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 (e.g., refusal to adhere to scheduled visits).

See the SoA for data to be collected at the time of treatment discontinuation and follow-up and for any further evaluations that need to be completed.

7.1.1 Procedures for discontinuation of study treatment

The investigator should instruct the subject to contact the site before or at the time of docontinuation of investigational product. If the investigational product is permanently discontinued as judged by the Investigator, the subject will be followed for protocol-specified assessments at Visit 12/Withdrawal except for MMT as well as Visit 13. Any AEs that are not resolved at the subject's last AE assessment in the study are followed up as instructed in the Section 8.3.3. The date of last intake of Study treatment should be documented in the eCRF. All investigational product should be returned by the subject at their next on-site study

visit (e.g., Visit 13). Subjects permanently discontinuing Study treatment should be given locally available standard of care therapy, at the discretion of the Investigator.

7.2 Lost to follow-up

A subject will be considered potentially lost to follow-up if he or she fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a subject fails to return to the clinic for a required study visit:

- The site must attempt to contact the subject and reschedule the missed visit as soon as possible and counsel the subject on the importance of maintaining the assigned visit schedule.
- Before a subject is deemed lost to follow up, the investigator or designee must make every effort to regain contact with the subject or next of kin by e.g. repeat telephone calls, certified letter to the subject´s last known mailing address or local equivalent methods. These contact attempts should be documented in the subject's medical record.
- Should the subject be unreachable at the end of the study the subject should be considered to be lost to follow up with unknown vital status at end of study and censored at latest follow up contact.

7.3 Withdrawal from the study

A subject may withdraw from the study (e.g., withdraw consent), at any time at his/her own request, without prejudice to further treatment. A subject who discontinues study medication should be encouraged to continue in the study.

If the subject withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.

If a subject withdraws from the study, he/she may request destruction of any samples taken, and the investigator must document this in the site study records.

A subject who withdraws consent will always be asked about the reason(s) and the presence of any adverse events (AE). The Investigator will follow up subjects as medically indicated.

See SoA, Table 2, for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed. All investigational product should be returned by the subject.

8 STUDY ASSESSMENTS AND PROCEDURES

Study procedures and their timing are summarised in the SoA.

The investigator will ensure that data are recorded on the eCRFs. The Electronic Data Capture (EDC) system will be used for data collection and query handling.

The investigator ensures the accuracy and completeness of study data. For eCRFs, this includes: legibility 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 electronic Case Report Forms. A copy of the completed electronic Case Report Forms will be archived at the study site.

Immediate safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the subject should continue or discontinue Study treatment.

Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.

All screening evaluations must be completed and reviewed to confirm that potential subjects meet all eligibility criteria. The investigator will maintain a screening log to record details of all subjects screened and to confirm eligibility or record reasons for screening failure, as applicable.

Procedures conducted as part of the subject's routine clinical management (e.g., blood count) and obtained before signing of the ICF may be utilised for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the SoA.

The maximum amount of blood collected from each subject over the duration of the study, including any extra assessments that may be required, will not exceed about 352.9 mL. Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

8.1 Efficacy assessments

8.1.1 Mixed-meal Test

Refer to Section 8.7

8.1.2 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.

8.1.3 HbA1c, Fasting plasma glucose and fructosamine

Blood samples for measurement of HbA1c, fasting plasma glucose and fructosamine will be collected according to the schedule presented in the Study Plan (Table 1 and Table 2). The instructions for collection, processing, packaging, and shipping of the samples will be detailed in the Laboratory Manual.

8.1.4 Continuous glucose monitoring (CGM)

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 the investigator should avoid review of baseline readings taken on at screening.

Data collected by FreeStyleLibrePro will be stored at the study site as source data. An unblinded study site personnel will electronically store the data collected by FreeStyleLibrePro in a secure external media managed by an unblinded Sponsor personnel. The unblinded Sponsor personnel will regularly review integrity of the data provided by the study site. Frequency and procedure of the data provision by the study site as well as the procedure to review and manage the data by the unblinded Sponsor personnel will be specified separately as a procedure manual.

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.

8.2 Safety assessments

Planned time points for all safety assessments are provided in the SoA.

8.2.1 Clinical safety laboratory assessments

See Table 8 for the list of clinical safety laboratory tests to be performed and to the SoA for the timing and frequency. All protocol-required laboratory assessments, as defined in the table, must be conducted in accordance with the laboratory manual and the SoA.

The Investigator should make an assessment of the available results with regard to clinically relevant abnormalities. The laboratory results should be signed and dated and retained at centre as source data for laboratory variables.

For information on how AEs based on laboratory tests should be recorded and reported, see Section 8.3.7.

Additional safety samples may be collected if clinically indicated at the discretion of the Investigator. The date, time of collection and results (values, units and reference ranges) will be recorded on the appropriate eCRF.

The clinical chemistry, haematology and hemostasis will be performed at a central laboratory. The urinalysis will be performed at a local laboratory.

Table 8 Laboratory safety variables

Haematology/Haemostasis (whole blood)	Clinical Chemistry (serum)
B-Haemoglobin	S-Creatinine
B-Leukocyte count	S-Bilirubin, total
B-Leukocyte differential count (absolute count)	S-Alkaline phosphatise (ALP)
B-Platelet count	S-AST
B-Red blood cell	S-ALT
B-Hematocrit	S-Albumin
B-Mean corpuscular volume	S-Potassium
B-Mean corpuscular hemoglobin concentration	S-Calcium
	S-Sodium
Coagulation	S-Chloride
Prothrombin time (screening only)	S-Gamma glutamyl transferase

Activated partial thromboplastin time (screening only)	S-Blood urea nitrogen
	S-Glucose
U-Urinalysis	S-Bicarbonate
Colour/Appearance	beta-hydroxybutyrate
Specific gravity	
potential of hydrogen	
Protein	
Glucose	
Ketones	
Blood	
Leucocyte esterase	
Bilirubin	
Urobilinogen	
Nitrite	

Notes: Tests for AST, ALT, ALP, and total bilirubin must be conducted concurrently and assessed concurrently. Urinalysis for specific gravity, pH, protein, glucose, ketones, blood, leucocyte esterase, bilirubin, urobilinogen, and nitrite may be performed at the site using a licensed test (dipstick).
NB. In case a subject shows an AST or ALT ≥ 3xULN together with total bilirubin ≥ 2xULN please refer to Appendix E 'Actions required in cases of increases in liver biochemistry and evaluation of Hy's Law', for further instructions.

Other Tests

- Calcitonin (screening only), thyroid-stimulating hormone (screening only), pancreatic amylase, lipase
- Blood lactate
- HbA1c
- Anti-drug antibodies
- Total immunoglobulin (Ig) and subsets (Ig A/E/G/M)
- Urine or serum (human chorionic gonadotropin) pregnancy test (females only)
- Hepatitis B surface antigen, hepatitis C antibody (screening only)
- Glucose metabolism panel for MMT: Timed glucose, insulin, pro-insulin, c-peptide, GLP-1, and glucagon.
- Fructosamine

- Fasting lipid profile: HDL-C, LDL-C, TG, and FFA
- TG

8.2.2 Physical examinations

A complete physical examination will be performed and include an assessment of the following: general appearance, respiratory, cardiovascular, abdomen, skin, head and neck (including ears, eyes, nose and throat), lymph nodes, thyroid, musculo-skeletal (including spine and extremities) and neurological systems.

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

Physical examination will be performed at timelines as specified in the SoA, Investigators should pay special attention to clinical signs related to previous serious illnesses, new or worsening abnormalities may qualify as adverse events, see Sections 8.3.6 and 8.3.7 for details. Height will be measured at screening.

8.2.3 Vital signs

- Axillary temperature, pulse rate, respiratory rate, and blood pressure will be assessed.
- Blood pressure and pulse measurements will be assessed in the supine position for at least 10 minutes with a completely automated device. Manual techniques will be used only if an automated device is not available.
- Blood pressure and pulse measurements should be preceded by at least 10 minutes of rest for the subject in a quiet setting without distractions (e.g., television, cell phones).
- Vital signs (to be taken before blood collection for laboratory tests) will consist of 1 pulse and 3 blood pressure measurements (3 consecutive blood pressure readings will be recorded at intervals of at least 1 minute). The average of the 3 blood pressure readings will be recorded on the eCRF.
- ABPM will be used for the 24-hour period at Visit 2 (as a baseline) and at Visit 10, Visit 12 after receipt of the SC dose at the clinic visit.
- The subject should do a Ketostix® test daily on non-clinic-visit days during the at-home self-administration period

8.2.4 Electrocardiograms

Triplicate 12-lead ECG will be obtained as outlined in the SoA (see Section 1.1) using an ECG machine that automatically calculates the heart rate and measures respiration rate, pulse rate, QRS, and QT intervals. Derived parameters (such as HR, QTcF and others as applicable) will be calculated.

At each time point at which triplicate ECG are required, 3 individual ECG tracings should be obtained in succession, no more than 2 minutes apart. The full set of triplicates should be completed within 5 minutes.

8.2.5 Other safety assessments

8.2.5.1 Ambulatory Blood Pressure Monitoring

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

Data collected by ABPM device will be stored at the study site as source data. The data collected by ABPM device will be stored in a secure external media managed by the Sponsor. The Sponsor will regularly review integrity of the data provided by the study site. Frequency and procedure of the data provision by the study site as well as the procedure to review and manage the data by the Sponsor will be specified separately as a procedure manual.

8.2.5.2 Daily Diaries

On Day -1 (Visit 2), each subject will be trained on how to complete the Daily Diary according to the schedule outlined in SoA. Subjects will be encouraged to complete the Daily Diary as accurately as possible.

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

- Date
- Confirmation that the acceptable temperature was maintained
- Unique kit number of dose
- Time of self-dose administration
- Start time of each meal

- Daily Ketostix® result (negative or positive) (Note: In case a Ketostix® [ketone] test result is positive, the subject will be instructed to call the site.)
- Any new medications or changes to standard medications (Note: Subjects will be instructed to contact the site in the event of any new medications or changes to medication.)
- Any vomiting and time of each episode
- Any other events

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

8.3 Collection of adverse events

The investigator is responsible for ensuring that all staff involved in the study are familiar with the content of this section

The definitions of an AE or SAE can be found in Appendix B.

AE will be reported by the subject (or, when appropriate, by a caregiver, surrogate, or the subject's legally authorized representative).

The investigator and any designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE. For information on how to follow/up AEs see section 8.3.3.

8.3.1 Method of detecting AEs and SAEs

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the subject is the preferred method to inquire about AE occurrences.

8.3.2 Time period and frequency for collecting AE and SAE information

Adverse Events will be collected from Visit 2 or Visit 3 (randomisation) throughout the treatment period and including the follow-up period, Visit 13.

SAEs will be recorded from the time of signing of informed consent form.

All SAEs will be recorded and reported to the sponsor or designee within 24 hours, as indicated in Appendix B. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.

Investigators are not obligated to actively seek AE or SAE in former study subjects. However, if the investigator learns of any SAE, including a death, at any time after a subject’s last visit

and he/she considers the event to be reasonably related to the Study treatment or study participation, the investigator may notify the sponsor.

The method of recording, evaluating, and assessing causality of AE and SAE is provided in Appendix B.

8.3.3 Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each subject at subsequent visits/contacts. All SAE/non-serious AEs will be followed until resolution, stabilization, the event is otherwise explained, or the subject is lost to follow-up.

Any AEs that are unresolved at the subject's last AE assessment in the study are followed up by the Investigator for as long as medically indicated, but without further recording in the eCRF. AstraZeneca 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.

8.3.4 Adverse event data collection

'The following variables will be collected for each AE:

- AE
- The date when the AE started and stopped
- Maximum intensity
- Whether the AE is serious or not
- Investigator causality rating against the Investigational Product(s) (yes or no)
- Action taken with regard to Investigational Product(s)
- AE causing subject's withdrawal from study (yes or no)
- Outcome.

In addition, the following variables will be collected for SAEs:

- Date AE met criteria for serious AE
- Date Investigator became aware of serious AE
- AE is serious due to
- Date of hospitalisation
- Date of discharge
- Probable cause of death
- Date of death
- Autopsy performed
- Causality assessment in relation to Study procedure(s)
- Causality assessment to other medication

8.3.5 Causality collection

The Investigator will assess causal relationship between Investigational Product and each Adverse Event, and answer 'yes' or 'no' to the question 'Do you consider that there is a reasonable possibility that the event may have been caused by the investigational product?'

For SAEs, causal relationship will also be assessed for other medication and study procedures and/or AstraZeneca (AZ) Medical device. Note that for SAEs that could be associated with any study procedure the causal relationship is implied as 'yes'.

A guide to the interpretation of the causality question is found in Appendix B.

8.3.6 Adverse events based on signs and symptoms

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

8.3.7 Adverse events based on examinations and tests

The results from the Clinical Study Protocol mandated laboratory tests and vital signs will be summarised in the CSR. Deterioration as compared to baseline in protocol-mandated laboratory values, vital signs and physical examinations should therefore only be reported as AEs if they fulfil any of the SAE criteria or are the reason for discontinuation of treatment with the investigational product.

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

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

8.3.8 Hy's law

Cases where a subject shows elevations in liver biochemistry may require further evaluation and occurrences of AST or ALT ≥ 3xULN together with total bilirubin ≥ 2xULN may need to

be reported as SAEs. Please refer to Appendix E for further instruction in the case of increases in liver biochemistry and evaluation of Hy's Law

8.4 Safety reporting and medical management

8.4.1 Reporting of serious adverse events

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

If any SAE occurs in the course of the study, then Investigators or other site personnel inform the appropriate AstraZeneca representatives within one day i.e., immediately but **no later than 24 hours** of when he or she becomes aware of it.

The designated AstraZeneca representative works with the Investigator to ensure that all the necessary information is provided to the AstraZeneca 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 adverse events where important or relevant information is missing, active follow-up is undertaken immediately. Investigators or other site personnel inform AstraZeneca representatives of any follow-up information on a previously reported SAE within one calendar day i.e., immediately but **no later than 24 hours** of when he or she becomes aware of it.

Once the Investigators or other site personnel indicate an AE is serious in the EDC system, an automated email alert is sent to the designated AstraZeneca representative.

If the EDC system is not available, then the Investigator or other study site staff reports an SAE to the appropriate AstraZeneca representative by telephone.

The AstraZeneca representative will advise the Investigator/study site staff how to proceed.

For further guidance on the definition of a SAE, see Appendix B of the Clinical Study Protocol.

8.4.2 Pregnancy

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

- If the pregnancy is discovered before the study subject has received any study drug
- If a pregnancy is reported, the investigator should inform the sponsor within 24 hours of learning of the pregnancy.
- If the investigator become aware of a pregnancy in the partner of a male study subject who has received investigational product, then the investigator or other site personnel will

inform the appropriate sponsor representatives within 24 hours of learning of the pregnancy.

- Abnormal pregnancy outcomes (e.g., spontaneous abortion, foetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs.

8.4.2.1 Maternal exposure

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

Pregnancy itself is not regarded as an adverse event 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 informs the appropriate AstraZeneca representatives within 1day i.e., immediately but **no later than 24 hours** of when he or she becomes aware of it.

The designated AstraZeneca representative works with the Investigator to ensure that all relevant information is provided to the AstraZeneca Patient Safety data entry site within 1 or 5 calendar days for SAEs (see Section 8.4.1) and within 30 days for all other pregnancies.

The same timelines apply when outcome information is available.

The PREGREP module in the eCRF is used to report the pregnancy.

8.4.3 Overdose

For this study, any dose of MEDI0382 greater than the dose at > 300 µg will be considered an overdose. The investigator should report an overdose to the sponsor when the subject injects more than once a day.

No specific treatment is recommended for an overdose.

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

If an overdose on an AstraZeneca study drug occurs in the course of the study, then the Investigator or other site personnel inform appropriate AstraZeneca representatives immediately, or **no later than 24 hours** of when he or she becomes aware of it.

The designated AstraZeneca representative works with the Investigator to ensure that all relevant information is provided to the AstraZeneca Patient Safety data entry site.

- For overdoses associated with a SAE, the standard reporting timelines apply, see Section 8.3.2. For other overdoses, reporting must occur within 30 days.

8.4.4 Medical device incidents (including malfunctions)

Medical devices are being provided for use in this study. In order to fulfil regulatory reporting obligations worldwide, the investigator is responsible for the detection and documentation of events meeting the definitions of incident or malfunction that occur during the study with such devices.

The definition of a Medical Device Incident can be found in Appendix F

NOTE: Incidents fulfilling the definition of an AE/SAE will also follow the processes outlined in Section 8.3 and Appendix B.

8.4.4.1 Time period for detecting medical device incidents

- Medical device incidents or malfunctions of the device that result in an incident will be detected, documented, and reported during all periods of the study in which the medical device is used.
- If the investigator learns of any incident at any time after a subject has been discharged from the study, and such incident is considered reasonably related to a medical device provided for the study, the investigator will promptly notify the sponsor.

The method of documenting Medical Device Incidents is provided in Appendix F.

8.4.4.2 Follow-up of medical device incidents

- All medical device incidents involving an AE will be followed and reported in the same manner as other AEs (see Section 8.3.3). This applies to all subjects, including those who discontinue Study treatment.
- The investigator is responsible for ensuring that follow-up includes any supplemental investigations as indicated to elucidate the nature and/or causality of the incident.
- New or updated information will be recorded on the originally completed form with all changes signed and dated by the investigator.

8.4.4.3 Reporting of medical device incidents to sponsor

- Medical device incidents will be reported to the sponsor within 24 hours after the investigator determines that the event meets the protocol definition of a medical device incident.
- Medical Device Incident will be reported via eCRF. If eCRF is unavailable, then e-mail communication should be utilized.
- The same individual will be the contact for the receipt of medical device reports and SAE.
- If an investigational medical device is used, the Study Representative will send the SAE report to AZ data entry site within **one calendar day**.

8.4.4.4 Regulatory reporting requirements for medical device incidents

- The investigator will promptly report all incidents occurring with any medical device provided for use in the study in order for the sponsor to fulfil the legal responsibility to notify appropriate regulatory authorities and other entities about certain safety information relating to medical devices being used in clinical studies.
- The investigator, or responsible person according to local requirements (e.g., the head of the medical institution), will comply with the applicable local regulatory requirements relating to the reporting of incidents to the IRB/IEC.

8.4.5 Medication error

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

The designated AstraZeneca representative works with the Investigator to ensure that all relevant information is completed within 1 (Initial Fatal/Life-Threatening or follow up Fatal/Life-Threatening) or 5 (other serious initial and follow up) calendar days if there is an SAE associated with the medication error (see Section 8.3.2) and within 30 days for all other medication errors.

The definition of a Medication Error can be found in Appendix B.

8.5 Pharmacokinetics

Blood samples for determination of MEDI0382 in plasma will be taken at the times presented in the Study Plan (Table 2).

Drug concentration information that would unblind the study will not be reported to investigative sites or blinded personnel until the study has been unblinded.

8.5.1 Determination of drug concentration

Samples for determination of drug concentration will be analysed by a selected laboratory on behalf of AstraZeneca, using an appropriate bioanalytical method. Full details of the analytical method used will be described in a separate bioanalytical report.

8.5.2 Storage and destruction of pharmacokinetic samples

PK samples will be disposed of after the Bioanalytical Report finalization or six months after issuance of the draft Bioanalytical Report (whichever is earlier), unless requested for future analyses.

Pharmacokinetic samples may be disposed of or destroyed and anonymised by pooling. Additional analyses may be conducted on the anonymised, pooled pharmacokinetic samples to further evaluate and validate the analytical method. Any results from such analyses may be reported separately from the CSR.

8.6 Immunogenicity

Instructions for MEDI0382 immunogenicity (ADA) sample collection, processing, storage, and shipment can be found in the Laboratory Manual. Serum samples for analysis of ADA will be collected for subjects on MEDI0382/Placebo arms according to the schedule presented in the Study Plan (Table 2). 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. For subjects with a confirmed positive ADA result, a qualitative analysis of incretin hormone levels in response to MMT (i.e., glucagon, GLP-1, glucose, and insulin) will also be performed to assess whether any correlation exists between the response and ADA positivity.

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 as close as 3 months at the end of study visit to evaluate whether or not ADA positivity is 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 (Approximately 6 months after the end of study visit). If the sample is ADA positive at 6 months, the investigator and the study physician will discuss what further action will be taken. The results of ADA in 3 months and 6 months at the end of study will not be recorded in the CRF module and the database. 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.

8.7 Pharmacodynamics

Mixed-meal Test

Following a minimum 8-hour overnight fast and at 2.5 hours after administration of IP, the subject will undergo a MMT. For the MMT, the subject will consume a standardised meal (ENSURE H, a nutritional supplement containing the components of fat, carbohydrate and protein, which make up a standard MMT) within 5 minutes, and timed serial blood samples will be obtained for measurement of glucose and parameters related to glucose metabolism through 240 minutes after consumption of the standardised meal (with no additional food intake during this time). The MMT procedures will be performed at the time points specified in the schedules. The time points are also summarized in SoA.

The timed pre- and post-MMT blood sample collections are for measurement of a panel of glucose metabolism markers: glucose, insulin, pro-insulin, c-peptide, GLP-1 and glucagon, as indicated in the example schedule for PK and PD/efficacy in Table 3 and Table 4. Glucose measurements from these pre- and post-MMT samples will be used for the primary efficacy assessment. All MMT test results will be used to generate PD profiles.

8.7.1 Collection of samples

Blood will be drawn 15 minutes before consuming the standardised meal, 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 MMT. Sampling ± 5 minutes of the specified time will not be considered a protocol deviation but the exact time of sampling should be recorded.

8.7.2 Storage, re-use and destruction of pharmacodynamic samples

The primary PD 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 CSR itself or as an addendum, or separately in a scientific report or publication.

8.8 Genetics

Participation is optional. Subjects who do not wish to participate in the genetic research may still participate in the study.

See Appendix D for Information regarding genetic research. Details on processes for collection and shipment and destruction of these samples can be found in Appendix D.

8.9 Biomarkers

Biomarkers are not evaluated in this study.

9 STATISTICAL CONSIDERATIONS

9.1 Statistical hypotheses

One of the primary objectives of this study is to assess the safety of MEDI 0382 100 μg, 200 μg, or 300 μg up-titration regimen compared with Placebo, as measured by the incidence of AEs (including SAEs), 24-hour heart rate and ABPM, safety laboratory measurements and digital ECGs. For the safety objective, no formal hypothesis testing will be carried out. Safety evaluation will be done in a descriptive manner.

The other primary objective is to explore the efficacy of MEDI0382 100 μg, 200 μg or 300 μg up-titration regimen compared with placebo, as measured by percent change from baseline to Day 48 in MMT glucose $AUC_{(0\text{-}4h)}$ and body weight. For efficacy objective, pair-wise comparison of each MEDI0382 dose vs. Placebo will be made in an exploratory manner, each at significance level of 0.05, without multiplicity adjustment.

9.2 Sample size determination

Approximately 60 patients are to be randomized to Placebo, MEDI0382 100 μg, 200 μg, and 300 μg in a ratio 1:1:1:1.

Assuming approximately 10% drop out during study, approximately 13 subjects are expected to be evaluable per treatment groups.

Assuming standard deviation of percent change in MMT glucose $AUC_{(0\text{-}4h)}$ of 20%, approximately 13 patients per arm would provide more than 80% power to detect 23% difference in percent change of MMT glucose $AUC_{(0\text{-}4h)}$ for pair‐wise comparison between each of MEDI0382 dose group and Placebo each at two-sided alpha = 0.05, without formal multiplicity adjustment.

Assuming standard deviation of percent change from baseline in body weight of 2.5%, the same number of subjects would provide approximately 68% power to detect mean difference of 2.5% at two-sided alpha =0.05 without formal multiplicity adjustment.

9.3 Populations for analyses

For purposes of analysis, the following populations are defined:

Population	Description
Enrolled	All subjects who signed the ICF
Randomised Set	All subjects who received randomisation number.
Full Analysis Set	All randomised subjects who received at least one dose of IP. Subjects will be analysed according to randomized treatment.
Safety analysis set	All randomised subjects who take at least 1 dose of IP. Subjects will be analysed according to treatment they received.
PK analysis set	The PK population includes all subjects who received at least one dose of MEDI0382 and had at least one post-baseline MEDI0382 PK sample taken that is above the lower limit of quantitation.

9.4 Statistical analyses

All personnel involved with the analysis of the study will remain blinded until database lock and Clinical Study Protocol deviations identified.

Analyses will be performed by AstraZeneca or its representatives. A comprehensive statistical analysis plan (SAP) will be developed and finalised before database lock and will describe the subject populations to be included in the analyses, and procedures for accounting for missing, unused, and spurious data. This section is a summary of the planned statistical analyses of the primary and secondary endpoints. Any deviations from this plan will be reported in the clinical study report.

9.4.1 Efficacy analyses

Efficacy analyses will be carried out for FAS.

Percent change from baseline in MMT Glucose $AUC_{(0\text{-}4h)}$ to Day 48 will be analysed with ANCOVA model with treatment group as a factor and baseline as a covariate. Least squares mean (LSMean)s and their 95%CIs for percent changes from baseline for each treatment group, as well as difference in LSMeans, 95%CI and nominal p-values will be provided for pair-wise comparison of each MEDI0382 dose vs. Placebo group. For subjects who prematurely discontinued study drug, the last on-treatment measurement regardless of rescue will be used for this analysis. Percent change from baseline to Day 48 in body weight will be analysed similarly.

Secondary efficacy variables will be analysed by ANCOVA or other appropriate models. Details will be provided in Statistical Analysis Plan.

9.4.2 Safety analyses

Safety analysis will be based on Safety set.

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). The type, incidence, severity and relationship to investigational product of each AE will be summarized by MedDRA System Organ Class and Preferred Term, using number and percentage of patients with certain events. AEs with onset on or after first day of IP will be mainly evaluated. Other safety variables such as 24-hour ABPM, vital signs, ECG and safety laboratory tests will be summarized descriptively by treatment and visit, as appropriate.

9.4.3 Other analyses (PK)

Individual MEDI0382 plasma concentrations will be summarised by treatment and visit. MEDI0382 plasma concentration at trough (C_{trough}) may be summarised by treatment and visit using descriptive statistics for the MEDI0382 treatment arms.

A population PK analysis may be performed to further evaluate the PK properties of MEDI0382, but will not be reported in the CSR.

The immunogenicity of 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.

Pharmacodynamic, and biomarker exploratory analyses will be described in the SAP finalised before database lock. The pharmacodynamic analyses will be presented separately from the main CSR.

9.5 Interim analyses

Not applicable.

9.5.1 Data monitoring committee (DMC)

Not applicable.

10 REFERENCES

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11 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

Appendix A Regulatory, ethical and study oversight considerations

A 1 Regulatory and ethical considerations

This study will be conducted in accordance with the protocol and with the following:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences International Ethical Guidelines
- Applicable ICH GCP Guidelines
- Applicable laws and regulations

The protocol, protocol amendments, ICF, Investigator Brochure, and other relevant documents (e.g., advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.

Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study subjects.

The head of the study site will be responsible for the following:

- Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
- Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
- Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations

The study will be performed in accordance with the AstraZeneca policy on Bioethics and Human Biological Samples.

A 2 Financial disclosure

Not applicable.

A 3 Informed consent process

The investigator or his/her representative will explain the nature of the study to the subject or his/her legally authorised representative and answer all questions regarding the study.

Subjects must be informed that their participation is voluntary. Subjects or their legal representatives will be required to sign a statement of informed consent that meets the

requirements of local regulations, ICH guidelines, Health Insurance Portability and Accountability Act, where applicable, and the IRB/IEC or study centre.

The medical record must include a statement that written informed consent was obtained before the subject was enrolled in the study and the date the written consent was obtained. The authorised person obtaining the informed consent must also sign the ICF.

Subjects must be re-consented to the most current version of the ICF(s) during their participation in the study.

A copy of the ICF(s) must be provided to the subject or the subject's legally authorised representative.

The investigator or authorised designee will explain to each subject the objectives of the exploratory research. Subjects will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the storage period. The subject will give a separate agreement to allow any remaining specimens to be used for exploratory research. Subjects who decline to participate in this optional research will indicate this in the ICF. 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 already have been analysed at the time of the request, AstraZeneca will not be obliged to destroy the results of this research.

A 4 Data protection

Each subject will be assigned a unique identifier by the sponsor. Any subject records or data sets transferred to the sponsor will contain only the identifier; subject names or any information which would make the subject identifiable will not be transferred.

The subject must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the subject.

The subject must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorised personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

A 5 Committee's structure

The safety of all AstraZeneca clinical studies is closely monitored on an on-going basis by AstraZeneca representatives in consultation with Patient Safety. Issues identified will be addressed; for instance this could involve amendments to the Clinical Study Protocol and letters to Investigators.

A 6 Dissemination of clinical study data

A description of this clinical trial will be available on *http://astrazenecaclinicaltrials.com* and *http://www.clinicaltrials.gov* as will the summary of the study results when they are available. The clinical trial and/or summary of study results may also be available on other websites according to the regulations of the countries in which the study is conducted.

A 7 Data quality assurance

All subject data relating to the study will be recorded on printed or eCRF unless transmitted to the sponsor or designee electronically (e.g., laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the eCRF.

The investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.

The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.

The sponsor or designee is responsible for the data management of this study including quality checking of the data.

Study monitors will perform ongoing source data verification to confirm that data entered into the eCRF by authorised site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of subjects are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator for 15 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

A 8 Source documents

Source documents provide evidence for the existence of the subject and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.

Data reported on the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

Definitions of what constitutes source data can be found in Clinical Study Agreement.

A 9 Publication policy

The results of this study may be published or presented at scientific meetings. If this is foreseen, the investigator agrees to submit all manuscripts or abstracts to the sponsor before submission. This allows the sponsor to protect proprietary information and to provide comments.

The sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the sponsor will generally support publication of multicentre studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

Appendix B Adverse event definitions and additional safety information

B 1 Definition of adverse events

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

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

B 2 Definitions of serious adverse event

A serious adverse event is an AE occurring during any study phase (i.e., run-in, treatment, washout, follow-up), that fulfils one or more of the following criteria:

- Results in death
- Is immediately life-threatening
- Requires in-subject hospitalisation or prolongation of existing hospitalisation
- Results in persistent or significant disability or incapacity.
- Is a congenital abnormality or birth defect
- Is an important medical event that may jeopardise the subject or may require medical treatment to prevent one of the outcomes listed above.

B 3 Life threatening

'Life-threatening' means that the subject was at immediate risk of death from the 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 (e.g., hepatitis that resolved without hepatic failure).

B 4 Hospitalisation

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

B 5 Important medical event or medical treatment

Medical and scientific judgement 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 treatment 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 judgement must be used.

Examples of such events are:

- Angioedema not severe enough to require intubation but requiring iv 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 (e.g., neutropenia or anaemia requiring blood transfusion, etc.) or convulsions that do not result in hospitalisation
- Development of drug dependency or drug abuse

B 6 Assessment of Severity

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

Grade 1 An event of mild intensity that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.

Grade 2 An event of moderate intensity that is usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the subject.

Grade 3 A severe event that requires intensive therapeutic intervention. The event interrupts usual activities of daily living, or significantly affects the clinical status of the subject.

Grade 4 An event, and/or its immediate sequelae, that is associated with an imminent risk of death.

Grade 5 Death (loss of life) as a result of an event.

It is important to distinguish between serious criteria and severity of an AE. Severity is a measure of intensity whereas seriousness is defined by the criteria in Appendix B 2. A Grade 3 AE needs 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.

B 7 A Guide to Interpreting the Causality Question

When making an assessment of causality consider the following factors when deciding if there is a 'reasonable possibility' that an AE may have been caused by the drug.

- Time Course. Exposure to suspect drug. Has the subject actually received the suspect drug? Did the AE occur in a reasonable temporal relationship to the administration of the suspect drug?
- Consistency with known drug profile. Was the AE consistent with the previous knowledge of the suspect drug (pharmacology and toxicology) or drugs of the same pharmacological class? Or could the AE be anticipated from its pharmacological properties?
- De-challenge experience. Did the AE resolve or improve on stopping or reducing the dose of the suspect drug?
- No alternative cause. The AE cannot be reasonably explained by another aetiology such as the underlying disease, other drugs, other host or environmental factors.
- Re-challenge experience. Did the AE reoccur if the suspected drug was reintroduced after having been stopped? AstraZeneca would not normally recommend or support a re-challenge.
- Laboratory tests. A specific laboratory investigation (if performed) has confirmed the relationship.

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

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

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

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

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

B 8 Medication Error

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

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

Medication error includes situations where an error.

- occurred
- was identified and intercepted before the participant received the drug
- did not occur, but circumstances were recognised that could have led to an error

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

- Drug name confusion
- Dispensing error e.g. medication prepared incorrectly, even if it was not actually given to the participant
- Drug not administered as indicated, for example, wrong route or wrong site of administration
- Drug not taken as indicated e.g. tablet dissolved in water when it should be taken as a solid tablet
- Drug not stored as instructed e.g. kept in the fridge when it should be at room temperature
- Wrong participant received the medication (excluding IVRS/IWRS errors)
- Wrong drug administered to participant (excluding IVRS/IWRS errors)

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

- Errors related to or resulting from IVRS/IWRS - including those which lead to one of the above listed events that would otherwise have been a medication error
- Participant accidentally missed drug dose(s) e.g. forgot to take medication
- Accidental overdose (will be captured as an overdose)
- Participant failed to return unused medication or empty packaging
- Errors related to background and rescue medication, or standard of care medication in open label studies, even if an AZ product

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

Appendix C Handling of Human Biological Samples

C 1 Chain of custody of biological samples

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

The Investigator at each centre keeps full traceability of collected biological samples from the subjects while in storage at the centre until shipment or disposal (where appropriate).

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.

AstraZeneca will keep oversight of the entire life cycle through internal procedures, monitoring of study sites, auditing or process checks, and contractual requirements of external laboratory providers.

Samples retained for further use will be stored in the AZ-assigned biobanks and will be registered by the AstraZeneca Biobank Team during the entire life cycle.

C 2 Withdrawal of Informed Consent for donated biological samples

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, AstraZeneca is not obliged to destroy the results of this research.

As collection of the biological sample(s) is an optional part of the study, then the subject may continue in the study.

The Investigator:

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

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

C 3 International Airline Transportation Association (IATA) 6.2 Guidance Document

LABELLING AND SHIPMENT OF BIOHAZARD SAMPLES

International Airline Transportation Association (IATA) classifies biohazardous agents into 3 categories For transport purposes the classification of infectious substances according to risk groups was removed from the Dangerous Goods Regulations in the 46th edition (2005). Infectious substances are now classified either as Category A, Category B or Exempt. There is no direct relationship between Risk Groups and Categories A and B.

Category A Infectious Substances are infectious substances in a form that, when exposure to it occurs, is capable of causing permanent disability, life-threatening or fatal disease in otherwise healthy humans or animals. Category A pathogens are e.g., Ebola, Lassa fever virus:

- are to be packed and shipped in accordance with IATA Instruction 602.

Category B Infectious Substances are infectious Substances that do not meet the criteria for inclusion in Category A. Category B pathogens are e.g., Hepatitis A, B, C, D, and E viruses, Human immunodeficiency virus types 1 and 2. They are assigned the following UN number and proper shipping name:

- UN 3373 – Biological Substance, Category B
- are to be packed in accordance with UN3373 and IATA 650

Exempt - all other materials with minimal risk of containing pathogens

- Clinical trial samples will fall into Category B or exempt under IATA regulations
- Clinical trial samples will routinely be packed and transported at ambient temperature in IATA 650 compliant packaging
- **Biological samples transported in dry ice require additional dangerous goods specification for the dry-ice content**
- IATA compliant courier and packaging materials should be used for packing and transportation and packing should be done by an IATA certified person, as applicable
- Samples routinely transported by road or rail are subject to local regulations which require that they are also packed and transported in a safe and appropriate way to contain any risk of infection or contamination by using approved couriers and packaging/containment materials at all times. The IATA 650 biological sample containment standards are encouraged wherever possible when road or rail transport is used.

Appendix D Genetics

D 1 Use/analysis of deoxyribonucleic acid (DNA)

Genetic variation may impact a subject's response to therapy, susceptibility to, and severity and progression of disease. Variable response to therapy may be due to genetic determinants that impact drug absorption, distribution, metabolism, and excretion; mechanism of action of the drug; disease aetiology; and/or molecular subtype of the disease being treated. Therefore, where local regulations and IRB/IEC allow, a blood sample will be collected for DNA analysis from consenting subjects.

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

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

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

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

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

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

D 2 Genetic research plan and procedures

Selection of genetic research population

Subject selection record

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

Inclusion criteria

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

Exclusion criteria

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

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

Withdrawal of consent for genetic research

Subjects may withdraw from this genetic research at any time, independent of any decision concerning participation in other aspects of the main study. Voluntary withdrawal will not prejudice further treatment. Procedures for withdrawal are outlined in Section 7.3.

Collection of samples for genetic research

The blood sample for genetic research will be obtained from the subjects predose at Visit 12. If for any reason the sample is not drawn at Visit 12, it may be taken at Visit 13. Only one sample should be collected per subject for genetics during the study. Samples will be collected, labelled, stored, and shipped as detailed in the Laboratory Manual.

Coding and storage of DNA samples

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

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

The link between the subject enrolment/randomisation code and the second number will be maintained and stored in a secure environment, with restricted access at AstraZeneca or

designated organisations. The link will be used to identify the relevant DNA samples for analysis, facilitate correlation of genotypic results with clinical data, allow regulatory audit, and permit tracing of samples for destruction in the case of withdrawal of consent.

Ethical and regulatory requirements

The principles for ethical and regulatory requirements for the study are outlined in Appendix A .

Informed consent

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

Subject data protection

AstraZeneca will not provide individual genotype results to subjects, any insurance company, any employer, their family members, general physician unless required to do so by law.

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

Data management

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

AstraZeneca and its designated organisations may share summary results (such as genetic differences from groups of individuals with a disease) from this genetic research with other researchers, such as hospitals, academic organisations or health insurance companies. This can be done by placing the results in scientific databases, where they can be combined with the results of similar studies to learn even more about health and disease. The researchers can

only use this information for health-related research purposes. Researchers may see summary results but they will not be able to see individual subject data or any personal identifiers.

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

Statistical methods and determination of sample size

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

Appendix E Actions required in cases of increases in liver biochemistry and evaluation of Hy's Law

E 1 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 AstraZeneca 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 medicinal product (IP).

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

E 2 Definitions

Potential Hy's Law (PHL)
Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) ≥ 3× upper limit of normal (ULN) **together with** total bilirubin (TBL) ≥ 2×ULN at any point during the study following the start of study medication irrespective of an increase in alkaline phosphatase (ALP).

Hy's Law (HL)
AST or ALT ≥ 3 × ULN **together with** TBL ≥ 2 ×ULN, where no other reason, other than the IP, can be found to explain the combination of increases, e.g., elevated ALP indicating cholestasis, viral hepatitis, another drug.

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

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

When a subject meets any of the identification criteria, in isolation or in combination, the central laboratory will immediately send an alert to the Investigator (and also to the AstraZeneca representative).

The Investigator will also remain vigilant for any local laboratory reports where the identification criteria are met, where this is the case the Investigator will:

- Notify the AstraZeneca representative
- Request a repeat of the test (new blood draw) by the central laboratory
- Complete the appropriate unscheduled laboratory eCRF module(s) with the original local laboratory test result

When the identification criteria are met from central or local laboratory results the Investigator will without delay:

- Determine whether the subject meets PHL criteria (see Appendix E 2 for definition) by reviewing laboratory reports from all previous visits (including both central and local laboratory results)

E 4 Follow-up

E 4.1 Potential Hy's Law criteria not met

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

- Inform the AstraZeneca 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.

E 4.2 Potential Hy's Law criteria met

If the subject does meet PHL criteria the Investigator will:

- Determine whether PHL criteria were met at any study visit prior to starting Study treatment (See Appendix E 2)
- Notify the AstraZeneca 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 aetiology of the event and perform diagnostic investigations as discussed with the Study Physician.
- Complete the three Liver CRF Modules as information becomes available
- If at any time (in consultation with the Study Physician the PHL case meets serious criteria, report it as an SAE using standard reporting procedures.

E 5 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 Study Physician contacts 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 IP. The AstraZeneca Global Clinical Lead or equivalent 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 AZ standard processes

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

- Report an SAE (report term 'Hy's Law') according to AstraZeneca 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 amending the reported term if an alternative explanation for the liver biochemistry elevations is determined.

Appendix F Medical device incidents: definition and procedures for recording, evaluating, follow-up, and reporting

F 1 Definitions of a Medical Device Incident

The detection and documentation procedures described in this protocol apply to all sponsor provided medical devices provided for use in the study (see Section 6.1.2) for the list of sponsor provided medical devices).

Medical Device Incident Definition
• A medical device incident is any malfunction or deterioration in the characteristics and/or performance of a device as well as any inadequacy in the labelling or the instructions for use which, directly or indirectly, might lead to or might have led to the death of a subject/user/other person or to a serious deterioration in his/her state of health. • Not all incidents lead to death or serious deterioration in health. The non-occurrence of such a result might have been due to other fortunate circumstances or to the treatment of health care personnel.

It is sufficient that:

- An **incident** associated with a device happened.
  AND
- The incident was such that, if it occurred again, might lead to death or a serious deterioration in health.

A serious deterioration in state of health can include any of the following:

- Life-threatening illness
- Permanent impairment of body function or permanent damage to body structure
- Condition necessitating medical or surgical treatment to prevent one of the above
- Foetal distress, foetal death, or any congenital abnormality or birth defects

Examples of incidents:
• A subject, user, caregiver, or healthcare professional is injured as a result of a medical device failure or its misuse. • A subject's Study treatment is interrupted or compromised by a medical device failure. • A misdiagnosis due to medical device failure leads to inappropriate treatment. A subject's health deteriorates due to medical device failure.

Documenting medical device incidents

Medical device incident documentation
• Any medical device incident occurring during the study will be documented in the subject's medical records, in accordance with the investigator's normal clinical practice, and on the appropriate form of the eCRF. • For incidents fulfilling the definition of an AE or an SAE, the appropriate AE/SAE eCRF page will be completed as described in Appendix B. • The eCRF will be completed as thoroughly as possible and signed by the investigator before transmittal to the sponsor or designee. • It is very important that the investigator provides his/her assessment of causality (relationship to the medical device provided by the sponsor) at the time of the initial AE or SAE report and describes any corrective or remedial actions taken to prevent recurrence of the incident. • A remedial action is any action other than routine maintenance or servicing of a medical device where such action is necessary to prevent recurrence of an incident. This includes any amendment to the device design to prevent recurrence.

Appendix G Summary of gastrointestinal events in Studies D5670C00002 and D5670C00011

Table 9 Study D5670C00002: Treatment-emergent Vomiting and/or Nausea by Study Day – All Cohorts – As-treated Population

MedImmune
MEDI0382-D5670C00002
CSR, DB lock updated 31AUG2017

Table 14.3.1_13
Treatment-emergent Vomiting and/or Nausea by Study Day – All Cohorts – As-treated Population

Study Day	MEDI0382 100µg N=6	MEDI0382 150µg N=6	MEDI0382 200µg (Coh3) N=7	MEDI0382 200µg (Coh4) N=25	MEDI0382 300µg (Coh5) N=11	MEDI0382 300µg (Coh6) N=12
1	0	3 (50.0%)	3 (42.9%)	7 (28.0%)	1 (9.1%)	1 (8.3%)
2	0	0	3 (42.9%)	5 (20.0%)	0	1 (8.3%)
3	0	1 (16.7%)	0	5 (20.0%)	0	0
4	0	0	0	3 (12.0%)	1 (9.1%)	0
5	0	3 (50.0%)	1 (14.3%)	6 (24.0%)	0	0
6	0	0	0	4 (16.0%)	2 (18.2%)	1 (8.3%)
7	0	0	0	5 (20.0%)	1 (9.1%)	1 (8.3%)
8		0	0	3 (12.0%)	1 (9.1%)	0
9		0	0	3 (12.0%)	0	0
10		0	0	2 (8.0%)	0	2 (16.7%)
11		1 (16.7%)	0	1 (4.0%)	2 (18.2%)	3 (25.0%)
12			0	3 (12.0%)	2 (18.2%)	1 (8.3%)
13			0	2 (8.0%)	2 (18.2%)	1 (8.3%)
14			0	1 (4.0%)	1 (9.1%)	1 (8.3%)
15			0	2 (8.0%)	1 (9.1%)	1 (8.3%)
16				2 (8.0%)	3 (27.3%)	1 (8.3%)
17				1 (4.0%)	1 (9.1%)	1 (8.3%)
18				2 (8.0%)	2 (18.2%)	1 (8.3%)
19				3 (12.0%)	1 (9.1%)	
20				3 (12.0%)	1 (9.1%)	
21				3 (12.0%)	1 (9.1%)	

Cohorts have different lengths of treatment period.
Subjects are counted once for each System Organ Class and Preferred Term regardless of the number of events.
Refers to Supporting Data Listing(s) 16.2_7.2.

Program (Output): /SASDATA/cars/prod/medi0382/d5670c00002/csr/tables/aete_vomnaus2.sas (aete_vomnaus2.rtf)
Standard Template NA

Validated
11SEP2017 9:22

MedImmune
MEDI0382-D5670C00002
CSR, DB lock updated 31AUG2017

Table 14.3.1_13
Treatment-emergent Vomiting and/or Nausea by Study Day – All Cohorts – As-treated Population

Study Day	MEDI0382 100µg N=6	MEDI0382 150µg N=6	MEDI0382 200µg (Coh3) N=7	MEDI0382 200µg (Coh4) N=25	MEDI0382 300µg (Coh5) N=11	MEDI0382 300µg (Coh6) N=12
22				3 (12.0%)	0	
23				3 (12.0%)		
24				3 (12.0%)		
25				4 (16.0%)		
26				4 (16.0%)		
27				4 (16.0%)		
28				3 (12.0%)		
29				3 (12.0%)		
30				3 (12.0%)		
31				4 (16.0%)		
32				4 (16.0%)		
33				3 (12.0%)		
34				6 (24.0%)		
35				4 (16.0%)		
36				4 (16.0%)		
37				4 (16.0%)		
38				4 (16.0%)		
39				4 (16.0%)		
40				4 (16.0%)		
41				3 (12.0%)		
42				1 (4.0%)		

Cohorts have different lengths of treatment period.
Subjects are counted once for each System Organ Class and Preferred Term regardless of the number of events.
Refers to Supporting Data Listing(s) 16.2_7.2.

Program (Output): /SASDATA/cars/prod/medi0382/d5670c00002/csr/tables/aete_vomnaus2.sas (aete_vomnaus2.rtf)
Standard Template NA

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MedImmune
MEDI0382-D5670C00002
CSR, DB lock updated 31AUG2017

Table 14.3.1_13
Treatment-emergent Vomiting and/or Nausea by Study Day – All Cohorts – As-treated Population

Study Day	MEDI0382 100µg N=6	MEDI0382 150µg N=6	MEDI0382 200µg (Coh3) N=7	MEDI0382 200µg (Coh4) N=25	MEDI0382 300µg (Coh5) N=11	MEDI0382 300µg (Coh6) N=12
43				1 (4.0%)		

Cohorts have different lengths of treatment period.
Subjects are counted once for each System Organ Class and Preferred Term regardless of the number of events.
Refers to Supporting Data Listing(s) 16.2_7.2.

Program (Output): /SASDATA/cars/prod/medi0382/d5670c00002/csr/tables/aete_vomnaus2.sas Validated
(aete_vomnaus2.rtf)
Standard Template NA 11SEP2017 9:22

Table 10 Study D5670C00011: Number and Percentage of Subjects with Nausea and/or Vomiting and Associated Event Rate by Dosing Period – Cohort 1 - As-treated Population

MedImmune
MEDI0382-D5670C00011
CSR, DB lock 28FEB2018

Table 14.3.1.9.2
Number and Percentage of Subjects with Nausea and/or Vomiting and Associated Event Rate by Dosing Period – Cohort 1 - As-treated Population

	Placebo Cohort 1 N = 13	MEDI0382 Cohort 1 N = 26
Day 1 - Day 7		
n[a]	13	26
Nausea[b]	0	4 (15.4%)
80% CI for percentage	(NA, NA)	(6.9, 28.4)
Event rate[c] (per person per day)	0	0.038
Vomiting[b]	0	1 (3.8%)
80% CI for percentage	(NA, NA)	(0.4, 14.2)
Event rate[c] (per person per day)	0	0.005
Nausea or Vomiting[b]	0	4 (15.4%)
80% CI for percentage	(NA, NA)	(6.9, 28.4)
Event rate[c] (per person per day)	0	0.044

[a] 'n' is the number of subjects who are ever exposed to study IP within the specific period.
[b] percentage is based on 'n'.
[c] Event rate = total number of events when subjects are on study IP / total person-days of exposure to study IP for the whole relevant arm.
Refers to Supporting Data Listing(s) 16.2.7.2.

Program (Output): /SASDATA/cars/prod/medi0382/d5670c00011/csr/tables/evrat_pdc1_2.sas (evrat_pdc1_2.rtf)

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16MAR2018 14:27

MedImmune
MEDI0382-D5670C00011
CSR, DB lock 28FEB2018

Table 14.3.1.9.2
Number and Percentage of Subjects with Nausea and/or Vomiting and Associated Event Rate by Dosing Period – Cohort 1 - As-treated Population

	Placebo Cohort 1 N = 13	MEDI0382 Cohort 1 N = 26
Day 8 - Day 14		
n[a]	13	26
Nausea[b]	0	1 (3.8%)
80% CI for percentage	(NA, NA)	(0.4, 14.2)
Event rate[c] (per person per day)	0	0.005
Vomiting[b]	0	0
80% CI for percentage	(NA, NA)	(NA, NA)
Event rate[c] (per person per day)	0	0
Nausea or Vomiting[b]	0	1 (3.8%)
80% CI for percentage	(NA, NA)	(0.4, 14.2)
Event rate[c] (per person per day)	0	0.005

[a] 'n' is the number of subjects who are ever exposed to study IP within the specific period.
[b] percentage is based on 'n'.
[c] Event rate = total number of events when subjects are on study IP / total person-days of exposure to study IP for the whole relevant arm.
Refers to Supporting Data Listing(s) 16.2.7.2.

Program (Output): /SASDATA/cars/prod/medi0382/d5670c00011/csr/tables/evrat_pdc1_2.sas (evrat_pdc1_2.rtf)

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16MAR2018 14:27

MedImmune
MEDI0382-D5670C00011
CSR, DB lock 28FEB2018

Table 14.3.1.9.2
Number and Percentage of Subjects with Nausea and/or Vomiting and Associated Event Rate by Dosing Period – Cohort 1 - As-treated Population

	Placebo Cohort 1 N = 13	MEDI0382 Cohort 1 N = 26
Day 15 - Day 21		
n[a]	13	26
Nausea[b]	0	0
80% CI for percentage	(NA, NA)	(NA, NA)
Event rate[c] (per person per day)	0	0
Vomiting[b]	0	0
80% CI for percentage	(NA, NA)	(NA, NA)
Event rate[c] (per person per day)	0	0
Nausea or Vomiting[b]	0	0
80% CI for percentage	(NA, NA)	(NA, NA)
Event rate[c] (per person per day)	0	0

[a] 'n' is the number of subjects who are ever exposed to study IP within the specific period.
[b] percentage is based on 'n'.
[c] Event rate = total number of events when subjects are on study IP / total person-days of exposure to study IP for the whole relevant arm.
Refers to Supporting Data Listing(s) 16.2.7.2.

Program (Output): /SASDATA/cars/prod/medi0382/d5670c00011/csr/tables/evrat_pdc1_2.sas (evrat_pdc1_2.rtf)

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MedImmune
MEDI0382-D5670C00011
CSR, DB lock 28FEB2018

Table 14.3.1.9.2
Number and Percentage of Subjects with Nausea and/or Vomiting and Associated Event Rate by Dosing Period – Cohort 1 - As-treated Population

	Placebo Cohort 1 N = 13	MEDI0382 Cohort 1 N = 26
Day 22 - Day 28		
n[a]	13	26
Nausea[b]	0	0
80% CI for percentage	(NA, NA)	(NA, NA)
Event rate[c] (per person per day)	0	0
Vomiting[b]	0	1 (3.8%)
80% CI for percentage	(NA, NA)	(0.4, 14.2)
Event rate[c] (per person per day)	0	0.011
Nausea or Vomiting[b]	0	1 (3.8%)
80% CI for percentage	(NA, NA)	(0.4, 14.2)
Event rate[c] (per person per day)	0	0.011

[a] 'n' is the number of subjects who are ever exposed to study IP within the specific period.
[b] percentage is based on 'n'.
[c] Event rate = total number of events when subjects are on study IP / total person-days of exposure to study IP for the whole relevant arm.
Refers to Supporting Data Listing(s) 16.2.7.2.

Program (Output): /SASDATA/cars/prod/medi0382/d5670c00011/csr/tables/evrat_pdc1_2.sas (evrat_pdc1_2.rtf)

Validated
16MAR2018 14:27

MedImmune
MEDI0382-D5670C00011
CSR, DB lock 28FEB2018

Table 14.3.1.9.2
Number and Percentage of Subjects with Nausea and/or Vomiting and Associated Event Rate by Dosing Period – Cohort 1 - As-treated Population

	Placebo Cohort 1 N = 13	MEDI0382 Cohort 1 N = 26
Day 29 - Day 49		
n[a]	13	26
Nausea[b]	0	1 (3.8%)
80% CI for percentage	(NA, NA)	(0.4, 14.2)
Event rate[c] (per person per day)	0	0.002
Vomiting[b]	0	2 (7.7%)
80% CI for percentage	(NA, NA)	(2.1, 19.2)
Event rate[c] (per person per day)	0	0.004
Nausea or Vomiting[b]	0	3 (11.5%)
80% CI for percentage	(NA, NA)	(4.3, 23.9)
Event rate[c] (per person per day)	0	0.006

[a] 'n' is the number of subjects who are ever exposed to study IP within the specific period.
[b] percentage is based on 'n'.
[c] Event rate = total number of events when subjects are on study IP / total person-days of exposure to study IP for the whole relevant arm.
Refers to Supporting Data Listing(s) 16.2.7.2.

Program (Output): /SASDATA/cars/prod/medi0382/d5670c00011/csr/tables/evrat_pdc1_2.sas (evrat_pdc1_2.rtf)

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Table 14.3.1.9.2
Number and Percentage of Subjects with Nausea and/or Vomiting and Associated Event Rate by Dosing Period – Cohort 1 - As-treated Population

	Placebo Cohort 1 N = 13	MEDI0382 Cohort 1 N = 26
Day 1 - Day 49		
n[a]	13	26
Nausea[b]	0	5 (19.2%)
80% CI for percentage	(NA, NA)	(9.7, 32.8)
Event rate[c] (per person per day)	0	0.006
Vomiting[b]	0	3 (11.5%)
80% CI for percentage	(NA, NA)	(4.3, 23.9)
Event rate[c] (per person per day)	0	0.004
Nausea or Vomiting[b]	0	7 (26.9%)
80% CI for percentage	(NA, NA)	(15.7, 41.1)
Event rate[c] (per person per day)	0	0.010

[a] 'n' is the number of subjects who are ever exposed to study IP within the specific period.
[b] percentage is based on 'n'.
[c] Event rate = total number of events when subjects are on study IP / total person-days of exposure to study IP for the whole relevant arm.
Refers to Supporting Data Listing(s) 16.2.7.2.

Program (Output): /SASDATA/cars/prod/medi0382/d5670c00011/csr/tables/evrat_pdc1_2.sas (evrat_pdc1_2.rtf)

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Appendix H Abbreviations

Abbreviation or special term	Explanation
ADA	antidrug antibody
AE	adverse event
ABPM	ambulatory blood pressure monitoring
ALP	alkaline phosphatise
ALT	alanine transaminase
ANCOVA	analysis of covariate
AST	aspartate transaminase
AUC	area under the curve
AZ	AstraZeneca
BMI	body mass index
BP	blood pressure
CGM	continuous glucose monitoring
CI	confidence interval
CRF	case report form
CSR	clinical study report
C_{trough}	trough plasma concentration
DNA	deoxyribonucleic acid
ECG	electrocardiogram
eCRF	electronic case report form
EDC	Electronic Data Capture
FPG	fasting plasma glucose
GCP	Good Clinical Practice
GI	gastrointestinal
GLP-1	glucagon-like peptide-1
GMP	Good Manufacturing Practice
HbA1c	glycated hemoglobin
HOMA	Homeostatic Model Assessment
HR	heart rate
IATA	International Airline Transportation Association
ICF	informed consent form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IP	investigational product

Abbreviation or special term	Explanation
IRB	Institutional Review Board
IVRS	interactive voice response system
IWRS	interactive web response system
LSMean	least squares mean
MedDRA	Medical Dictionary for Regulatory Activities
MMT	mixed-meal test
PD	pharmacodynamics
PHL	potential Hy's Law
PK	pharmacokinetics
QTcF	QT interval corrected for heart rate using Fridericia's formula
SAE	serious adverse event
SAP	statistical analysis
SC	subcutaneous
SoA	Schedule of Activities
TBL	total bilirubin
TEAE	treatment emergent adverse event
TESAE	treatment emergent serious adverse event
$t_{1/2}$	terminal half-life
T2DM	Type 2 diabetes mellitus
ULN	upper limit of normal