Clinical Study Protocol	
Drug Substance	MEDI0382
Study Code	D5670C00004
Version	5.0
Date	*04 December 2018*

A Phase IIb, Randomised, Parallel, Double-Blind Placebo-Controlled and Open-Label Active Comparator Study to Evaluate the Efficacy and Safety of MEDI0382 in the Treatment of Overweight and Obese Subjects with Type 2 Diabetes Mellitus

Sponsor: AstraZeneca AB, 151 85 Södertälje, Sweden

VERSION HISTORY

Version 5.0, 04 Dec 2018 Changes to the protocol are summarised below.
Synopsis and Sections 1 through 8 were modified to reduce the length of the treatment extension period from 92 to 40 weeks. Week 54 (Visit 14) will be the minimum required time point for treatment comparisons. Study duration will now be a minimum of 62 weeks, including a 2-week screening period, a 2-week run-in period, a 14-week treatment period, a minimum 40-week treatment extension, and a 4-week follow-up. The rationale for this change is to allow subjects adequate time to transition to other therapies and allow continued collection of safety and efficacy data to inform further decisions regarding MEDI0382 doses. Figure 1 was modified to reduce the length of the treatment extension period from 92 to a minimum of 40 weeks. Table 2 and Table 3 were modified to reduce the length of the treatment extension period from 92 to a minimum of 40 weeks. All subjects must complete an end of treatment schedule of assessments. Appendix D was modified to be consistent with the updated potential Hy's Law/ Hy's Law reporting process.

Version 4.0, 20 Apr 2018 Changes to the protocol are summarised below.
Synopsis, section 3.7 (Methods for unblinding), section 8.1 (Statistical considerations): These sections were modified to include an analysis when all subject reach 26 weeks treatment. The rationale for introducing the 26 week analysis is to inform about efficacy at 6 months and guide the selection process of the optimal dose regimen because the impact of weight loss on improved insulin sensitivity and glucose control may not be adequately captured at 14 weeks. Table 2, Table 3 and section 4.2.1.5 (Rescue visit): These tables and the rescue visit description were modified to remove the requirement of bringing used/unused IP to the rescue visit. Subjects should continue receiving IP while receiving rescue therapy. Section 4.3 (Last dose of investigational product follow-up visit): PK sample collection was added to the visit description to keep consistency with Table 2 and Table 3.

Section 6.3.9 (Pancreatitis): This section was modified to indicate more detailed information to be collected for events of pancreatitis.

Section 6.3.10 (Pancreatic carcinoma) was added to include collection of specific information for events of pancreatic carcinoma. Section 6.4 (Clinical Event Adjudication) was updated to include pancreatic carcinoma and thyroid neoplasm to the list of adjudicated events. Given the controversy of whether GLP-1–based therapy increases the risk for specific malignant disease like pancreatic carcinoma and thyroid cancer, we plan to adjudicate pancreatic carcinoma and thyroid cancer in the phase IIb study.

Version 3.0, 05 Feb 2018

Changes to the protocol are summarised below.

Synopsis, section 1.4 (Study design), section 3.5 (Methods for assigning treatment groups), section 3.7 (Methods for unblinding), section 8.1 (Statistical considerations) and section 8.5.4 (Interim analysis): These sections were modified to exclude the interim analysis and the analysis associated with the 26 week data. Due to fast enrolment to the study, timing for the primary analysis advanced so there is no longer a need for the interim analysis. Similarly, the separate analysis associated with the 26 week data is removed because fast enrolment leads to an insufficient number of subjects reaching 26 weeks at the time of the primary analysis to provide satisfactory statistical power.

Version 2.0, 09 Oct 2017

Changes to the protocol are summarised below.

Section 1.2.3.1 (Recruitment of subjects with T2DM and a body mass index ≥25 kg/m^2), section 3.1 (Inclusion criteria): This section and inclusion criterion 3 were modified to remove the upper BMI limit for the study. The rationale is to improve rate of enrolment and to increase ability to demonstrate significant weight loss when including subjects with very high BMI.

Section 1.4 (Study design): The number of countries and participating sites was updated.

Study flow diagram: The diagram was corrected to reflect that MEDI0382 and liraglutide dosing does not depend on the time of day.

Section 3.1 (Inclusion criteria): The metformin monotherapy inclusion criterion (#5) was modified to allow use of another glucose-lowering medication for up to 2 weeks in the 2 months prior to screening. The rationale is to improve rate of enrolment and still include subjects on Metformin monotherapy who may have been offered another glucose-lowering

agent on top of metformin but only took it briefly for less than 2 weeks. Additionally the birth control criterion for women of childbearing potential was clarified to require at least one appropriate birth control method in effect prior to receiving the first IP dose and to include total sexual abstinence as an appropriate birth control method based on Best Practice Reference Guideline: Human Exposure Limits Committee (HELC) Guideline for Information Required Before Inclusion of Women in AstraZeneca/MedImmune Clinical Trials

Section 3.2 (Exclusion criteria): Exclusion criterion number 5 was modified to allow daily SC insulin treatment for up to 2 weeks within 90 days prior to screening. Exclusion criterion number 13 was updated to present basal calcitonin values in pg/ml. Exclusion criterion number 18 was clarified to restrict enrolment of subjects with any history of psychosis or bipolar disorder; subjects with a history of major depressive disorder within the past year with the subject being clinically unstable.

Section 3.8 (Restrictions): Fasting requirement was modified to include all study site visits except for Visits 2, 12, 13, 15, 16, 17 and 18. These visits do not require weight measurement or fasting laboratory sampling. Restriction to withhold tobacco and caffeine 24 hours prior to each study site visit was removed.

Section 3.9 (Discontinuation of investigational product) and section 3.9.1 (Procedures for discontinuation of a subject from investigational product): These sections were corrected to refer only to discontinuation from the IP. Additional options for visits after the IP discontinuation were added.

Section 3.10.1 (Screen failures): Screening was clarified to refer to a period instead of window.

Section 3.10.2 (Withdrawal of informed consent): This section was modified to include collection of subjects vital status at the end of study.

Section 4 (Study plan and timing of procedures): Table 1 was modified to remove the visit window from Screening. Fasting requirement was clarified to include Visit 1. IVRS/IXRS contact was removed from FU visit. Provision of the subject diary and instructions was clarified to include further study visits, if needed. As requested by the FDA, Immunogenicity blood sampling was added to Visits 4 and 6. Table 3 was modified to include IVRS/IXRS contact at applicable study visits. [redacted] The arrow covering the 4-weekly interval IP supply visits was corrected to span the period between Visit 12 and Visit 19. In addition, the requirement to collect adverse events and concomitant medication changes at IP supply visits was removed.

Section 4.1.1 (Visit 1 assessments – Screening): These section was updated to refer to a 2 week period. Restrictions for tobacco and caffeine us for 24 hours prior to the visit was removed and additional options for re-testing laboratory results was added.

Section 4.1.3 (Visit 2 assessments – 2-week run in period): This section was updated to clarify the screening period and visit window for Visit 2. Tobacco and caffeine restrictions in addition to the fasting requirement were removed.

Section 4.2 (Treatment period): This section was updated to remove the tobacco and caffeine restriction for 24 hours prior to scheduled visits.

Section 4.2.1.1 (Visit 3 assessments – Baseline): The visit window for Visit 3 was corrected to a maximum of 2 days upon completion of the run-in period, to keep consistency with Table 1. Fundoscopy was clarified to refer to dilated funduscopic examination.

Section 4.2.1.2 (Visit 4 to 5 assessments – Up-titration) and section 4.2.1.3 (Visit 6 to 8 assessments – maintenance period) were updated to include immunogenicity laboratory sampling at Visits 4 and 6.

Section 4.2.1.4 (Initiation of rescue medication (14 week treatment period) was corrected to include the period from Week 0 to the criteria for initiation of rescue medication, as described in Table 4. Note on rescue medication not being provided by the sponsor was removed.

Section 4.2.2 (92-week extension period): This section was modified to remove the requirement of adverse event collection, concomitant medication review, vital signs collection and brief physical examination during the IP resupply visits. Clarification on urine collection for urinalysis was added.

Section 4.2.3 (Resupply of investigational product visits): Section clarified to include need for collection, review and resupply of IP and IFU.

Section 4.2.5 (Early termination): This section was updated to refer to discontinuation from IP. Additional clarification of return for visit no later than 7 days post last IP dose was added.

Section 5.2.1.4 (Serum calcitonin): This section was updated to include the calcitonin level of clinical concern.

Section 5.2.1.6 (Urinalysis): Section referring to recording and analysis of lab samples by the central laboratory moved to section 5.2.1 (Laboratory safety assessments).

Section 5.2.1.8 (Immunogenicity) Added clarification that ADA samples will be collected for subjects in MEDI0382/Placebo arm.

Section 5.2.4.1 (Pulse and blood pressure): This section was updated with additional guidance on pulse collection by a semi-automatic device or manual measurement. Clarification on the same time of day, with a two hour window was added.

Section 5.3.2.3 (Retinal assessment): Fundoscopy was clarified to refer to dilated funduscopic examination.

Section 6.4 (Clinical Event Adjudication): Term pancreatitis as one of the adjudicated events was updated to pancreatic disease.

Section 6.9.1 (Tolerability): This section was updated to allow for metformin withhold during persistent symptoms of nausea and vomiting.

Section 7.7.1 (Permitted concomitant medications): Section updated to keep consistency with Inclusion criterion #5. Additional clarifications added on use of anti-emetic therapy. 5HT-3 antagonist treatment recommendation removed from the text.

Section 8.1 (Statistical considerations) and section 8.5.4 (Interim analysis): Sample size updated to allow a margin for any low-quality or untestable samples.

Section 8.3.3 (PK analysis set): Clarification added on PK population to refer to MEDI0382 treated subjects only.

Clinical Study Protocol Synopsis: Modifications and clarifications from the Clinical Study Protocol have also been included in the Synopsis. A clarification has been added on the use of liraglutide in patients with congestive heart failure New York Heart Association (NYHA) class III and label updates with the data from the LEADER trial.

[redacted]

Version 1.0, 16 May 2017
Initial creation

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.

CLINICAL STUDY PROTOCOL SYNOPSIS

A Phase IIb, Randomised, Parallel, Double-Blind Placebo-Controlled and Open-Label Active Comparator Study to Evaluate the Efficacy and Safety of MEDI0382 in the Treatment of Overweight and Obese Subjects with Type 2 Diabetes Mellitus

International Co-ordinating Investigators

Study site(s) and number of subjects planned

This will be a global, multicentre study conducted at approximately 150 sites in 8 countries. It is planned that approximately 750 subjects will be enrolled (approximately 5 subjects per centre), and that approximately 542 subjects will complete the study, taking into account a projected annual study drop-out rate of 15%.

Phase of development IIb

Study design

This is a randomised, parallel, double-blind, placebo-controlled study with an open-label active comparator (liraglutide) arm designed to evaluate 100 µg, 200 µg, and 300 µg of MEDI0382 in overweight and obese subjects with type 2 diabetes mellitus (T2DM) and an haemoglobin A1c (HbA1c) of 7.0% to 10.5%, who are concurrently treated with metformin.

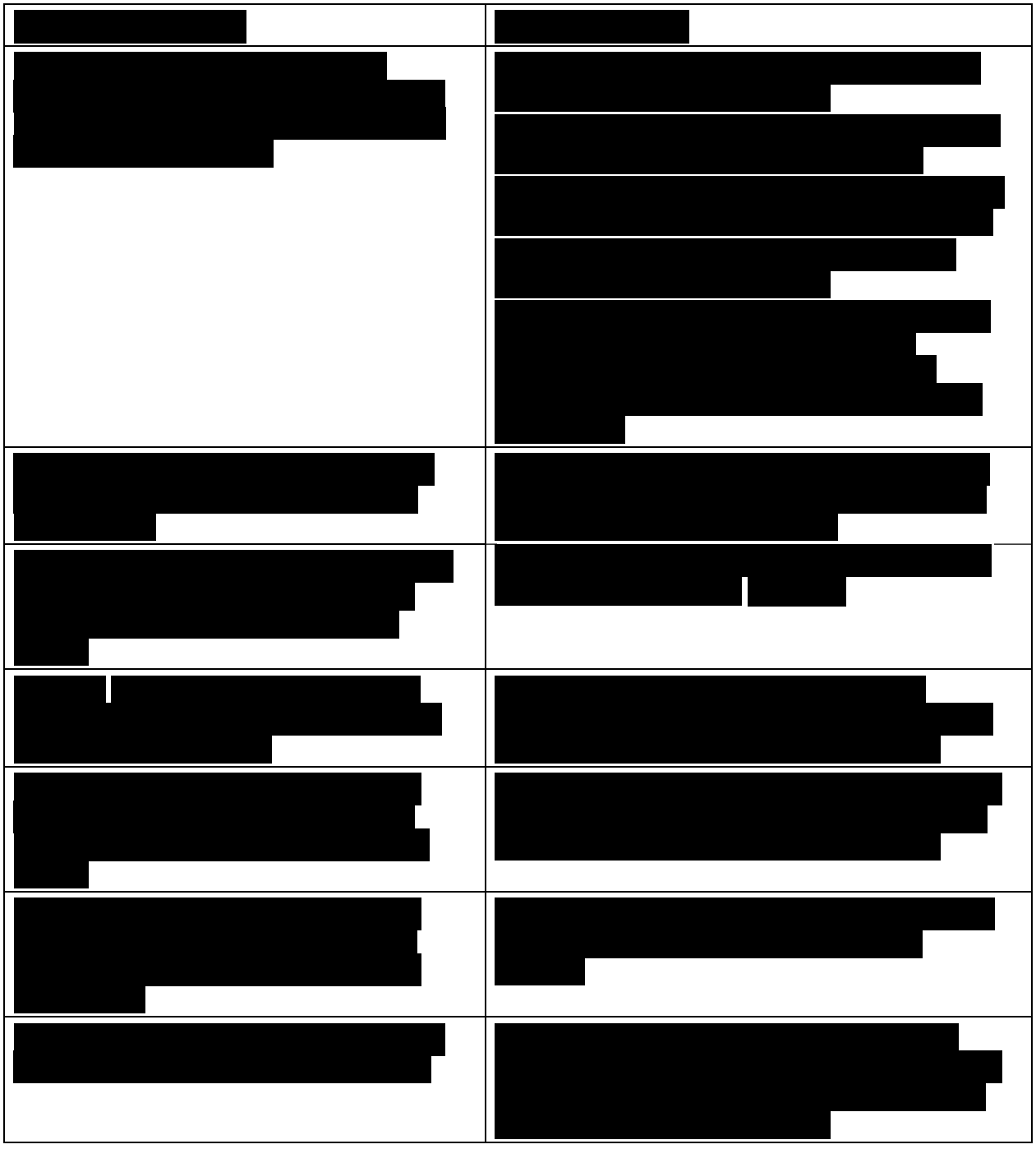
The study has a run-in period of 2 weeks, and following randomisation, a 14-week treatment period for the primary analysis, followed by a minimum 40-week treatment extension.

Objectives

Primary objective:	**Outcome measure:**
To assess the effect of 100 µg, 200 µg and 300 µg of MEDI0382 on haemoglobin A1c (HbA1c) and body weight versus placebo	Change in HbA1c from baseline to 14 weeks Percent change in body weight from baseline to 14 weeks

Secondary objective:	**Outcome measure:**
To assess the effect of 100 µg, 200 µg and 300 µg of MEDI0382 on additional measures of glycaemic control and body weight versus placebo	Change in HbA1c from baseline to 26 weeks, and 54 weeks Percentage of subjects achieving an HbA1c target < 7.0% after 14 weeks, 26 weeks, and 54 weeks Percent change in body weight from baseline to 26 weeks, and 54 weeks Absolute change in body weight from baseline to 14 weeks, 26 weeks, and 54 weeks Percentage of subjects achieving weight loss of ≥5% and ≥10% after 14 weeks, 26 weeks, and 54 weeks
To assess the effect of 100 µg, 200 µg and 300 µg of MEDI0382 on the requirement for additional blood glucose lowering therapies versus placebo	Proportion of subjects rescued or discontinued for lack of glycaemic control at 14 weeks, 26 weeks, and 54 weeks
To assess the effect of 100 µg, 200 µg and 300 µg of MEDI0382 on weight versus liraglutide 1.8 mg once daily	Percent and absolute change in body weight from baseline to 14 weeks, 26 weeks, and 54 weeks
To characterise the pharmacokinetic (PK) profile and immunogenicity of 100 µg, 200 µg, and 300 µg of MEDI0382	PK endpoints (trough plasma concentration, C_{min}) Development of antidrug antibodies and titre (if positive) during dosing and follow-up

Safety objective:	**Outcome measure:**
To characterise the safety profile, and tolerability of 100 µg, 200 µg and 300 µg of MEDI0382	Measures of safety and tolerability [(vital signs, laboratory test results, adverse events (AEs)] during treatment and follow-up



Target subject population

Male or female subjects aged ≥18 years of age, with body mass index (BMI) ≥25 kg/m^2, a diagnosis of T2DM and inadequate blood glucose control as defined by an HbA1c of 7.0 to 10.5% who are on metformin monotherapy.

Duration of treatment

Study duration will be a minimum of 62 weeks, including a 2-week screening period, a 2-week run-in period, a 14-week treatment period, a minimum 40-week treatment extension, and a 4-week follow-up.

Dosage and mode of administration – investigational product, oral antidiabetic agents, and rescue therapy

Investigational product

Investigational product (IP) in this clinical study protocol (CSP) refers to either MEDI0382, placebo, or liraglutide.

MEDI0382 and placebo:

All IP will be packed into kits with supplies for 1 week treatment (8 syringes – 7 day supply and one spare syringe). MEDI0382 or placebo will be administered by subcutaneous (SC) injection once daily for the 14-week treatment period and a minimum 40-week treatment extension.

Liraglutide:

Liraglutide (6.0 mg/mL, open label) as active drug will be administered by SC injection once daily for the 14-week treatment period and a minimum 40-week treatment extension using a 3 mL pen-injector. Liraglutide should be administered and stored according to product-specific and country-specific labelling. We recognise that in some markets the liraglutide label has not been updated with the data from the LEADER trial, as so is currently not recommended in patients with congestive heart failure New York Heart Association (NYHA) class III. However, based on recent data and updates to the EU summary of product characteristics, which was submitted with the CTA, we plan to include patients with congestive heart failure NYHA class III in our study.

Oral antidiabetic agents:

Throughout the study, subjects should continue to administer the same type and dose of metformin therapy that they were using at study entry. Metformin should be administered and stored according to product-specific and country-specific labelling.

Rescue therapy:

Subjects who require rescue therapy will receive open-label insulin as a preferred option. Subjects should continue receiving IP while receiving rescue therapy.

Statistical methods

Populations for analyses

The Intent-to-treat (ITT) analysis set for the efficacy evaluation will be the primary analysis set and will include subjects who received at least one dose of IP, and will be analysed according to their randomised treatment group.

The Per Protocol (PP) analysis set will include only treatment completers and exclude those with important protocol violation(s). Important protocol violations are those that have the potential to affect the result of the primary analysis.

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 receive.

The Pharmacokinetic (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 quantification.

[redacted]

Statistical analysis methods

The co-primary efficacy endpoints of HbA1c change and weight change from baseline to 14 weeks will be compared between MEDI0382 and placebo arms. For these endpoints, an analysis of covariance (ANCOVA) model with last-observation-carried-forward (LOCF) approach to handle missing data will be used and adjusted for treatment and measurement at baseline. For weight loss, the strata of screening HbA1c (≤8% or >8%) will be added into the model as a covariate. Analyses will be based on the ITT population, which includes all randomised subjects who received at least one dose of IP. The analysis will include the post IP-discontinuation data and post-rescue data for those subjects who discontinue from study treatments or are rescued, but are still followed up for their scheduled visits.

Secondary efficacy endpoints of body weight and HbA1c change at 26 weeks and 54 weeks will be analysed by ANCOVA model with LOCF. For the secondary proportion-related endpoints, a logistic regression model will be used. These analyses will be performed for the ITT population. Anti-drug antibody incidence rate and titre will be tabulated for each treatment. Individual MEDI0382 plasma concentrations will be summarised by treatment and visit.

All safety [(vital signs, laboratory test results, adverse events (including cardiovascular events)] and tolerability variables will be summarised descriptively for each treatment group for the Safety population. Details on the safety analyses will be provided in the statistical analysis plan.

[redacted]

A primary analysis when all subjects reach 14 weeks treatment, an analysis when all subjects reach 26 weeks treatment, and a final analysis at the end of the study are planned.

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

The following abbreviations and special terms are used in this Clinical Study Protocol.

Abbreviation or special term	Explanation
ADA	Anti-drug antibodies
AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine transaminase
ANCOVA	Analysis of covariance
AST	Aspartate transaminase
AUC	Area under concentration-time curve
BMI	Body mass index
BP	Blood pressure
CKD-EPI	Chronic kidney disease epidemiology collaboration
CEA	Clinical Event Adjudication
CK-MB	Creatine kinase (muscle and brain)
CI	Confidence interval
Cmax	Maximum observed concentration
Cmin	Minimum plasma concentration
CPK	Creatine phosphokinase
CRF	Case Report Form
CSA	Clinical Study Agreement
CSR	Clinical Study Report
CV	Cardiovascular
DILI	Drug induced liver injury
DPP4	Dipeptidyl peptidase-4
[redacted]	[redacted]
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
eGFR	Estimated glomerular filtration rate
EoT	End of treatment
[redacted]	[redacted]
[redacted]	[redacted]

Abbreviation or special term	Explanation
FPG	Fasting plasma glucose
GCP	Good Clinical Practice
GFR	Glomerular filtration rate
GI	Gastrointestinal
GLP-1	Glucagon-like peptide-1
HbA1c	Haemoglobin A1c
[redacted]	[redacted]
HIV	Human immunodeficiency virus
HL	Hy's Law
[redacted]	[redacted]
IB	Investigator's Brochure
ICF	Informed consent form
ICH	International Council on Harmonisation
IFU	Instructions for use
IP	Investigational product
ITT	Intent-to-treat
IVRS	Interactive Voice Response System
IWRS	Interactive Web Response System
LOCF	Last-observation-carried-forward
MedDRA	Medical Dictionary for Regulatory Activities
MI	Myocardial infarction
NOAEL	No-observed-adverse-effect level
[redacted]	[redacted]
PHL	Potential Hy's Law
PK	Pharmacokinetic(s)
PP	Per Protocol
PRO	Patient Reported Outcomes
SAE	Serious adverse event
SAP	Statistical analysis plan
SC	Subcutaneous(ly)
T2DM	Type 2 diabetes mellitus
TBL	Total bilirubin level

Abbreviation or special term	Explanation
TIA	Transient ischaemic attack
ULN	Upper limit of normal
WBDC	Web Based Data Capture

1. INTRODUCTION

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1.3 Benefit/risk and ethical assessment

This study will provide efficacy and safety information for 3 doses of MEDI0382 compared with placebo and liraglutide in subjects with T2DM who are taking metformin. All subjects will be monitored throughout the study to ensure adequate glycaemic control. Refer to the current IB for information on the potential benefits of MEDI0382, and an assessment of the potential and known risks. Refer to the prescribing information for the potential benefits of liraglutide, and an assessment of the potential and known risks.

1.4 Study design

This is a randomised, double-blind, placebo-controlled study with an open-label active comparator (liraglutide) arm, designed to evaluate the efficacy and safety of MEDI0382 in overweight and obese subjects with T2DM. This study will enrol male and female subjects aged ≥18 years, with a BMI ≥25 kg/m^2. Subjects will have a diagnosis of T2DM, and inadequate blood glucose control as defined by an HbA1c of 7.0% to 10.5%, and are on metformin monotherapy. Approximately 750 subjects will be randomised at approximately 150 sites in approximately 8 countries, and it is anticipated that approximately 542 subjects will complete the study, taking into account a projected annual study drop-out rate of 15%. The study has a run-in period of 2 weeks, a 14-week treatment period, followed by a minimum 40-week treatment extension.

Prior to the run-in period, subjects will be consented and screened for suitability. During the run-in period, subjects will refrain from taking prohibited medications (see Section 7.7 for details of prohibited medications), but will continue to take their prescribed stable dose of metformin for the remainder of the study. After completion of run-in, subjects who are still eligible will be randomised within 1 week. Diet and exercise counselling will be provided from the beginning and throughout the duration of the study. Only subjects who are treated with metformin monotherapy will be enrolled; this will ensure that subjects with an early stage of T2DM are treated in this study.

To achieve the enrolment goal for the initially planned interim analysis (see previous versions of the protocol), subjects will be randomly assigned with a ratio of 2:2:2:1:1 to 1 of 5 treatment arms to receive MEDI0382 at dose level of 300 µg, 200 µg, or 100 µg, placebo or liraglutide respectively. After approximately the first 400 subjects have been enrolled, the randomisation ratio will be changed to 5:5:0:2:2 to fully enrol the remaining 350 subjects. Analysis will be stratified with respect to screening HbA1c (≤8% or >8%).

For subjects randomised to MEDI0382 or placebo, MEDI0382 will be initiated at 100 µg, and dose increments may occur in 100 µg steps every week until the predefined maintenance dose is reached. Subjects and Investigators will be advised that there may be dose increments. During the 14-week treatment period, open-label liraglutide will be initiated at 0.6 mg and up titrated by an additional 0.6 mg weekly until a stable daily dose of 1.8 mg is reached. After the

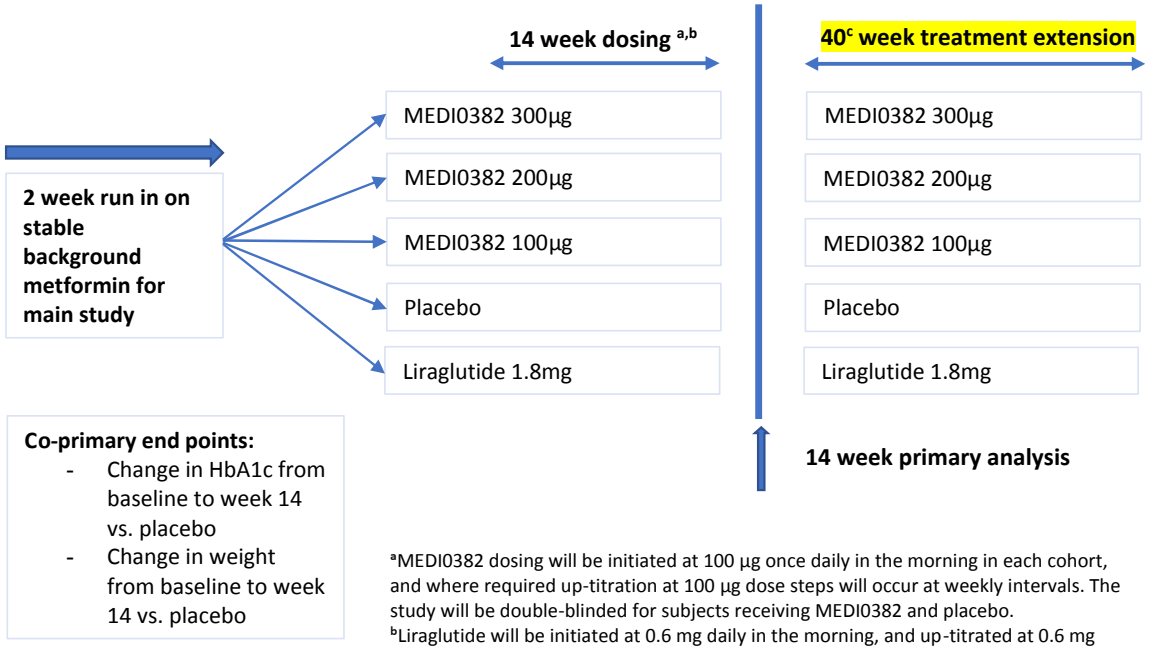
14-week treatment period, subjects will continue with the allocated treatment for a further minimum of 40 weeks of extension treatment, after which study treatment will end.

Subjects receiving study treatment who have completed more than 40 weeks of extension treatment will end study treatment as soon as possible, preferably at the next scheduled visit (including IP-supply visits), but in no case longer than 4 weeks beyond the next scheduled visit.

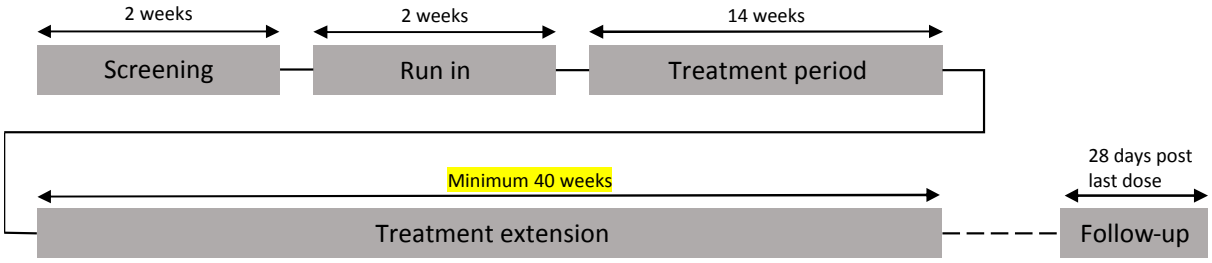
An Early Termination visit will be performed for subjects who discontinue treatment prematurely at any time and for any reason as soon as possible, but not later than 7 days from last IP dose. A follow-up visit will be performed for final safety assessments 4 weeks after the last dose of IP.

See Figure 1 for a summary of the study design. Details of assessments at each visit are summarised in Table 2 and Table 3.

Figure 1 Study flow diagram



[a]MEDI0382 dosing will be initiated at 100 µg once daily in the morning in each cohort, and where required up-titration at 100 µg dose steps will occur at weekly intervals. The study will be double-blinded for subjects receiving MEDI0382 and placebo.
[b]Liraglutide will be initiated at 0.6 mg daily in the morning, and up-titrated at 0.6 mg dose steps over 2 weeks then a stable dose of 1.8 mg will be maintained. The study will be open-labeled for the subjects receiving liraglutide.
[c]Treatment extension will be a minimum of 40 weeks.
Subjects will remain on background stable metformin throughout the study.



1.5 Study governance and oversight

1.5.1 Steering Committee – Not Applicable

1.5.2 Data Monitoring Committee – Not Applicable

1.5.3 Scientific Advisory Committee – Not Applicable

1.5.4 Clinical Event Adjudication Committee

A Clinical Event Adjudication (CEA) Committee, blinded to the treatment of the subject, will independently adjudicate certain clinical events including CV AEs, and it will operate in accordance with a CEA Charter and Event Handling Manual for Sites and Monitors. For details, see Section 6.4.

2. STUDY OBJECTIVES

2.1 Primary objective

Primary objective:	**Outcome measure:**
To assess the effect of 100 µg, 200 µg and 300 µg of MEDI0382 on haemoglobin A1c (HbA1c) and body weight versus placebo	Change in HbA1c from baseline to 14 weeks Percent change in body weight from baseline to 14 weeks

2.2 Secondary objectives

Secondary objective:	**Outcome measure:**
To assess the effect of 100 µg, 200 µg and 300 µg of MEDI0382 on additional measures of glycaemic control and body weight versus placebo	Change in HbA1c from baseline to 26 weeks and 54 weeks Percentage of subjects achieving an HbA1c target of <7.0% at 14 weeks, 26 weeks, and 54 weeks Percent change in body weight from baseline to 26 weeks, and 54 weeks Absolute change in body weight from baseline to 14 weeks, 26 weeks, and 54 weeks Percentage of subjects achieving weight loss of ≥5% and ≥10% after 14 weeks, 26 weeks, and 54 weeks
To assess the effect of 100 µg, 200 µg and 300 µg of MEDI0382 on the requirement for additional blood glucose lowering therapies versus placebo	Proportion of subjects rescued or discontinued for lack of glycaemic control at 14 weeks, 26 weeks, and 54 weeks
To assess the effect of 100 µg, 200 µg and 300 µg of MEDI0382 on weight versus liraglutide 1.8 mg once daily	Percent and absolute change in body weight from baseline to 14 weeks, 26 weeks, and 54 weeks

Secondary objective:	Outcome measure:
To characterise the PK profile and immunogenicity of 100 µg, 200 µg and 300 µg of MEDI0382	PK endpoints (trough plasma concentration, C_{min} Development of anti-drug antibodies and titre (if positive) during dosing and follow-up

2.3 Safety objectives

Safety objective:	Outcome measure:
To characterise the safety profile, and tolerability of 100 µg, 200 µg and 300 µg of MEDI0382	Measures of safety and tolerability [(vital signs, laboratory test results, adverse events] during treatment and follow-up

2.4 [redacted]

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3. SUBJECT SELECTION, ENROLMENT, RANDOMISATION, RESTRICTIONS, DISCONTINUATION AND WITHDRAWAL

Each subject should meet all of the inclusion criteria and none of the exclusion criteria for this study. Under no circumstances can there be exceptions to this rule. The subjects may be recruited from primary or specialist care, or any systems for referral or advertisements.

3.1 Inclusion criteria

For inclusion in the study, subjects should fulfil the following criteria:

1. Provision of informed consent prior to any study-specific procedures

2. Male and female subjects aged ≥ 18 years at screening

3. Body mass index ≥ 25 kg/m^2 at screening

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

5. Diagnosed with T2DM with glucose control managed with metformin monotherapy where no significant dose change (increase or decrease ≥500 mg/day) has occurred in at least the 2 months prior to screening and the total daily dose of metformin is ≥1500 mg unless metformin is only tolerated at a lower dose. Use of another glucose-lowering medication for up to 2 weeks in the 2 months prior to screening is acceptable (a GLP-1 receptor agonist containing preparation cannot be used within the last 30 days or 5 half-lives of the drug, whichever is longer, at the time of screening)

6. For women of childbearing potential:

   – Must be using appropriate birth control to avoid pregnancy throughout the study and for up to 4 weeks after the last dose of IP. Appropriate birth control is defined as a method which results in a low failure rate, ie, less than 1% per year, when used consistently and correctly, such as implants, injectables, hormonal contraceptives [pills, vaginal rings, or patches], some intrauterine

contraceptive devices (levonorgestrel-releasing or copper-T), tubal ligation or occlusion, total sexual abstinence that is in line with the preferred and usual lifestyle choice of the subject, or a vasectomized partner during the entire duration of the study. As applicable, at least one method must be in effect prior to receiving the first dose of IP

- Must have a negative serum or urine pregnancy test within 72 hours prior to the start of IP

- Must not be breastfeeding

3.2 Exclusion criteria

Subjects should not enter the study if any of the following exclusion criteria are fulfilled:

1. History of, or any existing condition that, in the opinion of the Investigator, 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 and/or any subject unable or unwilling to follow study procedures during the run-in period

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

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

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

9. Impaired renal function defined as estimated glomerular filtration rate (eGFR) ≤30 mL/minute/1.73m^2 at screening (GFR estimated according to chronic kidney disease epidemiology collaboration [CKD-EPI]). For more details see Section 5.3.5.

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

11. Unstable angina pectoris, myocardial infarction (MI), transient ischaemic attack (TIA), 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. Basal calcitonin level >50 ng/L or pg/mL at screening or history/family history of medullary thyroid carcinoma or multiple endocrine neoplasia

14. Haemoglobinopathy, haemolytic anaemia, or chronic anaemia (haemoglobin concentration <11.5 g/dL [115 g/L] for males, <10.5 g/dL [105 g/L] for females) at screening or any other condition known to interfere with interpretation of HbA1c measurement

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

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

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

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

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

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

For the procedures for withdrawal of incorrectly enrolled subjects, see Section 3.4.

3.3 Subject enrolment and randomisation

Investigator(s) should keep a record, the subject screening log, of subjects who entered study screening.

The Investigator(s) will:

1. Obtain signed informed consent from the potential subject before any study-specific procedures are performed.

2. Assign potential subject a unique enrolment number, beginning with 'E#'.

3. Determine subject eligibility. See Section 3.1 and 3.2.

4. Assign eligible subject unique randomisation code.

If a subject withdraws from participation in the study, then his/her enrolment/randomisation code cannot be reused.

Randomisation codes will be generated by screening HbA1c (≤8% or >8%) strata and regions (Europe, US/Canada, Russia, Mexico). Specific information concerning the use of interactive voice/web response system (IVRS/IWRS) will be provided in a separate manual. Randomised subjects who discontinue from IP administration will not be replaced.

3.4 Procedures for handling incorrectly enrolled or randomised subjects

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

3.5 Methods for assigning treatment groups

Assignment to treatment groups will be determined by a computer-generated random sequence using an IVRS/IWRS. To achieve the enrolment goal for the initially planned interim analysis (see previous versions of the protocol), subjects will be randomly assigned with a ratio of 2:2:2:1:1 to 1 of 5 treatment arms to receive MEDI0382 at dose level of 300 µg, 200 µg, or 100 µg, placebo or liraglutide respectively. After approximately the first 400 subjects have been enrolled, the randomisation ratio will be changed to 5:5:0:2:2 to fully enrol the remaining 350 subjects.

3.6 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). 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 (International Council on Harmonisation [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.

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

The results for fasting plasma glucose (FPG) and HbA1c are blinded to the Investigator for all visits except Visits 1 to 3. FPG and HbA1c values are blinded to the Investigator site until the unblinding criteria for rescue therapy are met. Once the criteria are met, FPG and HbA1c will be reported to the site for an individual subject (see Section 4.2.1.4 and 4.2.2.1). Previous values will remain blinded and the site will only receive the values going forward from the point the criteria were met. However, after Week 26, during the treatment extension period, a different glycaemic rescue criterion has been defined for the safety of the subjects (see Section 4.2.2.1). The central laboratory will notify the Investigator to repeat HbA1c without providing an explanation, and if the repeated HbA1c 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.

3.7 Methods for unblinding

Individual treatment codes, indicating the treatment randomisation for each randomised subject, will be available to the Investigator(s) or pharmacists from the IVRS/IWRS. Routines for this will be described in the IVRS/IWRS user manual that will be provided to each centre.

The treatment 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 the subject to the AstraZeneca staff.

AstraZeneca retains the right to break the code for serious adverse events (SAEs) that are unexpected and are suspected to be causally related to an IP and that potentially require expedited reporting to regulatory authorities. Treatment 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.

The exception to the above is for those personnel analysing the PK samples. The randomisation code will be provided to ensure that only samples from subjects who were on active study treatment are analysed. Samples from subjects not dosed with the relevant active study treatment will only be analysed on a 'for cause' basis, for example, if there is suspicion that a subject has been dosed incorrectly. The treatment allocation information will be kept in a secure location until the end of the study.

For the purpose of the primary analysis and the 26-week analysis, any study team members who serve in the unblinded analysis group will stop day-to-day work on the study and other pre-selected personnel will take over these roles for the remainder of the trial. The study team members will remain blinded to treatment assignment until the data base lock after the treatment extension is finished.

3.8 Restrictions

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

- Any new prescription medications or over-the-counter preparations must be reported to study site staff. For restrictions on concomitant medications, see Section 3.1 and Section 3.2 (Inclusion and Exclusion Criteria) and Section 7 (Investigational Product and Other Treatments).
- Continue metformin therapy at current dosage (if applicable) and at approximately the same time each day.
- Fast overnight for at least 8 hours prior to study site visits (all except Visits 2, 12, 13, 15, 16, 17 and 18), ie, no food or beverage except water.
- Withhold alcohol, and refrain from intense exercise 24 hours prior to each study site visit.
- Do not donate blood for the duration of the study.
- Delay administering the morning dose of metformin therapy (if applicable) and IP (as applicable) on the morning of each study site visit and bring antidiabetic medication (as applicable) and IP to each study site visit.
- Subjects should not be prescribed GLP-1 receptor agonists (Byetta®, Bydureon®, or Victoza®) or any other GLP-1 analogs during the 4-week safety follow-up period.

- If a subject comes to a visit without having followed at least one of the above instructions, then the subject should be re-scheduled for the entire visit (if possible within the allowed time-window and feasible in Investigator's judgment). The sponsor or designee should be contacted if the Investigator is informed of any restriction violations. The sponsor will decide whether a subject with restriction violations will be allowed to continue study participation.

3.9 Discontinuation of investigational product

Subjects may be discontinued from the IP in the following situations:

- Subject decision. The subject is at any time free to discontinue treatment, without prejudice to further treatment.
- An AE that, in the opinion of the Investigator or the sponsor, warrants discontinuation from further dosing.
- Subject noncompliance that, in the opinion of the Investigator or sponsor, warrants withdrawal (eg, refusal to adhere to scheduled visits).
- Pregnancy in a female subject.
- Calculated creatinine clearance <30 mL/min confirmed by repeat testing or a decrease in renal function that would preclude continued treatment with metformin according to local guidance.
- Loss of glucose control. If any subject experiences a loss of glucose control, in addition to IP, the Investigator should initiate rescue therapy and the subject may continue study participation. The Investigator should follow local prescribing information for the rescue therapy and may discuss appropriate rescue therapy with the AstraZeneca Medical Monitor if needed. Subjects must first complete the Rescue visit procedures before receiving open-label rescue therapy. Rescued subjects judged by the Investigator to have inadequate glycaemic control despite a maximum tolerated dose of rescue therapy will be discontinued from the IP and referred for additional anti-hyperglycaemic therapy (see Sections 4.2.1.4 and 4.2.2.1).
- Subjects with a central laboratory ALT and/or AST >3 × ULN will be scheduled for a follow-up visit within 3 days following the receipt of the result (see Appendix D). Subjects should be discontinued from study medication if the initial and repeat laboratory tests meet any of the following criteria:
  - ALT and/or AST are >3 × ULN and TBL >2 × ULN
  - ALT and/or AST are >5 × ULN for ≥14 consecutive days, at any time after initial confirmatory results

  - ALT and /or AST are >8 × ULN.

- Lost to follow-up.

Every effort will be made to ensure that the subject continues to return to the clinic for study visits and to avoid "lost to follow-up" during the conduct of the study. It is important that Investigators and site staff familiarise themselves with procedures for maintaining such subjects in the study to collect their data as scheduled. The study staff should make diligent attempts to contact subjects who fail to return for study visits by using institutional databases, subject's health professionals, and any other means that comply with country and local laws and regulations. After the first missed visit, subjects who are considered temporarily lost to follow-up will have 2 documented telephone contact attempts and 1 certified letter in an effort to contact them.

Any withdrawal must be fully documented in the subject's source records and recorded in the electronic Case Report Form (eCRF). The documentation must include the reason for the withdrawal and details of any sequelae (followed until symptoms resolve or improve, as appropriate).

If a subject is withdrawn from the study during treatment phase, he/she must complete the procedures outlined in Section 3.9.1 and the sponsor should be contacted.

3.9.1 Procedures for discontinuation of a subject from investigational product

At any time, subjects are free to discontinue IP or withdraw from the study (ie, IP and assessments – Section 3.10), without prejudice to further treatment. A subject who decides to discontinue IP will always be asked about the reason(s) and the presence of any AEs. The reasons for premature discontinuation of IP should be recorded in the eCRF. If possible, the subject will be seen and assessed by an Investigator(s). Adverse events will be followed up (Section 6). All IP should be returned by the subject.

If a subject discontinues from the IP, he or she should be asked, at the discretion of the treating physician, to return to the study site for the Early Termination Visit as soon as possible, but not later than 7 days from last IP dose. All endpoint assessments must be performed at this visit (Table 2). The subject should also be asked to return 4 weeks (±3 days) after the last IP dose, for follow-up assessments (see Section 4.3). If the subject is unable or unwilling to return, a phone follow-up should be conducted.

Subjects who discontinue IP will be recommended to continue on the study and follow the original visit schedule without taking IP. A follow-up visit should be performed as advised by the study plan. The next visits should be planned in accordance to the original visit schedule (apart from the IP resupply visits). If the subject is unable or unwilling to return to the study site for visits according to the original visit schedule, the subject should be asked to undergo modified visits and schedule (eg, less frequent visits, regular telephone contacts, a contact at study closure, or other means).

If a subject is withdrawn from the study, see Section 3.10.

3.10 Criteria for withdrawal

3.10.1 Screen failures

Screening failures are subjects who do not fulfil the eligibility criteria for the study, and therefore must not be randomised. These subjects should have the reason for study withdrawal recorded as 'Screen failure'. 'Failure to meet randomisation criteria' should be selected for an indication that the subject has been unable to fulfil/satisfy the criteria required for assignment into a randomised group.

Given some variability in HbA1c, subjects may be eligible for re-testing of HbA1c, if deemed applicable by the Investigator. These subjects will not be automatically listed as screen failures. For such subjects the results measured as part of Screening will be replaced by a re-test result obtained within the screening period. For these subjects, the screening will be extended to up to 18 days.

3.10.2 Withdrawal of the informed consent

Subjects are free to withdraw from the study at any time (IP and assessments), without prejudice to further treatment.

A subject who withdraws consent will always be asked about the reason(s) and the presence of any AEs. The Investigator will follow up AEs outside of the clinical study.

AstraZeneca or its delegate may request investigators to collect information on subjects' vital status (dead or alive; date of death when applicable) at the end of the study from publicly available sources, in accordance with local regulations. Knowledge of the vital status at study end in all subject is crucial for the integrity of the study.

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

3.11 Discontinuation of the study

The study may be stopped if, in the judgment of AstraZeneca, trial subjects are placed at undue risk because of clinically significant findings that:

- are assessed as causally related to IP
- are not considered to be consistent with continuation of the study

Regardless of the reason for termination, all data available for the subject at the time of discontinuation of follow-up must be recorded in the Case Report Form (CRF). All reasons for discontinuation of treatment must be documented. In terminating the study, the sponsor will ensure that adequate consideration is given to the protection of the subjects' interests.

4. STUDY PLAN AND TIMING OF PROCEDURES

Table 2 Study plan (screening, run-in, and 14-week treatment period)

Evaluation	For details refer to CSP section	Screening[i]	Run-in	Baseline	Dosing period					ET[t]	FU[u]	Rescue treatment
Visit Number		**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**			
Study Day		**-28 to -15**	**-14 to 0**	**1**	**8**	**15**	**43**	**71**	**99**			
Study Week				**0**	**1**	**2**	**6**	**10**	**14**			
Visit Window (days)			**Up to 7**	**Up to 2**	**± 2**	**± 2**	**± 3**	**± 3**	**± 3**		**± 3**	
Outpatient visit		X	X	X	X	X	X	X	X	X	X	X
Telephone contact 1 day after dosing visit during treatment up-titration[a]	4.2.1.2				X	X						
Verify subject has fasted 8 hours	4.1, 4.2	X		X	X	X	X	X	X	X	X	
Contact IVRS/IWRS	4.1.1	X	X	X	X	X	X	X	X	X		
Informed consent (written, general)	4.1.1	X										
[redacted]	4.1.1	X										
Demographics	4.1.1	X										
Medical and disease history (including smoking, drug, and alcohol history)	4.1.1	X										
Complete physical examination (including screening for diabetic neuropathy)	5.2.2	X							X			
Brief physical examination	5.2.2		X	X	X	X	X	X		X	X	
[redacted]	5.3.3			X					X	X		
[redacted]	5.3.3								X	X		
[redacted]	5.3.4		X								X	
Body weight	5.1.2	X		X					X	X	X	
Height	5.3.2.1	X										
Body mass index[c]	5.3.2.1	X										

Table 2 Study plan (screening, run-in, and 14-week treatment period)

Evaluation	For details refer to CSP section	Screening[i]	Run-in	Baseline	Dosing period					ET[t]	FU[u]	Rescue treatment
Visit Number		**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**			
Study Day		**-28 to -15**	**-14 to 0**	**1**	**8**	**15**	**43**	**71**	**99**			
Study Week				**0**	**1**	**2**	**6**	**10**	**14**			
Visit Window (days)			**Up to 7**	**Up to 2**	**± 2**	**± 2**	**± 3**	**± 3**	**± 3**		**± 3**	
Waist circumference	5.3.2.2			X					X	X	X	
Digital 12-lead ECG	5.2.3	X		X					X	X	X	
Vital signs (BP, pulse)	5.2.4.1	X	X	X	X	X	X	X	X	X	X	X
Assessment of AEs and SAEs[d]	5.2, 6		X	X	X	X	X	X	X	X	X	X
Concomitant medication review (including any dose changes to medications for diabetes)[e]	7.7	X	X	X	X	X	X	X	X	X	X	X
Retinal assessment[f]	5.3.2.3			X								
Glucometer provision/training[g]	4.1.3		X									
Provide subject diary/instructions[g]	4.1.3		X	X	X	X	X	X	X			X
Review subject's diary and blood glucose measurements	5.3.1			X	X	X	X	X	X	X	X	X
Calcitonin	5.2.1.4	X		X						X		
HIV-1 and HIV-2 antibodies	5.3.6	X										
Hepatitis screen[h]	5.3.6	X										
HbA1c[i]	5.1.1	X		X			X	X	X	X	X	
Serum chemistry	5.2.1.2	X		X		X	X	X	X	X	X	
Haematology	5.2.1.1	X		X		X			X	X	X	
Pancreatic amylase and lipase	5.2.1.3			X					X			

Table 2 Study plan (screening, run-in, and 14-week treatment period)

Evaluation	For details refer to CSP section	Screening[i]	Run-in	Baseline	Dosing period					ET[t]	FU[u]	Rescue treatment
Visit Number		**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**			
Study Day		**-28 to -15**	**-14 to 0**	**1**	**8**	**15**	**43**	**71**	**99**			
Study Week				**0**	**1**	**2**	**6**	**10**	**14**			
Visit Window (days)			**Up to 7**	**Up to 2**	**± 2**	**± 2**	**± 3**	**± 3**	**± 3**		**± 3**	
Fasting blood sample for glucose	5.2.1.5	X		X	X	X	X	X	X	X	X	
[redacted][j]	5.2.1.8	X		X					X	X	X	
Fasting blood sample for C-peptide and insulin, GLP-1 and glucagon	5.2.1.8			X						X		
Coagulation studies[k]	5.2.1.7			X								
Pre-dose pharmacokinetics for MEDI0382	5.4			X	X	X	X	X	X	X	X	
Immunogenicity blood sample	5.2.1.8			X	X		X	X	X	X	X	
[redacted]	5.6			X								
[redacted]	5.7			X					X			
Urine 'drug' screen	4.1.1	X										
Urine βhCG Test (pregnancy test)[m]	5.2.1.8	X		X						X	X	
Urinalysis	5.2.1.6	X		X					X	X	X	
Check subject's ability to self-administer SC injection[n]	4.1.3	X	X	X								X
Provide education on diet and exercise	4.1.3		X	X	X	X	X	X	X			X
[redacted]	4.2.1.3								X			
Verify eligibility criteria[p]	3.1, 3.2	X		X								
Randomisation	4.2.1.1			X								

Table 2 Study plan (screening, run-in, and 14-week treatment period)

Evaluation	For details refer to CSP section	Screening[i]	Run-in	Baseline	Dosing period					ET[t]	FU[u]	Rescue treatment
Visit Number		**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**			
Study Day		**-28 to -15**	**-14 to 0**	**1**	**8**	**15**	**43**	**71**	**99**			
Study Week				**0**	**1**	**2**	**6**	**10**	**14**			
Visit Window (days)			**Up to 7**	**Up to 2**	**± 2**	**± 2**	**± 3**	**± 3**	**± 3**		**± 3**	
MEDI0382/ placebo/ liraglutide dispensation[q]	4.1, 7.2			X	X	X	X	X	X			
Placebo kit dispensation (for run-in)	4.1.3		X									
Collect used/unused IP[r]	4.2.3			X[s]	X	X	X	X	X	X		
Provide instructions for use[r]	4.1.3		X	X	X	X	X	X	X			
Collect instructions for use[r]	4.1.3			X	X	X	X	X	X	X		

AE adverse event; βhCG beta subunit of human chorionic gonadotropin; BMI body mass index; BP blood pressure; CRF case report form; CSP clinical study protocol; [redacted]; ECG electrocardiogram; [redacted]; ET early termination; FU follow-up; GLP-1 glucagon-like peptide-1; HbA1c haemoglobin A1c; [redacted]; HIV human immunodeficiency virus; IFU instructions for use; IVRS/IWRS interactive voice/web response system; IP investigational product; [redacted]; PK pharmacokinetics; SAE serious adverse event; SC subcutaneous.

a During the up-titration phase, the subjects will be contacted via telephone 1 day following on-site dosing visit. The adverse events/concomitant medication changes will be collected, if applicable

b [redacted]

c Body mass index will be calculated directly in RAVE [BMI = weight/ (height)^2] where weight is measured in kg and height in metres.

d AEs will be recorded from the time of first IP dose and SAEs will be recorded from the time of informed consent.

e Subjects should be specifically asked at each visit if there have been any changes to the type and/or doses of their diabetes medications, or if they have needed treatment for a hypoglycaemic episode and this information should be recorded in the CRF

f Window for retinal assessment is 6 months prior to administration of first dose of IP if performed according to local standard requirements, and as long as the assessment can be entered and stored in the subject's source documentation

g Subjects will be provided with a glucometer and training at the beginning of run-in period. Supply of the glucometer related materials will be provided on an ongoing basis as needed if reported by the subject. Subjects will be asked to complete their glucose diaries at the discretion of the Investigator.

h Hepatitis B surface antigen and Hepatitis C virus antibody.

i Given some variability in HbA1c, subjects may be eligible for re-testing of HbA1c, if deemed applicable by the Investigator. For such subjects the results measured as part of Screening will be replaced by a re-test result obtained within the screening period. For these subjects, the screening will be extended to up to 18 days.

j [redacted]

k Coagulation studies should only be done in subjects taking oral anticoagulants/ or SC low molecular weight heparin.

l [redacted]

m Female subjects with childbearing potential only

n At screening, the Investigator will judge if the subject is able to self-administer SC injection. Later, subjects will be trained on subcutaneous self-injection technique by administering placebo doses during 2 weeks run-in period until the subject is deemed competent by the Investigator or designee. Further visits may occur for training as required

o [redacted]

p Subjects must meet all screening eligibility criteria with the exception of the clause relating to a stable dose of metformin in subjects who have had a dose modification of metformin due to renal impairment detected at screening.

q All subjects, together with open-label liraglutide subjects, will be asked to attend all outpatient clinic visits, including weekly dosing visits, as listed in the protocol.

r From Visit 2, subjects will be provided with instructions for use (IFU) for MEDI0382 and placebo by the IP manager at the site. For the open-label arm, IFU for liraglutide will be provided at Visit 3 following randomisation. The IFUs will be collected and resupplied at each visit thereafter, till end of treatment or early termination visit. If needed, the IFU can be provided in between the visits. The IP manager will dispense the IP, collect used IP boxes along with unused doses, perform drug accountability, instruct the subject on self-administration, as well as, if required, administer the IP during the subject's on-site visits.

s At Visit 3, subject will be returning used/unused placebo kit doses dispensed at the beginning of run-in

t ET is an early termination visit for subjects who discontinued the treatment with IP prematurely at any time, and for any reason. IVRS/IWRS should be contacted for discontinuation transaction

u FU is a follow-up visit that should be scheduled 4 weeks (±3 days) following the last dose of IP administered, and is applicable for subjects who either discontinued the treatment with IP prematurely at any time and for any reason or completed a minimum of 54 weeks of treatment with IP

Table 3 Study plan (minimum 40-week treatment extension period and follow-up)

Evaluation	For details refer to CSP section	Minimum 40-Week Treatment Extension Period											ET[j]	FU[k]	Rescue treatment
Visit Number		**9**	**10**	**11**	**12**	**13**	**14[l]**	**15[l]**	**16[l]**	**17[l]**	**18[l]**	**19/ EoT[l]**			
Study Week		**18**	**22**	**26**	**30**	**42**	**54[l]**	**66[l]**	**78[l]**	**90[l]**	**102[l]**	**EoT[l]**			
Visit window (days)		**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**		**± 3**	
Outpatient visit[ab]		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Contact IVRS/IWRS		X	X	X	X	X	X	X	X	X	X	X	X		
Brief physical examination	5.2.2	X	X	X	X	X	X	X	X	X	X	X	X	X	
[redacted]	5.3.3			X			X					X	X		
[redacted]	5.3.4				X		X							X	
Body weight	5.1.2			X			X					X	X	X	
Waist circumference	5.3.2.2			X			X					X	X	X	
Digital 12-lead ECG[d]	5.2.3						X					X	X	X	
Vital signs (BP, pulse)	5.2.4	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Assessment of AEs/SAEs	5.2, 6	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medication review (including any dose changes to medications for diabetes)[e]	7.7	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Provide subject diary/instructions	4.1.3	X	X	X	X	X	X	X	X	X	X	X			X
Review subject's diary and blood glucose measurements	5.2.1.5	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Serum chemistry	5.2.1.2			X			X		X			X	X	X	
Haematology	5.2.1.1			X			X					X	X	X	
HbA1c[e]	5.1.1			X	X	X	X	X	X	X	X	X	X	X	
Pancreatic amylase and lipase	5.2.1.3											X			
Calcitonin	5.2.1.4											X	X		
Fasting blood sample for glucose	5.2.1.8	X	X	X			X					X	X	X	

Table 3 Study plan (minimum 40-week treatment extension period and follow-up)

Evaluation	For details refer to CSP section	Minimum 40-Week Treatment Extension Period											ET[j]	FU[k]	Rescue treatment
Visit Number		**9**	**10**	**11**	**12**	**13**	**14[l]**	**15[l]**	**16[l]**	**17[l]**	**18[l]**	**19/ EoT[l]**			
Study Week		**18**	**22**	**26**	**30**	**42**	**54[l]**	**66[l]**	**78[l]**	**90[l]**	**102[l]**	**EoT[l]**			
Visit window (days)		**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**		**± 3**	
Fasting serum lipids[f]	5.2.1.8			X			X					X	X	X	
Fasting blood sample for C-peptide and insulin, GLP-1, and glucagon	5.2.1.8			X			X					X	X		
Pre-dose pharmacokinetics for MEDI0382	5.4	X	X	X			X	X				X	X	X	
Immunogenicity blood sample	5.2.1.8			X			X	X				X	X	X	
[redacted]	5.7											X			
Urinalysis	5.2.1.6			X			X					X	X	X	
Urine βhCG Test (pregnancy test)[g]	5.2.1.8											X	X	X	
Provide education on diet and exercise	4.1.3	X	X	X	X	X	X	X	X	X	X	X			X
MEDI0382/placebo/liraglutide dispensation	4.1, 7.2	X	X	X	X	X	X	X	X	X	X				
4-weekly interval IP supply[h]	4.2.3				→	→	→	→	→	→	→				
Collect used/unused IP	4.2.3	X	X	X	X	X	X	X	X	X	X	X	X		
Provide instructions for use[i]	4.1.3	X	X	X	X	X	X	X	X	X	X				
Collect instructions for use[i]	4.1.3	X	X	X	X	X	X	X	X	X	X	X	X		

AE adverse event; βhCG beta subunit of human chorionic gonadotropin; BP blood pressure; CRF case report form; CSP clinical study protocol; [redacted] ECG electrocardiogram; EoT End of treatment; [redacted] ET early termination; FU follow-up; HbA1c haemoglobin A1c; GLP-1 glucagon-like peptide-1; [redacted]; IFU instructions for use; IP investigational product; [redacted]; PK pharmacokinetics; SAE serious adverse event

[a] During the minimum 40-week treatment extension period, when diabetes medication is changed an unscheduled telephone visit should be performed one week after the occurrence

[b] Subjects should be fasted for at least 8 hours prior to all study visits except Visits 12, 13, 15, 16, 17 and 18

[c] Applicable for English speaking subjects in the US and Canada only

[d] A single ECG will be performed at Week 54 and at Visit 19 (EoT)

[e] Subjects should be specifically asked at each visit if there have been any changes to the type and/or doses of their diabetes medications, or if they have needed treatment for a hypoglycaemic episode and this information should be recorded in the CRF

[f] [redacted]

[g] Female subjects with childbearing potential only

[h] The subjects will be asked to return to study site between visits, every 4 weeks (±3 days) to collect the resupply of investigational product (IP).

[i] Subjects will be provided with instructions for use (IFU) for MEDI0382 and placebo, or liraglutide. The IFU will be collected and re-dispensed at each visit.

[j] ET is an early termination visit for subjects who discontinued the treatment with IP prematurely at any time, and for any reason. IVRS/IWRS should be contacted for discontinuation transaction

[k] FU is a follow-up visit that should be scheduled 4 weeks (±3 days) following the last dose of IP administered, and is applicable for subjects who either discontinued the treatment with IP prematurely at any time and for any reason, or completed treatment with IP per protocol (see footnote 1, below).

[l] Per CSP Amendment 5, the end of study treatment visit is to be performed at Visit 19 (EoT), as follows:

- Subjects receiving study treatment who have not reached Week 54, will continue per protocol up to Week 54 at which time study treatment will end, subjects will complete the Visit 19 (EoT) schedule of assessments, and a FU visit schedule of assessments 4 weeks (±3 days) following the last dose of IP administered.
- Subjects receiving study treatment who have completed Week 54, will end study treatment as soon as possible, preferably at the next scheduled visit (including IP-supply visits), but in no case longer than 4 weeks beyond the next scheduled visit. These subjects will complete the Visit 19 (EoT) schedule of assessments, and a FU visit schedule of assessments 4 weeks (±3 days) following the last dose of IP administered.
- Subjects who are off drug and continuing in the study per protocol (see Section 3.9.1) but have not reached Week 54, will complete the study up to Week 54, at which time they will complete the Visit 19 (EoT) schedule of assessments.
- Subjects who are off drug and continuing in the study per protocol (see Section 3.9.1) but have completed Week 54, will complete the Visit 19 (EoT) scheduled of assessments, as soon as possible, but in no case longer than the next scheduled visit.

4.1 Screening/Enrolment period

Procedures will be performed according to the Study Plan (Table 2). At screening, consenting subjects are assessed to ensure that they meet eligibility criteria. Subjects who do not meet these criteria must not be enrolled in the study. Subjects will be instructed to arrive in the morning of each scheduled visit.

4.1.1 Visit 1 assessments - Screening

The maximum duration of the screening period will be 2 weeks (from provision of informed consent to completion of screening procedures).

Each potential subject will provide written informed consent prior to any study-specific procedures and undergo assessments applicable for the visit (see Table 2). Subjects must sign the Informed Consent Form (ICF) prior to any Visit 1 procedures and prior to being instructed to fast or withhold any medication unless it is usual site practice to ask all patients to come to regular visits having fasted. Registration of subject's enrolment via IVRS/IWRS should occur on the day of ICF signature. [redacted]

If a subject has not fasted, the subject will sign the informed consent, perform all non-laboratory screening assessments, and return at least 1 day later in a fasted state for collection of screening laboratory assessments.

Throughout the study, subjects will be instructed to delay administering their morning dose of metformin on the morning of study site visits, as well as to abstain from strenuous exercise and alcohol for 24 hours before each visit. As above, in case such requests are not usual practice, the procedures that could potentially be affected will be rescheduled for a later day within the maximum duration of 2 weeks planned for screening.

Demographics data collected will include age, gender, race, and ethnicity. Date of birth will be collected if allowed by local regulations. The subject's complete medical history will be recorded, and will include current medical conditions, past or present, and any diseases or disorders. Visit 1 assessments are primarily concerned with confirmation of the underlying disease state and the requisite level of severity based on background medications. A record of physician-diagnosed T2DM is required in source documentation prior to enrolment. A subject's verbal history suggestive of T2DM symptoms, but without supporting documentation, is not sufficient to satisfy this inclusion criterion.

All concomitant medications will be recorded. See Section 7.7 for more information on concomitant medications. The ability of the subject to self-administer SC injection will be checked.

A complete physical examination will be conducted, vital signs will be measured, and a digital 12-lead electrocardiogram (ECG) will be performed. Body weight and height will be measured, and BMI will be calculated directly in RAVE.

Blood samples will be taken for laboratory evaluations, including HbA1c measurements, calcitonin, serum chemistry, haematology, fasting blood glucose, and fasting serum lipids. Urine will be collected for urinalysis, pregnancy testing, and drug screening. A screen for hepatitis and tests for HIV-1 and HIV-2 antibodies will also be performed.

Given some variability in HbA1c, subjects may be eligible for re-testing of HbA1c, if deemed applicable by the Investigator. For such subjects the results measured as part of screening will be replaced by a re-test result obtained within the screening period. For these subjects, the screening will be extended to up to 18 days. Additionally, in case of laboratory results that are deemed questionable or unreliable by the investigator or if the blood sample is hemolyzed, re-testing is permitted.

Screening values will be used to determine if the subject is eligible for randomisation. In case of HbA1c, as described above, the re-test value may be used instead. All samples will be processed by a central laboratory and results will be reported back to the clinic. Subjects will not be randomised if results of any laboratory test are abnormal and clinically significant as judged by the Investigator or study physician. Individuals may requalify for study enrolment within 2 weeks of screening following an abnormal test result by having that test repeated once with acceptable results as judged by the Investigator and study physician (or designee).

When all of the screening results are available, individuals will be notified by telephone of their preliminary eligibility status.

4.1.2 Re-screening

If the reason for screen failure was transient (including but not limited to study-supplied equipment failure or unforeseen personal events that mandate missed screening visits), re-screening can be allowed only once. All study procedures of initial Visit 1 must be repeated at the re-screening visit (Table 2). Re-screened subjects should re-sign informed consent on the re-screening Visit 1. If a subject is re-screened, he/she must continue to meet all inclusion/exclusion criteria. All procedures from screening should be repeated.

The re-screening and HbA1c re-test are independent from one another. Subjects who fail the central HbA1c testing twice during screening may still be re-screened within the recommended window but not sooner than 12 weeks (or 3 months) following the date of second failed test.

Re-screened subjects keep an originally assigned enrolment number.

4.1.3 Visit 2 assessments - 2-week run-in period

Subjects must come to the clinic for Visit 2 within a maximum of 7 days upon completion of the screening period. Subjects will be instructed to arrive in the morning of the visit and to abstain from strenuous exercise and alcohol for 24 hours before the visit. Subjects should also delay administering their morning dose of metformin.

Visit 2 assessments are primarily concerned with preparing the subject for the study by providing education in diet and exercise, training in SC injection administration, and instruction on monitoring capillary blood glucose levels. Visit 2 will also be the initiation of placebo run-in. The assessments required during the 2-week run-in period are detailed in the Study Plan (Table 2).

During this visit, a brief physical examination will be conducted, vital signs will be measured. Serious AEs will be assessed. All concomitant medications will be reviewed.

All subjects will receive placebo IP kits to be administered daily during the 2-week placebo run-in. Subjects will be instructed to continue taking metformin as directed during this period. During Visit 2, designated IP manager/ caregiver will go through the Instructions for Use (IFU) for MEDI0382, placebo, or liraglutide in detail. Subjects will be trained in self-administration of IP, disposal of used needles, and all the other IP handling steps while they administer the drug at home. Moreover, subjects will be asked to return the used IP kit boxes along with sharp containers and unused syringes to investigational site at their next scheduled visit.

Moreover, subjects will receive education on diet and exercise to promote weight loss and will be asked to refrain from alternative weight loss programmes; they will be expected to follow this advice for the duration of the study and will receive periodic education updates and support.

During the run-in subjects will be provided with a blood glucometer and training for its use. Subjects will be asked to monitor their capillary blood glucose levels two times per day and complete a diary to record these levels while at home for the duration of run-in. For more details, see Section 5.3.1.

All concomitant medications will be reviewed and updated. Subjects will refrain from taking prohibited medications, but will continue to take their prescribed stable dose of metformin during the run-in and for the remainder of the study.

[redacted]

4.2 Treatment period

The study will comprise a 14-week treatment period, followed by a minimum 40-week treatment extension.

Subjects will be instructed to arrive in the morning of each visit and to abstain from strenuous exercise and alcohol for 24 hours before scheduled visits. Prior to each study visit subjects are to have fasted overnight for at least 8 hours (no food or beverage except water). Subjects should delay administering their morning dose of metformin and IP on the morning of study site visits, and bring the IP (used IP kit boxes, as well as the unused syringes) along with IFU with them to the study site for each visit in treatment period.

Subjects who complete the study will be asked to return to site 4 weeks (±3 days) after the last dose of IP administered for a follow-up visit (see Section 4.3). Subjects discontinued from the treatment prematurely will be asked to return to the study site as soon as possible but not later than 7 days from the last IP dose (see Section 3.9) for their Early Termination Visit, and 4 weeks (±3 days) after the last dose of IP administered for a follow-up visit.

Subjects will be randomised at Visit 3 (Day 1) to receive either MEDI0382, liraglutide, or placebo. The assessments required during the treatment period are detailed in the Study Plan (Table 2 and Table 3).

4.2.1 14-week treatment period

Procedures will be performed according to the Study Plan (Table 2). A 14-week treatment period is required to properly evaluate the dose range. The procedures and visit schedule is more frequent in this initial treatment period.

4.2.1.1 Visit 3 assessments - Baseline

Subjects must come to the clinic for Visit 3 (baseline) within a maximum of 2 days upon completion of the run-in period. Visit 3 assessments are primarily concerned with baseline assessments and randomisation.

Visit 3 will constitute the end of the placebo run-in period. The designated IP manager at the site will check that subjects are able to self-administer the SC injections and able to adhere to IP related study procedures (ie, if subject returned IFU, cartons after used doses, unused syringes etc).

[redacted] A brief physical examination will be conducted, vital signs will be measured, and a digital 12-lead ECG will be performed. Body weight and waist circumference will be measured. Serious AEs will be assessed and all concomitant medications will be reviewed.

For most inclusion and exclusion criteria, screening values will be used to determine if subject is eligible for randomisation. Eligibility criteria will be verified. The subject's diary and blood glucose measurements will be reviewed, and education and diet and exercise will be provided.

At Visit 3 blood samples will be taken to measure HbA1c. Samples will also be taken for the following laboratory safety assessments: haematology, serum clinical chemistry, pancreatic amylase and lipase, calcitonin, and coagulation panel. In addition, fasting blood tests will be performed for plasma glucose, serum lipids, C peptide, insulin, GLP-1, and glucagon. At Visit 3 samples will be taken for non-genetic research, [redacted] Urine will be collected for urinalysis, and pregnancy testing.

Blood samples for PK and immunogenicity will be taken prior to administering the randomised treatment.

During this visit, the subject will be randomised, and dosing will commence according to assigned treatment arm. A designated IP manager will go through the IFU for MEDI0382, placebo, or liraglutide in detail. The subject will be asked to self-administer SC IP under supervision, used IP will be collected, and the subject will be discharged home following 2 hours of observation with sufficient IP supply.

Standardised assessments of the eyes, such as dilated fundoscopic examination/fundus photography, will also be collected at this visit. For more details, see Section 5.3.2.3.

4.2.1.2 Visits 4 to 5 assessments – Up-titration

Visits 4 to 5 assessments are primarily concerned with up-titration and establishing a maintenance dose.

On Day 8 (Visit 4) and Day 15 (Visit 5), subjects will return to the clinical unit (outpatient visit). A brief physical examination will be conducted, and vital signs will be measured. Adverse events and SAEs will be assessed. All concomitant medications will be reviewed. Education on diet and exercise will be provided.

At Visits 4 and 5 samples will be taken for FPG. Pre-dose PK samples will also be taken at both visits. An immunogenicity sample will be taken at Visit 4. At Visit 5 samples will be taken for haematology and serum chemistry.

At each outpatient visit, an up-titration step will be made; this process will be repeated until all subjects are established on a maintenance dose which will be continued for the remainder of the treatment period. Subjects will be given additional supply of IP, and used/unused IP will be collected. A designated IP manager/ caregiver will go through the IFU for MEDI0382/placebo/liraglutide in detail; the IFU will also be collected at these visits (see Table 2).

Telephone contact with the subject will occur between outpatient clinic visits during the up-titration phase (see Table 2). The responses regarding concomitant medications, AEs and SAEs will be transferred into the eCRF. Telephone contact should be appropriately documented in the medical records.

The subject's diary and blood glucose measurements will be reviewed. Subjects will be expected to test capillary blood glucose levels at the discretion of the Investigator and per local treatment guidelines, before a study visit, and for 2 weeks following a change in diabetes medication. Subjects should also be advised to check their blood glucose level if they have symptoms of hypoglycaemia (hunger, dizziness, shaking, sweating etc.) or feel unwell. Any blood glucose level <3.0 mmol/L (54 mg/dL) is considered clinically significant hypoglycaemia and should be reported by Investigators as an AE (see Section 6.3.8). For more details, see Section 5.3.1. Rescue therapy will be considered for any subject with persistent hyperglycaemia (see Section 4.2.1.4 for more details).

4.2.1.3 Visits 6 to 8 assessments - maintenance period

Subjects will return to the clinical unit (outpatient visit) every 4 weeks (±3 days). A brief physical examination will be conducted at Visits 6 and 7 and a full physical examination at Visit 8. At each visit in the maintenance period (Visits 6 to 8), vital signs will be measured, AEs and SAEs will be assessed, and concomitant medications will be reviewed. Education on diet and exercise will be provided.

At Visits 6 to 8, HbA1c will be measured and samples will be taken for serum chemistry, and FPG. A pre-dose PK sample will also be taken at each visit. An immunogenicity sample will be taken at Visits 6, 7 and 8. At Visit 8 (Week 14) the following additional laboratory tests will be performed: haematology, pancreatic amylase and lipase, and fasting serum lipids. Samples will be collected at Week 8 for future non-genetic research. Additionally, complete urinalysis will be performed at Visit 8 (Week 14).

[redacted] At Visit 8, along with the complete physical evaluation, body weight and waist circumference will be measured and a digital 12-lead ECG will be performed. [redacted]

At all 3 visits, subjects will be given additional supply of IP, and used/unused IP will be collected. Subjects will be resupplied with IP for at least 4 weeks (±3 days). A designated IP manager will go through the IFU for MEDI0382, placebo, or liraglutide in detail; the IFU will also be collected and resupplied at all treatment visits (see Table 2).

The subject's diary and blood glucose measurements will also be reviewed. Subjects will be expected to test capillary blood glucose levels at the discretion of the Investigator and per local treatment guidelines before a study visit, and for two weeks following a change in diabetes medication. Subjects should also be advised to check their blood glucose level if they have symptoms of hypoglycaemia (hunger, dizziness, shaking, sweating etc.) or feel unwell. Any blood glucose level <3.0 mmol/L (54 mg/dL) is considered as clinically significant hypoglycaemia and should be reported by Investigators as an AE (See Section 6.3.8). For more details, see Section 5.3.1. Rescue therapy will be considered for any subject with persistent hyperglycaemia (see Section 4.2.1.4 for more details).

4.2.1.4 Initiation of rescue medication (14-week treatment period)

Pre-specified glycaemic criteria (see Table 4), based upon central laboratory FPG and repeat confirmatory FPG, have been established during the 14-week treatment period, starting at Week 0 and up to Week 14 visits, to determine eligibility for open-label rescue medication.

Subjects with a central laboratory FPG value meeting the lack of glycaemic control criterion at a pre-specified visit will be scheduled for a follow-up visit (within 3 to 5 days) to obtain a second central laboratory FPG value and review the subject's glucometer readings. If the repeat central laboratory FPG value still meets the criterion, the subject must be rescued.

Subjects who meet rescue criteria in the 14-week treatment period must first complete the rescue visit procedures before receiving open-label rescue medication to ensure that important trial endpoint measurements are collected.

Following completion of the rescue visit, rescued subjects will be given open-label antidiabetic rescue medication (insulin or other antidiabetic agents except GLP-1 receptor agonists, dipeptidyl peptidase-4 (DPP4) and/or sodium-glucose co-transporter 2 inhibitors or metformin) to be initiated at the lowest starting dose and titrated in accordance with the approved product label in the applicable country at the discretion of the Investigator, in addition to their metformin and IP. Rescued subjects will then continue in the treatment period according to their original visit schedule.

Following initiation of open-label rescue antidiabetic medication, rescued subjects should be scheduled for titration visits to increase their antidiabetic medication dose, as tolerated and in accordance with the approved product label for that country and by their glycaemic response and as per the Investigator's judgment.

Table 4 Criteria for initiation of rescue medication (14-week treatment period)

Time interval on treatment	Rescue therapy is recommended if any of the following apply
Week 0 to Week 6 including day of Visit 6	Fasting plasma glucose greater than 270 mg/dL (15 mmol/L)
Week 6 to Week 14 including day of Visit 8	Fasting plasma glucose greater than 240 mg/dL (13.3 mmol/L)

Rescue therapy with add-on insulin is the preferred option, but additional drug classes are permitted (see Table 6). Rescue therapy with any GLP-1 receptor agonist or DPP4 inhibitor based intervention is prohibited (see Section 7.7.3).

4.2.1.5 Rescue visit

Subjects who require rescue will complete rescue procedures. If subjects are still taking IP at the time of the rescue visit, they should delay administering the morning dose of metformin (if applicable) and IP on the day of the visit and bring oral antidiabetic medication to the study site visit.

Rescue procedures are detailed in Table 2 and Table 3.

4.2.2 Minimum 40-week extension period

All subjects will continue into the minimum 40-week treatment extension designed to evaluate safety, tolerability, and efficacy over the longer term. At all visits apart from the IP resupply visits, a brief physical examination will be conducted and vital signs will be measured. Adverse events and SAEs will be assessed. All concomitant medications will be reviewed. The subject's diary and blood glucose measurements will be reviewed. Education on diet and exercise will be provided. Procedures will be performed according to the Study Plan (Table 3).

All subjects will complete an end of treatment (EoT) visit, which is to be performed according to the Visit 19 (EoT) schedule of assessments, as follows:

Subjects receiving study treatment who have not reached Week 54	These subjects will continue per protocol up to Week 54, at which time study treatment will end. These subjects will complete the Visit 19 (EoT) schedule of assessments, and a FU visit schedule of assessments 4 weeks (±3 days) following the last dose of IP administered.
Subjects receiving study treatment who have completed Week 54	These subjects will end study treatment as soon as possible, preferably at the next scheduled visit (including IP-supply visits), but in no case longer than 4 weeks beyond the next scheduled visit. These subjects will complete the Visit 19 (EoT) schedule of assessments, and a FU visit schedule of assessments 4 weeks (±3 days) following the last dose of IP administered
Subjects who are off drug and continuing in the study per protocol (see Section 3.9.1) but have not reached Week 54	These subjects will complete the study up to Week 54, at which time they will complete the Visit 19 (EoT) schedule of assessments.
Subjects who are off drug and continuing in the study per protocol (see Section 3.9.1) but have completed Week 54	These subjects will complete the Visit 19 (EoT) scheduled of assessments, as soon as possible, but in no case longer than the next scheduled visit.

The first four visits – Visit 9 (Week 18), Visit 10 (Week 22), Visit 11 (Week 26), and Visit 12 (Week 30) will be scheduled in 4-week (±3 days) intervals to facilitate adequate safety monitoring of subjects during the initial approximate 6 months of treatment. For the

remainder of the visits in the treatment extension, subjects will return to the clinical unit (outpatient visit) every 3 months.

A pre-dose PK sample will be collected at Visits 9, 10, 11, 14, 15 and 19 (EoT).

At Visits 11, 14, and 19 (EoT) [redacted] body weight and waist circumference will be measured. Blood samples will be taken for haematology, fasting serum lipids, and fasting C-peptide, insulin, GLP-1, and glucagon. Urine will be collected for urinalysis with the same frequency.

At Visits 9, 10, 11, 14, and 19 (EoT), blood samples will be taken for fasting blood glucose.

At Visits 11, 14, 16, and 19 (EoT) a blood sample will be taken for serum chemistry. An immunogenicity blood sample will be collected at Visits 11, 14, 15, and 19 (EoT). A digital 12-lead ECG will be performed at Visits 14 and 19 (EoT).

HbA1c will be measured at Visits 11 to 19 (EoT).

[redacted]

At Visit 19 (EoT), blood samples will be collected for pancreatic amylase and lipase, for calcitonin, and for future non-genetic research. Additionally, at Visit 19 (EoT), urine will be collected for pregnancy testing.

As before, subjects will be expected to test capillary blood glucose levels at the discretion of the Investigator and per local treatment guidelines, before a study visit, and for two weeks following a change in diabetes medication. Subjects should also be advised to check their blood glucose level if they have symptoms of hypoglycaemia (hunger, dizziness, shaking, sweating etc.) or feel unwell. Any blood glucose level <3.0 mmol/L (54 mg/dL) is considered as clinically significant hypoglycaemia and should be reported by Investigator as an AE (see Section 6.3.8). For more details, see Section 5.3.1. Rescue therapy will be provided to subjects with persistent hyperglycaemia (see Section 4.2.2.1 for more details) and there will be periodic diet and exercise education updates.

At each visit, subjects will be given additional supply of IP, and used/unused IP will be collected. Subjects will be resupplied with IP every 4 weeks (±3 days). A designated IP manager will go through the IFU for MEDI0382/placebo, or liraglutide in detail; the IFU will also be collected at these visits (see Table 3).

4.2.2.1 Initiation of rescue medication (minimum 40-week treatment extension)

Pre-specified glycaemic criteria (see Table 5), based upon central laboratory FPG or HbA1c have been established during the period to determine eligibility for open-label rescue medication for subjects not previously rescued in the 14-week treatment period.

Table 5 Criteria for initiation of rescue medication (minimum 40-week treatment extension)

Time interval on treatment	Rescue therapy is recommended if any of the following apply
Week 14 to Week 26 including day of Visit 11	Fasting plasma glucose greater than 200 mg/dL (11.1 mmol/L) (repeated and confirmed)
Week 26 to Week 54 including day of Visit 14, but excluding day of Visit 19 (EoT)	Central laboratory HbA1c >8% (repeated and confirmed)
Week 54[a] to Week 66 including day of Visit 15, but excluding day of Visit 19 (EoT)	Central laboratory HbA1c >7.5% (repeated and confirmed)
Greater than Week 66 [a] excluding day of Visit 19 (EoT)	Central laboratory HbA1c >7.0% (repeated and confirmed)

[a] These time intervals apply to subjects who had completed Visit 14 at the time the CSP Amendment 5 was implemented.

Subjects who meet rescue criteria in the 40-week treatment extension period, must first complete the "Rescue" Visit procedures (see Table 3) before receiving open-label rescue medication to ensure that important trial endpoint measurements are collected. Rescued subjects will then continue in the 40-week treatment extension period according to their original visit schedule.

Rescue therapy with add-on insulin is the preferred option, but additional drug classes are permitted (see Table 6). Rescue therapy with any GLP-1 receptor agonist or DPP4 inhibitor based intervention is prohibited (see Section 7.7.3).

4.2.3 Resupply of investigational product visits

Subjects will be resupplied with IP every 4 weeks (±3 days). Used/unused IP will be collected. A designated IP manager will go through the IFU for MEDI0382/placebo, or liraglutide in detail; the IFU will also be collected and resupplied at these visits.

4.2.4 Unscheduled visits

Unscheduled visits may be initiated as needed, and any additional assessments might be performed at this visit at the discretion of the Investigator. In case safety laboratory assessments are required, the Investigator should refer to the Laboratory Manual for more details.

4.2.5 Early termination

If a subject discontinues early from the IP, he or she should be asked to return to the study site as soon as possible, but not later than 7 days from last IP dose (see Table 2 and Table 3). If the subject is unable or unwilling to return, a phone follow up should be conducted.

4.3 Last dose of investigational product follow-up visit

A follow-up outpatient visit should be scheduled 4 weeks (±3 days) following the last dose of IP administered, and is applicable for subjects who either discontinued the treatment with IP prematurely at any time, and for any reason, or completed treatment with IP at Visit 19 (EoT). Procedures will be performed according to the Study Plan (see Table 2 and Table 3).

At the follow-up visit, a brief physical examination will be performed and body weight, waist circumference, and vital signs will be measured. A 12-lead ECG will be performed. Adverse events and SAEs will be assessed. All concomitant medications will be reviewed. The subject's diary and blood glucose measurements will be reviewed. Blood samples will be taken for clinical laboratory evaluations, HbA1c, fasting blood glucose, and fasting serum lipids. Urine samples will be taken for urinalysis and pregnancy testing. A blood sample for immunogenicity and a PK sample will also be taken.

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

5. STUDY ASSESSMENTS

The Rave Web Based Data Capture (WBDC) system will be used for data collection and query handling. The Investigator will ensure that data are recorded on the eCRFs as specified in the Clinical Study Protocol and in accordance with the instructions provided.

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

5.1 Efficacy assessments

Study outcome measures are summarised in Section 8.4.

5.1.1 HbA1c

Blood samples for measurement of HbA1c will be collected according to the schedule presented in the Study Plan (Table 2 and Table 3). The instructions for collection, processing, packaging, and shipping of the samples will be detailed in the Laboratory Manual.

5.1.2 Body weight

Body weight will be measured according to the schedule presented in the Study Plan (Table 2 and Table 3). Body weight should be measured in the morning while the subject is fasted and prior to breakfast. At screening (Visit 1), baseline Visit 3 (Day 1), Visit 8 (Week 14), Visit 11 (Week 26), Visit 14 (Week 54), and Visit 19 (EoT), the subject's weight should be measured with the subject wearing a surgical gown and no shoes, and the weight of the surgical gown should be subtracted from the result. The subject's body weight will be recorded in kilograms

(kg) to one decimal place. All readings should be recorded as accurately as possible and the same scale should be used for all assessments for a given subject. The same scale should be used throughout the study and calibrated on a regular basis as recommended by the manufacturer.

5.2 Safety assessments

5.2.1 Laboratory safety assessments

The date, time of collection, and sample ID will be recorded on the appropriate eCRF. Clinical laboratory tests will be performed at a central laboratory. The samples will be processed by a central laboratory and results will be reported back to the clinic. The instructions for collection, processing, packaging, and shipping of the samples will be detailed in the Laboratory Manual.

Laboratory safety variables that will be measured are summarised in Section 5.2.1. Other clinical laboratory evaluations are summarised in Section 5.2.1.8.

5.2.1.1 Haematology

Blood samples will be drawn for measurement of haematology according to the schedule presented in the Study Plan (Table 2 and Table 3).

Haematology assessments will include the following: red cell count, haemoglobin, haematocrit, white cell count, platelets count, differential count, mean cell volume, mean corpuscular haemoglobin, and mean corpuscular haemoglobin concentration.

5.2.1.2 Serum clinical chemistry

Blood samples will be drawn for measurement of serum chemistry according to the schedule presented in the Study Plan (Table 2 and Table 3).

Chemistry assessments will include the following: blood urea nitrogen, creatinine, total protein, albumin, uric acid, TBL, alkaline phosphatase (ALP), ALT, AST, gamma glutamyl transpeptidase, amylase, lipase, creatine phosphokinase (CPK), creatine kinase, muscle and brain (CK-MB) (if CPK is elevated), troponin T (if CK-MB is elevated), sodium, potassium, chloride, bicarbonate, magnesium, phosphorus, and calcium. Note that, if a subject shows an AST **or** ALT ≥3 × ULN **AND** TBL ≥2 × ULN, refer to Appendix D 'Actions Required in Cases of Increases in Liver Biochemistry and Evaluation of Hy's Law', for further instructions.

5.2.1.3 Serum amylase and lipase

Blood samples will be drawn for measurement of amylase and lipase, along with the clinical chemistry according to the schedule presented in the Study Plan (Table 2 and Table 3).

If amylase and/or lipase values increase ≥3 × ULN:

- Confirm by repeat testing.

- Perform diagnostic work-up for evaluation of pancreatitis according to clinical practice.

The Investigator should make an assessment of the available clinical laboratory safety results with regard to clinically relevant abnormalities. The laboratory results should be signed and dated and retained at the centre as source data for laboratory variables. The Investigator should follow all clinically significant laboratory abnormalities occurring during the study that were not present at baseline. These abnormalities should be evaluated with additional tests, if necessary, until the underlying cause is diagnosed or resolution occurs. The diagnosis and resolution date must be reported to the sponsor. For information on how AEs based on laboratory tests should be recorded and reported, see Section 6.3.

5.2.1.4 Serum calcitonin

Blood samples will be drawn for measurement of serum calcitonin concentrations according to the schedule presented in the Study Plan (Table 2 and Table 3).

If an elevation of calcitonin is noted and deemed of clinical concern, typically a level above 10 ng/L or pg/mL:

- The Investigator should assess for factors that could be impacting calcitonin concentrations (ie, concomitant medications) and consider stopping concomitant medications prior to rechecking calcitonin concentrations.
- If calcitonin concentrations remain elevated upon recheck, the subject should be referred to their healthcare provider for appropriate follow-up.
- Any subsequent testing and interpretation of results should be provided to the study site personnel.

The Investigator should discuss subject continuation in the study with the study physician.

5.2.1.5 Fasting plasma glucose

Blood samples for measurement of FPG will be collected according to the schedule presented in the Study Plan (see Table 2 and Table 3), and analysed by a central laboratory. The instructions for collection, processing, packaging, and shipping of the samples will be detailed in the Laboratory Manual, which will be distributed to each study site during site initiation.

If the FPG (value from central laboratory) meets rescue limits (see Sections 4.2.1.4 and 4.2.2.1), the subject should return within 3 to 5 days for an unscheduled confirmatory visit to confirm the high FPG and assess eligibility for rescue during the treatment period.

5.2.1.6 Urinalysis

Urine samples will be collected for urinalysis according to the schedule presented in the Study Plan (Table 2 and Table 3).

Urinalysis assessments will include the following: pH, specific gravity, glucose (urine glucose will be blinded throughout the study), blood (urine haemoglobin/erythrocytes/blood), ketones, protein, and microscopic analysis.

5.2.1.7 Coagulation panel

Blood samples will be drawn for measurement of the coagulation panel according to the schedule presented in the Study Plan (Table 2).

- Prothrombin time (baseline only)
- Activated partial thromboplastin time (baseline only)

5.2.1.8 Other clinical laboratory evaluations

Fasting blood samples

Fasting blood samples will be taken for the measurement of the following according to the schedule presented in the Study Plan (Table 2 and Table 3):

- [redacted]
- Fasting plasma C-peptide and insulin
- Fasting plasma glucagon and GLP-1

The instructions for collection, processing, packaging, and shipping of the samples will be detailed in the Laboratory Manual.

Pregnancy testing

A pregnancy test should be conducted on any female subject of childbearing potential as detailed in the Study Plan (Table 2 and Table 3). Pregnancy tests do not need to be conducted in women who are surgically sterile (ie, bilateral tubal ligation, bilateral oophorectomy, or complete hysterectomy), or are postmenopausal. The presence of βHCG in urine is to be assessed at the study centre by dipstick. The first dose of IP or any other in-clinic dose of IP must not be administered until a negative urine pregnancy test result is obtained. A positive urine pregnancy test should be confirmed by a serum pregnancy test. Serum pregnancy tests will be tested by a central laboratory.

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 and Table 3). Samples for determination of ADA will be analysed by a selected laboratory on behalf of AstraZeneca, using a validated bioanalytical method. A summary of the analysis will be presented in the clinical study report (CSR). Details of the

analytical method used will be described in a bioanalytical report. Tiered analyses will be performed to include screening, confirmatory, and titre assay components, and the positive-negative cut points will be statistically determined from drug-naïve validation samples. 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.

5.2.2 Physical examination

A complete physical examination will be performed according to the schedule presented in the Study Plan (Table 2). The complete physical examination includes an assessment of the following: general appearance including skin inspection, lymph nodes, thyroid, musculoskeletal/extremities, CV, lungs, abdomen, and reflexes.

A brief physical examination should be conducted according to the schedule presented in the Study Plan (Table 2 and Table 3). A brief physical examination includes the following: skin, extremities, CV, lungs, and abdomen. Clinically significant abnormalities in physical examination findings at study termination must be followed up by the Investigator and evaluated with additional tests if necessary, until the underlying cause is diagnosed or resolution occurs. As appropriate, the diagnosis and resolution date of the physical examination abnormalities must be reported as AEs.

See Section 6 for information on reporting AEs.

5.2.3 Resting 12-lead ECG

A digital 12-lead ECG will be performed in accordance with the schedule provided in the Study Plan (Table 2 and Table 3). A 12-lead ECG will be taken in the supine position after the subject has been resting for at least 10 minutes. If the ECG must be performed with the subject in another position (sitting, standing, etc.), the Investigator should record the alternate position. The Investigator should date and sign the ECG tracing and record the clinical significance of any abnormal result on the tracing. The ECGs will be interpreted by a qualified physician (the Investigator or qualified designee) at the clinical study site. The ECGs will be stored at the study centre. ECG data and evaluation will be recorded in the eCRF. See Section 6 for information on reporting AEs.

5.2.4 Vital signs

Pre-dose vital signs (pulse and BP) are to be obtained in accordance with schedule provided in the Study Plan (Table 2 and Table 3). Vital signs are to be taken prior to IP administration, and, if possible, before blood drawing. Vital signs should be measured after the subject rests for approximately 5 minutes and with the subject in a sitting position.

5.2.4.1 Pulse and blood pressure

One pulse measurement will be taken after the subject has been sitting and resting for at least 5 minutes, and before blood samples are taken. If a semi-automatic device is used, extrapolation to 1 minute is recommended. If using manual BP measurements, a full sixty second period for recording the pulse is required. The pulse measurement will be followed by

two BP measurements separated by 2 minutes each. The two BP readings should be recorded. At Visit 1 the seated BP will be recorded two times in both the left and the right arms. The two measurements should be made in one arm before transferring the cuff to the other arm. The arm with the highest mean seated BP readings will be the one used for all subsequent readings throughout the study. Blood pressure readings should be taken while the subject is in a comfortable seated position with the arm supported at the level of the heart. All readings should be recorded. Ideally, BP should be measured with the same machine, at the same time of day with a two hour window, and by the same personnel at each visit.
At each visit, two BP measurements separated by 2 minutes each will be done. The two BP readings should be recorded and entered in eCRF.

5.2.4.2 Orthostatic blood pressure

In the event that the subject experiences symptoms of dizziness or light-headedness or visual blurring, orthostatic BP and pulse should be collected if deemed necessary by the Investigator. Supine and standing measurements should be made after the seated BP and pulse measurements have been made, using the same arm that was used for the seated BP measurements. All readings should be recorded.

Supine BP and pulse

The supine BP and pulse must be measured prior to the standing BP and pulse. After the subject rests in the supine position for at least 5 minutes, supine BP and pulse will be determined from two replicate measurements obtained 2 minutes apart. The two readings must be recorded.

Standing BP and pulse

After the supine BP and pulse measurements are obtained, the subject will stand for 2 to 3 minutes. After this time, the BP will be measured with the arm supported at the level of the heart. Standing BP and pulse will be determined from two replicate measurements obtained at least 2 minutes apart. The two readings must be recorded. If a new occurrence of previously absent orthostatic hypotension is demonstrated, it should be recorded in the appropriate section of the CRF. The Investigator may consider reducing concomitant anti-hypertensive medication to alleviate signs and symptoms of orthostatic hypotension, without discontinuation of IP.

5.2.5 Other safety assessments

5.2.5.1 Drug-induced liver injury

Liver enzymes (ALT, AST, and ALP) and TBL should be monitored for abnormalities indicative of drug-induced liver injury. Investigators should contact the study physician if a subject develops a liver function test abnormality.

Laboratory values meeting the criteria for Hy's Law are to be reported to AstraZeneca as SAEs in the same time frame as defined for other SAEs.

A Hy's Law case is defined as any subject with an increase in AST or ALT ≥3 × ULN together with TBL ≥2 × ULN, where no other reason can be found to explain these increases.

Potential Hy's Law cases that meet any of the identification criteria specified in Appendix D will require an unscheduled laboratory draw for assessment by the central laboratory (see central laboratory manual for further instructions on appropriate laboratory kit). See Appendix D for further details.

5.3 Other assessments

5.3.1 Glucose measurements

Subjects will be asked to monitor blood glucose levels at the discretion of the Investigator and per local treatment guidelines, before a study visit, and for 2 weeks following a change in diabetes medication (see Table 2 and Table 3) to help in the clinical management. The exception to this is during run-in, where subjects will be asked to monitor blood glucose twice per day for 1 week before this visit. Subjects should also be advised to check their blood glucose level if they have symptoms of hypoglycaemia (hunger, dizziness, shaking, sweating etc.) or feel unwell. Any blood glucose level <3.0 mmol/L (54 mg/dL) is considered as clinically significant hypoglycaemia and should be reported by Investigators as an AE (see Section 6.3.8). Pharmacological treatments administered for hypoglycaemia, eg, dextrose/glucose tablets, glucagon etc., should be recorded. Rescue therapy will be considered for any subject with persistent hyperglycaemia. Self-monitored plasma glucose or blood glucose readings and hypoglycaemic events will be collected and reviewed by the Investigator. Subjects may be expected to be educated and knowledgeable about their actions in case of hypoglycaemia, but study personnel will offer education and contact information during visits.

5.3.2 Clinical outcome assessments

5.3.2.1 Calculation of BMI

Weight and height will be measured, in accordance with schedules provided in the Study Plan (Table 2 and Table 3). The subject's weight will be recorded in kilograms (see Section 5.1.2 for more details); height will be recorded in centimetres. Body mass index will be calculated directly in RAVE [BMI =weight / (height)^2], where weight is measured in kg, and height in metres).

5.3.2.2 Waist circumference

For waist circumference measurement, the study site personnel must ensure that:

- The subject stands and the examiner places a measuring tape in a horizontal plane around the abdomen at the level of the umbilicus
- The measuring tape is snug, but does not compress the skin, is parallel to the floor, and is not twisted

- The measurement is taken at the end of a normal respiratory expiration.
- The measurement is recorded in centimeters to the first decimal point.

Waist circumference will be measured according to the schedules presented in the Study Plan (Table 2 and Table 3).

5.3.2.3 Retinal assessment

Standardised assessments of the eyes, such as dilated fundoscopic examination/fundus photography will be collected at baseline and stored in the subject's source documentation. If the subject has underlying retinopathy, the baseline assessment will be entered also in the eCRF. According to local practice the retina assessment may be in the form of detailed dilated fundoscopic examination by a healthcare professional experienced in the procedure, or a retinal photograph. Where AEs associated with worsening of diabetic eye disease are reported, baseline assessments of diabetic eye disease will be reviewed. The time window for baseline retinal assessment is 6 months prior to administration of first dose of IP if done in accordance to local standard requirements.

5.3.3 [redacted]

5.3.3.1 [redacted]

[redacted]

[redacted]

[redacted]

5.3.3.2 [redacted]

[redacted]

5.3.3.3 [redacted]

[redacted]

[redacted]

5.3.4 [redacted]

[redacted]

5.3.5 Calculation of eGFR

The central laboratory will calculate eGFR using CKD-EPI creatinine formula (Levey et al 2009).

5.3.6 Serology

At Visit 1 samples will be collected to test for serum hepatitis B surface antigen, serum hepatitis C antibody, and serum HIV-1 and serum HIV-2 antibodies. Testing will be performed at the central laboratory.

Instructions for sample collection, processing, storage, and shipment can be found in the separate Laboratory Manual provided to the study centres.

5.4 Pharmacokinetics

5.4.1 Collection of samples

Blood samples for determination of MEDI0382 in plasma will be taken at the times presented in the Study Plan (Table 2 and Table 3).

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

5.4.2 Determination of drug concentration

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

5.4.3 Storage and destruction of pharmacokinetic samples

Pharmacokinetic samples will be disposed of after the Bioanalytical Report finalisation or 6 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 PK samples to further evaluate and validate the analytical method. Any results from such analyses may be reported separately from the CSR.

Incurred sample reproducibility analysis, if any, will be performed alongside the bioanalysis of the test samples. The results from the evaluation will not be reported in the CSR but separately in a Bioanalytical Report.

Any residual back-up PK samples may be used for future exploratory biomarker research (in this case, residual back-up PK samples will be shipped to the appropriate AstraZeneca biobank; see details in the Laboratory Manual).

5.5 Pharmacodynamics - Not Applicable

5.6 [redacted]

[redacted]

5.6.1 [redacted]

5.6.2 [redacted]

[redacted]

5.7 Biomarker analysis

Three additional blood samples will be collected according to the schedule presented in the Study Plan (Table 2 and Table 3) for potential future measurement of other analytes, if indicated upon review of the data. Biological samples for future research will be retained at

the AstraZeneca Biobank or an AstraZeneca approved storage facility for a maximum of 15 years after the blood sample collection date or according to local legislation. Samples may be destroyed prior to this timeframe if the subject has withdrawn consent.

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

[redacted]

5.7.1 Storage, re-use, and destruction of biological samples

Samples will be stored for a maximum of 15 years from the date of the last subject's last visit, after which they will be destroyed. The results of this biomarker research will be reported either in the CSR itself or as an addendum, or separately in a scientific report or publication. The results of this biomarker research may be pooled with biomarker data from other studies with the IP to generate hypotheses to be tested in future research.

5.7.2 Labelling and shipment of biological samples

The Principal Investigator ensures that samples are labelled and shipped in accordance with the Laboratory Manual and the Biological Substance, Category B Regulations (materials containing or suspected to contain infectious substances that do not meet Category A criteria); see Appendix B, IATA 6.2 Guidance Document.

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

5.7.3 Chain of custody of biological samples

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

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

The sample receiver keeps full traceability of the samples while in storage and during use until used or disposed of or until further shipment and keeps documentation of receipt of arrival.

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

Samples retained for further use are registered in the appropriate AstraZeneca biobank during the entire life cycle.

5.7.4 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 samples is an integral part of the study, then the subject is withdrawn from further study participation.

The Principal Investigator:

- Ensures subject's 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 organisation(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 organisation(s) 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.

6. SAFETY REPORTING AND MEDICAL MANAGEMENT

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

6.1 Definition of adverse events

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

The term AE is used to include both serious and nonserious AEs and can include a deterioration of a pre-existing medical occurrence. An AE may occur at any time, including run-in period, even if no study treatment has been administered, but will for the purpose of this study only be recorded from the time of first IP dose (see Section 6.3.1).

6.2 Definitions of serious adverse event

An SAE is an AE occurring during any study phase (ie, run-in, treatment, follow-up), that fulfils 1 or more of the following criteria:

- Results in death
- Is immediately life-threatening
- Requires in-patient 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 intervention to prevent one of the outcomes listed above

For further guidance on the definition of an SAE, see Appendix A.

6.3 Recording of adverse events

6.3.1 Time period for collection of adverse events

Adverse events will be collected from time of first IP dose, throughout the treatment period and including the follow-up period, final visit (4 weeks post last dose ± 3 days).

Serious AEs will be recorded from the time of signature of informed consent.

6.3.2 Follow-up of unresolved adverse events

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

6.3.3 Variables

The following variables will be collected for each AE:

- AE (verbatim)
- The date when the AE started and stopped
- Maximum intensity
- Whether the AE is serious or not

- Investigator causality rating against the IP (yes or no)
- Action taken with regard to IP
- AE caused subject's withdrawal from study (yes or no)
- Outcome

In addition, the following variables will be collected for each SAE:

- Date AE met criteria for SAE
- Date Investigator became aware of SAE
- 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
- Description of AE

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria in Section 6.2. An AE of severe intensity need not necessarily be considered serious. For example, nausea that persists for several hours may be considered severe nausea, but not an SAE unless it meets the criteria shown in Section 6.2. On the other hand, a stroke that results in only a limited degree of disability may be considered a mild stroke but would be an SAE when it satisfies the criteria shown in Section 6.2.

6.3.4 Causality collection

The Investigator will assess causal relationship between the IP and each AE, 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. 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 A to the clinical study protocol.

6.3.5 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 CRF. When AEs are reported, 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.

6.3.6 Adverse events based on examinations and tests

The results from the mandated laboratory tests and vital signs will be summarised in the CSR. Deteriorations as compared to baseline in protocol-mandated laboratory values, vital signs 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 IP.

If deterioration in a laboratory value/vital sign is associated with clinical signs and symptoms, the sign or symptom will be reported as an AE and the associated laboratory result/vital sign will be considered as additional information. Wherever possible, the reporting Investigator uses the clinical, rather than the laboratory term (eg, anaemia versus low haemoglobin 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.

6.3.7 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 TBL ≥2xULN may need to be reported as SAEs. Refer to Appendix D for further instruction on cases of increases in liver biochemistry and evaluation of Hy's Law.

6.3.8 Hypoglycaemia

Spontaneous and clinically significant hypoglycaemia has not been experienced in prior studies with MEDI0382 up to a dose of 300 µg alongside metformin treatment.

Subjects will be asked to test their blood glucose if they develop symptoms suggestive of hypoglycaemia and to record specific symptoms and glucose values in the subject's diary.

Investigators should follow local protocols for treatment and follow-up of the hypoglycaemic episode. Clinically important biochemical hypoglycaemia defined as glucose levels less than 3.0 mmol/L (54 g/dL) by the recent joint position statement of the American Diabetes Association and the European Association for the Study of Diabetes (International Hypoglycaemia Study Group 2017) should be reported as an AE, and both the AE and the hypoglycaemia eCRF pages must be completed.

Following at least two clinically significant biochemical hypoglycaemia episodes (defined as a glucose <3.0 mmol/L or <54 mg/dL) arising over a period of less than 2 weeks, down-titration of metformin or liraglutide (if relevant) may be considered by the Investigator. In the event that hypoglycaemia is seen in subjects prescribed rescue medication, the rescue medication should be down-titrated first before dose reduction of either liraglutide (where relevant) or metformin is considered. Capillary blood glucose level readings recorded a week before a visit, or 2 weeks after a change in diabetes medications may be used as an adjunct to help guide decisions on dose modification of rescue medication, liraglutide, and metformin.

If the subject is no longer receiving metformin treatment and is receiving MEDI0382 or placebo alone, IP discontinuation may be the next step and this should be discussed with the study physician.

6.3.9 Pancreatitis

Information on the clinical course of the event, treatment, and relevant diagnostic, laboratory, or other investigations will be collected on the eCRF. All SAEs of pancreatitis should be reported according to Section 6.5.

6.3.10 Pancreatic carcinoma

Information on the clinical course of the event, treatment, and relevant diagnostic, laboratory, or other investigations will be collected on the eCRF. All SAEs of pancreatic carcinoma should be reported according to Section 6.5.

6.3.11 Thyroid neoplasm

Brief information on the clinical course of the event, treatment, and relevant diagnostic, laboratory or other investigations will be collected on the eCRF. All SAEs of thyroid neoplasm should be reported according to Section 6.5.

6.3.12 Clinical events for adjudication

A number of clinical events (including CV events and deaths) will be monitored in the study population and an independent adjudication committee will review events. These clinical events will be analysed in conjunction with events observed in Phase III studies and reported elsewhere. For details see Section 6.4.

6.3.13 Injection site adverse events

Injection sites should be routinely examined at each study site visit. If any injection-site reaction meets the criteria for an AE (see Section 6.1), the event is to be reported on the AE eCRF, with the reaction described as specifically as possible.

6.3.14 Disease under study – Not Applicable

6.4 Clinical Event Adjudication

A CEA committee, blinded to the treatment of the subject, will independently adjudicate certain clinical AEs, and they will operate in accordance with the CEA Charter and Event Handling Manual for Sites and Monitors. The CEA committee will adjudicate events possibly related to the following:

1. All deaths:
   - CV death
   - Non-CV death
2. Cardiac ischaemic events:
   - MI
   - Unstable angina (UA)
3. Cerebrovascular events:
   - Stroke
   - TIA
4. Hospitalisation for heart failure and urgent heart failure visit
5. Pancreatic disease including pancreatic carcinoma
6. Thyroid neoplasm

For all clinical events identified for adjudication, the Investigator will complete the appropriate modules of the eCRF, and provide source documentation. In order to provide the independent CEA with appropriate and adequate information for adjudication of the listed events, please consult the CEA Charter and Event Handling Manual for Sites and Monitors. These clinical events will be analysed in conjunction with similar clinical events observed in Phase III studies and reported elsewhere.

6.5 Reporting of serious adverse events

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

If any SAE occurs in the course of the study, then Investigators or other site personnel inform the appropriate AstraZeneca representatives within 1 day, ie, 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 AEs 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 1 calendar day, ie, 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 WBDC system, an automated email alert is sent to the designated AstraZeneca representative.

If the WBDC 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.

The reference document for definition of expectedness/listedness is the IB for the AstraZeneca drug and the EU Summary of Product Characteristics for the active comparator product (including any AstraZeneca comparator.).

6.6 Overdose

An overdose is defined as a subject receiving a dose of IP in excess of that specified in this protocol. No specific treatment is recommended for an overdose. The Investigator will use clinical judgment to treat any overdose.

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

For overdoses associated with an SAE, the standard reporting timelines apply; see Section 6.5. For other overdoses, reporting must occur within 30 days.

6.7 Pregnancy

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

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

6.7.1 Maternal exposure

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

Pregnancy itself is not regarded as an AE unless there is a suspicion that the IP 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 1 day, ie, 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 6.5 for timeframe guidelines) and within 30 days for all other pregnancies.

The same timelines apply when outcome information is available.

The PREGREP module in the CRF is used to report the pregnancy and the PREGOUT is used to report the outcome of the pregnancy.

6.8 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 IP that either causes harm to the subject or has the potential to cause harm to the subject.

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

Medication error includes situations where an error:

- occurred

- was identified and intercepted before the subject received the drug
- did not occur, but circumstances were 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, eg, medication prepared incorrectly, even if it was not actually given to the subject
- Drug not administered as indicated, eg, wrong route or wrong site of administration
- Drug not taken as indicated eg, tablet dissolved in water when it should be taken as a solid tablet
- Drug not stored as instructed eg, kept at room temperature when it should be stored in the fridge
- Wrong subject received the medication (excluding IVRS/IWRS errors)
- Wrong drug administered to subject (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
- Subject accidentally missed drug dose(s) (eg, forgot to take medication)
- Accidental overdose (will be captured as an overdose)
- Subject failed to return unused medication or empty packaging
- Errors related to background and rescue medication, or standard of care medication in open-label studies, even if an AstraZeneca product

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

If an medication error occurs in the course of the study, then the Investigator or other site personnel informs the appropriate AstraZeneca representatives within 1 day, ie, 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 or 5 calendar days if there is an SAE associated with the medication error (Section 6.5) and within 30 days for all other medication errors.

6.9 Management of investigational product-related toxicities (Dose reductions)

6.9.1 Tolerability

If symptoms of nausea and vomiting occur, subjects should be counselled about meal size and eating habits, notably consuming small, frequent meals four to five times a day that are low in fat and contain only soluble fiber, avoiding carbonated beverages, alcohol and smoking. If symptoms do not improve, it is possible to hold metformin for 3 days. Down-titration of IP is not permitted.

6.9.2 Renal impairment

For subjects who have an eGFR of 31 to 45 mL/min (inclusive) at screening and are taking an existing dose of metformin that is higher than the recommended dose for that degree of renal impairment, the dose of metformin should be reduced at Visit 2 in accordance with local guidelines on metformin prescription in renal impairment, or to 500 mg once daily if no guidance is in place. Similarly, any subject experiencing a decline in eGFR during the study to 31 to 45 mL/min (inclusive) should have their dose of metformin reduced.

For subjects who are found to have an eGFR ≤30 mL/min, the subject should undergo a repeat level 1 week later, and if the eGFR remains ≤30 mL/min on a second consecutive test, the IP (MEDI0382, placebo, and liraglutide) should be discontinued, but the subject should remain in the study for all other study procedures until their scheduled end of study.

7. INVESTIGATIONAL PRODUCT AND OTHER TREATMENTS

7.1 Identity of investigational product(s)

Investigational product	Dosage form and strength	Manufacturer
MEDI0382	Solution for injection in 1.0 mL pre-filled syringe, 100 μg per dose, 1 dose	AstraZeneca [a]
MEDI0382	Solution for injection in 1.0 mL pre-filled syringe 200 μg per dose, 1 dose	AstraZeneca [a]
MEDI0382	Solution for injection in 1.0 mL pre-filled syringe, 300 μg per dose, 1 dose	AstraZeneca [a]
Placebo	Solution for injection in 1.0 mL pre-filled syringe, 1 dose	AstraZeneca [a]
Liraglutide (Victoza)	Solution for injection in multi-dose pre-filled pen containing 3 mL	Sourced from Novo Nordisk [a].

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

The MEDI0382 and placebo 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.

Liraglutide (6.0 mg/mL, open label) as active drug will be administered by SC injection once daily for the 14-week treatment period and a minimum 40-week extension period using a 3 mL pen-injector. Liraglutide will be repacked/relabelled by AstraZeneca as applicable according to regulatory requirements.

7.2 Dose and treatment regimens

The study consists of a screening visit (Visit 1), a run-in period of 2 weeks (Visit 2), and a baseline visit (Visit 3), followed by a 14-week randomised, double-blind placebo-controlled treatment period with open-label active comparator, and a minimum 40-week double-blind placebo-controlled treatment extension with open-label active comparator.

AstraZeneca or a designated representative will provide all IPs (MEDI0382, placebo, liraglutide). At each visit, subjects will receive sufficient quantity of drug to last the duration of time between visits. In the event the subject loses her/his IP, the study centre should call into the IVRS/IWRS system to allow the system to determine the appropriate alternative kit identification number(s) to be dispensed from the study centre's remaining inventory.

Run-in period (Visit 2)

Subjects will receive placebo to be injected daily for the 2-week placebo run-in period. A medically qualified staff member will demonstrate injection techniques, after which the patient (or designated caregiver) will administer the placebo injection. Subjects will be instructed to continue taking metformin as directed during this period.

14-week treatment period (Visits 3 to 8)

At Visit 3 subjects will be randomly assigned to 1 of the 5 treatment arms and randomised IP will be dispensed. The first day of dosing is considered Day 1. For subjects randomised to MEDI0382 or placebo. MEDI0382 will be initiated at 100 μg, and dose increments may occur in 100 μg steps every week until the predefined maintenance dose is reached. Subjects and Investigators will be advised that there may be dose increments. During the 14-week treatment period, open label liraglutide will be initiated at 0.6 mg and up titrated by an additional 0.6 mg weekly until a stable daily dose of 1.8 mg is reached. All subjects, together with the open-label liraglutide subjects inclusive, will be asked to attend all outpatient clinic visits, including weekly dosing visits, as listed in the protocol. For MEDI0382, placebo and liraglutide, the initial doses of IP will be taken at the study site. Subjects will subsequently self-administer MEDI0382 or placebo or liraglutide at home (or have it administered by a caregiver) once daily through end of treatment.

Each subject will be provided with an IFU for self-administration at home. A once-daily dose is to be self-administered by SC injection at any time of day, preferably around the same time every day, independently of meals. There is no restriction to metformin co-administration. Storage requirement for the IP kit boxes are included in the IFU.

On weeks of scheduled study visits, subjects should bring their IP with them to the study site (subjects should be given instructions and supplies as appropriate for IP transportation to ensure proper temperature control, etc.) and will self-administer MEDI0382 or placebo or liraglutide as directed by designated study-site personnel (IP manager). If a dose of MEDI0382 or placebo or liraglutide is missed, advise subjects to take it as soon as it is remembered unless it is almost time for the next dose, in which case subjects should skip the missed dose and take the medicine at the next regularly scheduled time. Advise subjects not to take 2 doses of MEDI0382 or placebo or liraglutide at the same time. Doses of MEDI0382 or placebo are to be administered by SC injection in the abdomen, and doses of liraglutide are to be administered by SC injection in the abdomen, thigh, or upper arm. The site of injection should be rotated within or across regions on a regular basis so that the same site is not used repeatedly.

If deemed necessary by the Investigator, IP can be stopped temporarily for up to 3 days once during the 14-week treatment period and then re-started. In case there is a need to stop IP for a different time period, a discussion with the study physician should take place. Situations will be handled on a case by case basis and all decisions will be documented in the patient's study file.

Minimum 40-week treatment extension period (Visits 9 to Visit 19, EoT)

Investigational product will be dispensed every 4 weeks (±3 days) during this period. Each subject will be provided with an IFU for self-administration at home. A once-daily dose is to be self-administered by SC injection at any time of day, preferably around the same time every day, independently of meals. There is no restriction to metformin co-administration. Storage requirement for the IP kit boxes are included in the IFU.

On weeks of scheduled study visits, subjects should bring their IP with them to the study site (subjects should be given instructions and supplies as appropriate for IP transportation to ensure proper temperature control, etc.) and will self-administer MEDI0382 or placebo or liraglutide as directed by designate study-site personnel (IP manager). If a dose of MEDI0382 or placebo or liraglutide is missed, advise subjects to take it as soon as it is remembered unless it is almost time for the next dose, in which case subjects should skip the missed dose and take the medicine at the next regularly scheduled time.

If deemed necessary by the Investigator, IP can be stopped temporarily for up to 7 days and no more than 2 times during the minimum 40-week treatment period and then re-started. In case there is a need to stop IP for a different time period, a discussion with the study physician

should take place. Situations will be handled on a case by case basis and all decisions will be documented in the patient's study file.

Any defects with the IP must be reported immediately to the Site Monitor and delegated to IP management by the IP manager/pharmacist to initiate the product complaint process according to applicable guidelines.

7.3 Labelling

Labelling of the IP (including packaging and assembly) will be carried out by AstraZeneca or designee in accordance with Annex 13 and current Good Manufacturing Practice and regulatory requirements of each country participating in the study. The labels will be translated into local languages where applicable and required by local regulations.

7.4 Storage

All IP should be kept in a secure place under appropriate storage conditions. The IP label on the IP kit specifies the appropriate storage.

7.5 Compliance

The distribution of IP for self-administration should be recorded in the appropriate sections of the eCRF.

7.6 Accountability

The IP provided for this study will be used only as directed in the Clinical Study Protocol.

The designated IP Manager (pharmacist/ study nurse) is required to maintain accurate IP accountability records and will account for all IP dispensed to and returned from the subject.

Study site staff, if applicable, or the Site Monitor delegated to IP management will account for all IP received at the site, unused IP, and for appropriate destruction in accordance to local procedures. Certificates of delivery and destruction should be signed.

In the case of a malfunctioning pre-filled syringe, the designated IP Manager (pharmacist/ study nurse) should contact the Site Monitor delegated to IP management to initiate a product complaint process according to applicable guidelines.

7.7 Concomitant medication and other treatments

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

7.7.1 Permitted concomitant medications

Investigators may prescribe concomitant medications or treatments deemed necessary to provide adequate supportive care except for those medications described in Section 7.7.2. Specifically, subjects should continue to take their metformin therapy at their regular dose prescribed, and any other medication prescribed for the treatment of comorbidities associated with T2DM. Use of another glucose-lowering medication for up to 2 weeks in the 2 months prior to screening is acceptable (a GLP-1 receptor agonist containing preparation cannot be used within the last 30 days or 5 half-lives of the drug, whichever is longer, at the time of screening). A stable regimen of antihypertensive agents for a minimum of 2 months prior to screening is permitted. Similarly, a stable treatment regimen of thyroid replacement therapy for a minimum of 2 months prior to screening is permitted. Subjects should receive full supportive care during the study in accordance with their institutional guidelines. If nausea or vomiting occurs, 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 anti-emetic therapy in accordance with institutional and local practice guidelines as long as medications that are prokinetic agents such as domperidone or metoclopramide are avoided. Hormone replacement therapy and agents for benign prostatic hyperplasia are also permitted.

7.7.2 Prohibited concomitant medications

Other than the medications described above, use of the following medications is restricted, generally speaking, from the time specified in the entry criteria until after the final follow-up visit:

- Concurrent or prior use of any herbal preparations or dietary supplements marketed for control of body weight or appetite within 1 week prior to the start of screening
- Concurrent or previous use of drugs approved for weight loss (eg, orlistat, bupropion -naltrexone, phentermine-topiramate, phentermine, lorcaserin), as well as those drugs used off-label, within the last 30 days or 5 half-lives of the drug, whichever is longest, prior to the start of screening
- Antidepressant agents must either not be started or must be on a stable dose for a minimum of 2 months prior to screening.
- Systemic corticosteroids by oral, intravenous, intra-articular, or intramuscular route are prohibited within 3 months prior to screening and during the study unless prescribed for a very brief period of less than 7 days.

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

7.7.3 Rescue therapy for hyperglycaemia

Rescue therapy with add-on insulin is the preferred option, but additional drug classes are permitted. Rescue therapy with any GLP-1 receptor agonist or DPP4 inhibitor based intervention is prohibited. For details of permitted and prohibited rescue therapies, see Table 6.

Table 6 Permitted and prohibited rescue therapies

Permitted rescue therapies	Prohibited rescue therapies
Any type of insulin	GLP-1 receptor agonist
Sulphonylurea	DPP4 inhibitor
Glinide	GLP-1 receptor agonist/ insulin combination eg iDegLira
Acarbose	SGLT2 inhibitor
Increased dose of metformin	Pramlintide
	Thiazolidinediones

DPP4 dipeptidyl peptidase-4; GLP-1 glucagon-like peptide-1; SGLT2 sodium-glucose co-transporter 2

7.7.4 Other concomitant treatment

Medication other than that described above, which is considered necessary for the subject's safety and well-being, may be given at the discretion of the Investigator and recorded in the appropriate sections of the eCRF.

7.7.4.1 Anti-hypertensive drug dose reduction

During a study visit existing anti-hypertensive drug medication may be decreased if in the Investigator's judgment the subject has symptomatic hypotension or has documented orthostatic hypotension (see Section 5.2.4.2). Such a dose reduction does not reflect rescue or a rescue visit. Investigators can alter anti-hypertensive medication if in the subject's best interest for example in case of renal impairment or angina. Changes in anti-hypertensive drugs must be recorded in the appropriate section of the eCRF.

7.8 Post study access to study treatment – Not Applicable

8. STATISTICAL ANALYSES BY ASTRAZENECA

8.1 Statistical considerations

The following analyses are planned for this study:

- A primary analysis when all subjects reach 14 weeks treatment

- An analysis when all subjects reach 26 weeks treatment
- A final analysis at the end of the study.

All personnel involved with the conduct of the study will remain blinded until database lock. For the purpose of the primary and the 26-week analysis, any study team members who serve in the unblinded analysis group will stop day-to-day work on the study and other pre-selected personnel will take over these roles for the remainder of the trial.

Analyses will be performed by AstraZeneca or its representatives. More details will be provided in the statistical analysis plan (SAP).

8.2 [redacted]

[redacted]

8.3 Definitions of analysis sets

8.3.1 Efficacy analysis set

The Intent-to-treat (ITT) population includes all subjects who receive at least one dose of any IP and will be analysed according to their randomised treatment group. The analysis will include the post IP-discontinuation data and post rescue data for those subjects who discontinue from study treatments or are rescued, but are still followed up for their scheduled visits.

8.3.2 Safety analysis set

The As-treated population includes all subjects who receive at least one dose of any study IP and will be analysed according to the treatment they actually receive. Safety analyses will be based on this population.

8.3.3 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.

8.3.4 Other analysis sets

8.3.4.1 Per Protocol analysis set

The Per Protocol (PP) analysis set includes only treatment completers and excludes those with important protocol violation(s). Important protocol violations are those that have the potential to affect the result of the primary analysis. Detailed exclusion criteria for the PP population will be specified in the SAP. Subjects excluded from the PP analysis will be identified before the final database lock.

8.4 Outcome measures for analyses

8.4.1 Primary efficacy endpoint

The primary efficacy endpoints are the change in HbA1c and percent change in body weight from baseline to Week 14.

8.4.2 Secondary efficacy endpoints

The secondary efficacy endpoints are:

- Change in HbA1c from baseline to 26 weeks, and 54 weeks
- Percentage of subjects achieving an HbA1c target of <7.0% after 14 weeks, 26 weeks, and 54 weeks
- Percent and absolute change in body weight from baseline to 14 weeks, 26 weeks, and 54 weeks
- Percentage of subjects achieving weight loss of ≥5% and ≥10% after 14 weeks, 26 weeks, and 54 weeks

8.5 Methods for statistical analyses

In general, data will be provided in listings and tabular summaries. Categorical data will be summarised by the number and percentage of subjects in each category. Continuous variables will be summarised by descriptive statistics, including mean, standard deviation, median, minimum, and maximum. Baseline values will be defined as the last assessment prior to the first administration of IP. Additional details will be described in the SAP.

8.5.1 Analysis of primary variable (s)

The co-primary efficacy endpoints of HbA1c change and weight change from baseline to 14 weeks will be compared between MEDI0382 and placebo arms. For these endpoints, an analysis of covariance (ANCOVA) model with last-observation-carried-forward (LOCF) approach to handle missing data will be used and adjusted for treatment and measurement at baseline. For weight loss, the strata of screening HbA1c (≤8% or >8%) will be added into the model as a covariate. Analyses will be based on the ITT population, which includes all randomised subjects who received at least one dose of IP. The analysis will include the post

IP-discontinuation data and post rescue data for those subjects who discontinue from study treatments or are rescued, but are still followed up for their scheduled visits.

8.5.2 Analysis of secondary variable(s)

8.5.2.1 Efficacy

Secondary efficacy endpoints of body weight and HbA1c change at 26 weeks, and 54 weeks will be analysed by ANCOVA model with LOCF, including fixed effect and covariates of treatment, baseline measurement, strata of screening HbA1c (≤8% or >8%; except for HbA1c related analyses). For the secondary proportion-related endpoints, a logistic regression model will be used with similar fixed effect and covariates. These analyses will be performed for the ITT population.

8.5.2.2 Safety

Adverse events and SAEs will be coded by the most updated version of the Medical Dictionary for Regulatory Activities (MedDRA), and the type, incidence, severity and relationship to study IP will be summarised by MedDRA System Organ Class and Preferred Term and by treatment. Adverse events leading to discontinuation, AEs leading to death, and deaths will also be summarised. Specific AEs will be counted once for each subject for calculating percentages. In addition, if the same AE occurs multiple times within a particular subject, the highest severity and level of relationship observed will be reported. Subject-level data listings of all AEs will be presented.

Other safety data, such as vital signs, clinical laboratory data, ECG, and physical examination findings will be descriptively summarised at each time point by treatment.

8.5.2.3 Pharmacokinetics and immunogenicity

Individual MEDI0382 plasma concentrations will be summarised by treatment and visit. MEDI0382 plasma concentration at trough (C_{min}) 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 treatment. If possible, the incidence of ADA positivity will be correlated with the observed PK.

8.5.3 Subgroup analysis

For body weight and HbA1c related primary and secondary endpoints, subgroup summary or analysis by whether a subject received rescue therapy will be performed. Full details of any subgroup analysis will be pre-specified in the SAP.

8.5.4 Interim analysis – Not Applicable

8.5.5 Sensitivity analysis

For the primary endpoints, three sensitivity analyses will be performed. First, an ANCOVA analysis that only contains data before subjects discontinue study treatments and before subjects receive rescue therapy will be performed. Second, an ANCOVA analysis based on PP population will be done. Third, a multiple imputation based ANCOVA model will be done. Missing endpoints will be imputed based on only those subjects who discontinued study IP but still remain in the study and have endpoint measures. If there are not sufficient numbers of such subjects, then the missing endpoints will be imputed based on all available endpoint measures from the placebo group. Full details of any sensitivity analysis will be pre-specified in the SAP.

8.5.6 [redacted]

[redacted]

9. STUDY AND DATA MANAGEMENT BY ASTRAZENECA

9.1 Training of study site staff

Before the first subject is entered into the study, an AstraZeneca representative will review and discuss the requirements of the Clinical Study Protocol and related documents with the investigational staff and also train them in any study-specific procedures (including IP administration), and the WBDC, IVRS/IWRS, PROs, and other systems to be utilised.

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

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

9.2 Monitoring of the study

During the study, an AstraZeneca representative will have regular contacts with the study site, including visits to:

- Provide information and support to the Investigator(s).
- Confirm that facilities remain acceptable.
- Confirm that the investigational team is adhering to the Clinical Study Protocol, that data are being accurately and timely recorded in the eCRFs that biological samples are handled in accordance with the Laboratory Manual, and that IP accountability checks are being performed.

- Perform source data verification (a comparison of the data in the eCRFs with the subject's medical records at the hospital or practice, and other records relevant to the study) including verification of informed consent of participating subjects. This will require direct access to all original records for each subject (eg, clinic charts).

- Ensure withdrawal of informed consent to the use of the subject's biological samples is reported and biological samples are identified and disposed of/destroyed accordingly, and the action is documented, and reported to the subject.

The AstraZeneca representative will be available between visits if the Investigator(s) or other staff at the centre need information and advice about the study conduct.

9.2.1 Source data

Refer to the CSA for location of source data.

9.2.2 Study agreements

The Principal Investigator at each centre should comply with all the terms, conditions, and obligations of the CSA, or equivalent, for this study. In the event of any inconsistency between this Clinical Study Protocol and the CSA, the terms of the Clinical Study Protocol shall prevail with respect to the conduct of the study and the treatment of subjects and in all other respects, not relating to study conduct or treatment of subjects, the terms of the CSA shall prevail.

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

9.2.3 Archiving of study documents

The Investigator follows the principles outlined in the CSA.

9.3 Study timetable and end of study

The end of the study is defined as 'the last visit of the last subject undergoing the study'.

The study may be terminated at individual centres if the study procedures are not being performed according to Good Clinical Practice (GCP), or if recruitment is slow. AstraZeneca may also terminate the entire study prematurely if concerns for safety arise within this study or in any other study with MEDI0382.

9.4 Data management by AstraZeneca

Data management will be performed by AstraZeneca Data Management Centre staff according to the Data Management Plan (DMP).

The data collected through third-party sources will be obtained and reconciled against study data. Adverse events and medical/surgical history will be classified according to the terminology of the latest version the MedDRA. Medications will be classified according to

the WHODrug™ Dictionaries. Classification coding will be performed by the Medical Coding Team at the AstraZeneca Data Management Centre.

Data queries will be raised for inconsistent, impossible, or missing data. All entries to the study database will be available in an audit trail.

The data will be validated as defined in the DMP. Quality control procedures will be applied to each stage of data handling to ensure that all data are reliable and have been processed correctly. The DMP will also clarify the roles and responsibilities of the various functions and personnel involved in the data management process. When all data have been coded, validated, signed and locked, clean file will be declared. Any treatment revealing data may thereafter be added and the final database will be locked.

Serious adverse event reconciliation

Serious AE reconciliation reports are produced and reconciled with the Patient Safety database and/or the investigational site.

Data associated with human biological samples

Data associated with biological samples will be transferred from laboratory(ies) internal or external to AstraZeneca.

10. ETHICAL AND REGULATORY REQUIREMENTS

10.1 Ethical conduct of the study

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with ICH/GCP, applicable regulatory requirements, and the AstraZeneca policy on Bioethics and Human Biological Samples.

10.2 Subject data protection

The ICF will incorporate (or, in some cases, be accompanied by a separate document incorporating) wording that complies with relevant data protection and privacy legislation.

10.3 Ethics and regulatory review

An Ethics Committee should approve the final Clinical Study Protocol, including the final version of the ICF and any other written information and/or materials to be provided to the subjects. The Investigator will ensure the distribution of these documents to the applicable Ethics Committee and to the study site staff.

The opinion of the Ethics Committee should be given in writing. The Investigator should submit the written approval to AstraZeneca before enrolment of any subject into the study.

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

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

If required by local regulations, the Clinical Study Protocol should be re-approved by the Ethics Committee annually.

Before enrolment of any subject into the study, the final Clinical Study Protocol is approved by the national regulatory authority or a notification to the national regulatory authority is done, according to local regulations.

AstraZeneca will handle the distribution of any of these documents to the national regulatory authorities.

AstraZeneca will provide regulatory authorities, Ethics Committees, and Principal Investigators with safety updates/reports according to local requirements.

Each Principal Investigator is responsible for providing the Ethics Committees/Institutional Review Board (IRB) with reports of any serious and unexpected adverse drug reactions from any other study conducted with the IP. AstraZeneca will provide this information to the Principal Investigator so that he/she can meet these reporting requirements.

10.4 Informed consent

The Principal Investigator(s) at each centre will:

- Ensure each subject is given full and adequate oral and written information about the nature, purpose, possible risk, and benefit of the study.
- Ensure each subject is notified that he/she is free to discontinue from the study at any time.
- Ensure that each subject is given the opportunity to ask questions and allowed time to consider the information provided.
- Ensure each subject provides signed and dated informed consent before conducting any procedure specifically for the study.
- Ensure the original, signed (ICF[s]) is/are stored in the Investigator's Study File.
- Ensure a copy of the signed ICF is given to the subject.
- Ensure that any incentives for subjects who participate in the study as well as any provisions for subjects harmed as a consequence of study participation are described in the ICF that is approved by an Ethics Committee.

10.5 Changes to the Clinical Study Protocol and Informed Consent Form

Study procedures will not be changed without the mutual agreement of the International co-ordinating Investigator(s) and AstraZeneca.

If there are any substantial changes to the Clinical Study Protocol, then these changes will be documented in the study protocol amendment and where required in a new version of the study protocol (Revised CSP).

The protocol amendment and/or a new version of the Clinical Study Protocol (Revised CSP) is to be approved by the relevant Ethics Committee and if applicable, also the national regulatory authority approval, before implementation. Local requirements are to be followed for new versions of Clinical Study Protocols.

AstraZeneca will distribute any subsequent amendments and/ or new versions of the Clinical Study Protocol (Revised CSP) to each Principal Investigator(s). For distribution to Ethics Committee, see Section 10.3.

If a change to a Clinical Study Protocol requires a change to a centre's ICF, AstraZeneca and the centre's Ethics Committee are to approve the revised ICF before the revised form is used.

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

10.6 Audits and inspections

Authorised representatives of AstraZeneca, a regulatory authority, or an Ethics Committee may perform audits or inspections at the centre, including source data verification. The purpose of an audit or inspection is to systematically and independently examine all study-related activities and documents, to determine whether these activities were conducted, and data were recorded, analysed, and accurately reported according to the Clinical Study Protocol, GCP, guidelines of the ICH, and any applicable regulatory requirements. The Investigator will contact AstraZeneca immediately if contacted by a regulatory agency about an inspection at the centre.

11. LIST OF REFERENCES

American Diabetes Association 2017
American Diabetes Association. Standards of Medical Care in Diabetes – 2017: Summary of Revisions. Diabetes Care. 2017;40 Suppl 1:S4-S5.

Astrup et al 2012
Astrup A, Carraro R, Finer N, Harper A, Kunesova M, Lean MEJ, et al. Safety, tolerability and sustained weight loss over 2 years with the once-daily human GLP-1 analog, liraglutide. Int J Obes. 2012;36:843-54.

[redacted]

CDC 2004
Centers for Disease Control and Prevention (CDC): Prevalence of overweight and obesity among adults with diagnosed diabetes-United States, 1988-1994 and 1999-2002. MMWR Morb Mortal Wkly Rep. 2004;53:1066-8.

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

CDER Victoza 2009
Center for Drug Evaluation and Research. Victoza Pharmacology Review. In: USFDA, editor. 2009.

Cegla et al 2014
Cegla J, Troke RC, Jones B, Tharakan G, Kenkre J, McCullough KA, et al. Coinfusion of low-dose GLP-1 and glucagon in man results in a reduction in food intake. Diabetes 2014; 63(11):3711-20.

CHMP 2012
European Medicines Agency (EMA) Committee for Medicinal Products for Human Use (CHMP). Guideline on clinical investigation of medicinal products in the treatment or prevention of diabetes mellitus. CPMP/EWP/1080/00 Rev. 1. Available at:http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2012/06/WC500129256.pdf. Published 14 May 2012.

Davies et al 2015
Davies MJ, Bergenstal R, Bode B, Kushner RF, Lewin A, Vang Skjøth T, et al. Efficacy of Liraglutide for Weight Loss Among Patients With Type 2 Diabetes. The SCALE Diabetes Randomized Clinical Trial. JAMA. 2015;314(7):687-99.

Dworkin et al 2008
Dworkin RH, Turk DC, Wyrwich KW, Beaton D, Cleeland CS, Farrar JT, et al. Interpreting the Clinical Importance of Treatment Outcomes in Chronic Pain Clinical Trials: IMMPACT Recommendations. J Pain. 2008;9(2):105-21.

FDA 2008
Food and Drug Administration (FDA) Center for Drug Evaluation and Research (CDER). Guidance for Industry: Diabetes Mellitus: Developing Drugs and Therapeutic Biologics for Treatment and Prevention. Available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm071624.pdf. Published 13 February 2008.

Garber et al 2009
Garber A, Henry R, Ratner R, Garcia-Hernandez PA, Rodriguez-Pattzi H, Olvera-Alvarez I, et al. Liraglutide versus glimepiride monotherapy for type 2 diabetes (LEAD-3 Mono): a randomised, 52-week, phase III, double-blind, parallel-treatment trial. Lancet. 2009;373(9662):473-81.

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

Henderson et al 2016
Henderson SJ, Konkar A, Hornigold DC, Trevaskis JL, Jackson R, Fritsch Fredin M, et al. Robust anti-obesity and metabolic effects of a dual GLP-1/glucagon receptor peptide agonist in rodents and non-human primates. Diabetes Obes Metab. 2016;18(12):1176-90.

International Hypoglycaemia Study Group 2017
Glucose Concentrations of Less Than 3.0 mmol/L (54 mg/dL) Should Be Reported in Clinical Trials: A Joint Position Statement of the American Diabetes Association and the European Association for the Study of Diabetes. Diabetes Care 2017;40:155–7.

Japan PMDA 2009
Japanese Pharmaceuticals and Medical Devices Agency. Review Report (1) for Victoza subcutaneous injection 18 mg. Available at http://www.pmda.go.jp/english/service/pdf/drugs/victoza_jan2010_e.pdf2009

Levey et al 2009
Levey AS, Stevens LA, Schmid CH, Zhang YL, Castro AF 3rd, Feldman HI, Kusek JW, Eggers P, Van Lente F, Greene T, Coresh J; CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration). A new equation to estimate glomerular filtration rate. Ann Intern Med. 2009; 150(9):604-12.

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

Nauck et al 2009
Nauck M, Frid A, Hermansen K, Shah NS, Tankova T, Mitha IH, Zdravkovic M, During M, Matthews DR. Efficacy and Safety Comparison of Liraglutide,Glimepiride, and Placebo, All in Combination With Metformin, in Type 2 Diabetes. Diabetes Care. 2009;32(1):84–90.

NHLBI 1998
National Heart, Lung, and Blood Institute (NHLBI) Clinical Guidelines on the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults. NIH publication No. 98-

4083. Available at: http://www.nhlbi.nih.gov/guidelines/obesity/ob_home.htm. Published September 1998.

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

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

Appendix A Additional Safety Information

Further Guidance on the Definition of a Serious Adverse Event

Life threatening

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

Hospitalisation

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

Important medical event or medical intervention

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

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

- 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 (eg, neutropenia or anaemia requiring blood transfusion, etc.) or convulsions that do not result in hospitalization
- Development of drug dependency or drug abuse

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 recognised 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.

Appendix B International Airline Transportation Association 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 eg, 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 eg, 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 UN 3373 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 C

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

1. Introduction

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

Specific guidance on managing liver abnormalities can be found in Section 5.2.5.1 of the Clinical Study Protocol (CSP).

During the course of the study the Investigator will remain vigilant for increases in liver biochemistry. The Investigator is responsible for determining whether a subject meets PHL criteria at any point during the study.

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

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

The Investigator participates, together with AstraZeneca clinical project representatives, in review and assessment of cases meeting PHL criteria to agree whether 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 (IMP).

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

2. Definitions

Potential Hy's Law

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

Hy's Law

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

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

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 ≥ 3xULN
- AST ≥ 3xULN
- TBL ≥ 2xULN

Central laboratories being used

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

The Investigator will also remain vigilant for any local laboratory reports where the PHL 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 without delay.
- Complete the appropriate unscheduled laboratory Case Report Form (CRF) 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 Section 2 Definitions within this Appendix for definition) by reviewing laboratory reports from all previous visits (including both central and local laboratory results)

4. Follow-up

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 CSP.

4.2 Potential Hy's Law Criteria met

If the subject does meet PHL criteria, the Investigator will:

- Notify the AstraZeneca representative, who will then inform the central Study Team.
- Within 1 day of PHL criteria being met, the Investigator will report the case as an SAE of potential Hy's Law; serious criteria 'Important medical event' and causality assessment 'yes/related' according to CSP process for SAE reporting.
- For subjects that met PHL criteria prior to starting IMP, the investigator is not required to submit a PHL SAE unless there is a significant change in the subject's condition.
- The Study Physician contacts the Investigator to provide guidance and discuss and agree an approach for the study subjects' follow-up (including any further laboratory testing) and the continuous review of data.
    - Subsequent to this contact, the Investigator will:
        - Monitor the subject until liver biochemistry parameters and appropriate clinical symptoms and signs return to normal or baseline levels, or as long as medically indicated. Completes follow-up SAE form as required.
        - Investigate the aetiology of the event and perform diagnostic investigations as discussed with the Study Physician. This includes deciding which the tests available in the HL lab kit should be used.
        - Complete the 3 Liver CRF Modules as information becomes available.

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.

As soon as possible 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 IMP, to ensure timely analysis and reporting to health authorities within 15 calendar days form the date PHL criteria were met. 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.

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

- If the alternative explanation is **not** an AE, record the alternative explanation on the appropriate CRF.

- If the alternative explanation is an AE/SAE: update the previously submitted PHL SAE and AE CRFs accordingly, with the new information (reassessing event term; causality and seriousness criteria) following the 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 IMP:

- Send updated 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 15 calendar days, 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:

- Provides any further update to the previously submitted SAE of Potential Hy's Law, (report term now 'Hy's Law case') ensuring causality assessment is related to IMP and seriousness criteria is medically important, according to CSP process for SAE reporting.

- Continue follow-up and review according to agreed plan. Once the necessary supplementary information is obtained, repeat the review and assessment to determine whether HL criteria are met. Update the previously submitted PHL SAE report following CSP process for SAE reporting, according to the outcome of the review and amending the reported term if an alternative explanation for the liver biochemistry elevations is determined.

6. Laboratory Tests

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

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

Hy's Law lab kit for central laboratories	
Additional standard chemistry and coagulation tests	GGT LDH Prothrombin time INR
Viral hepatitis	IgM anti-HAV IgM and IgG anti-HBc HBsAg HBV DNA IgM and IgG anti-HCV HCV RNA IgM anti-HEV HEV RNA
Other viral infections	IgM & IgG anti-CMV IgM & IgG anti-HSV IgM & IgG anti-EBV
Alcoholic hepatitis	Carbohydrate deficient transferrin (CD-transferrin)
Autoimmune hepatitis	Antinuclear antibody (ANA) Anti-Liver/Kidney Microsomal Ab (Anti-LKM) Anti-Smooth Muscle Ab (ASMA)
Metabolic diseases	alpha-1-antitrypsin Ceruloplasmin Iron Ferritin Transferrin Transferrin saturation

References

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

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

Appendix E [redacted]

Appendix F [redacted]

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Clinical Study Protocol Appendix E

Drug Substance	Medi0382
Study Code:	D5670C00004

CSP Appendix E

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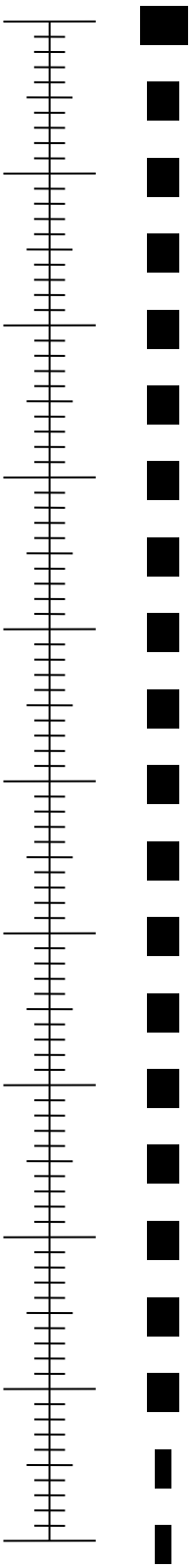

Clinical Study Protocol Appendix F

Drug Substance	MEDI382
Study Code:	D5670C00004

CSP Appendix F

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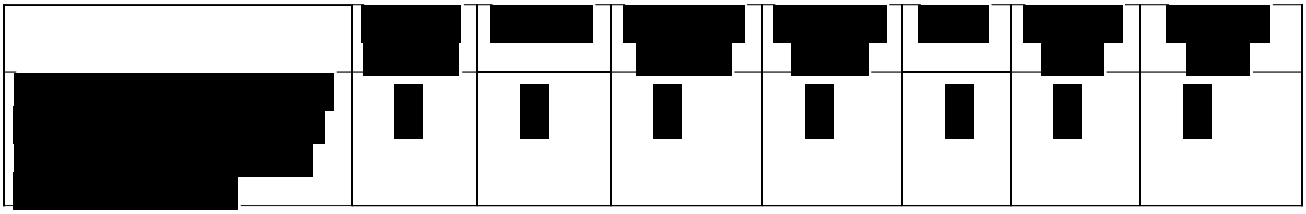

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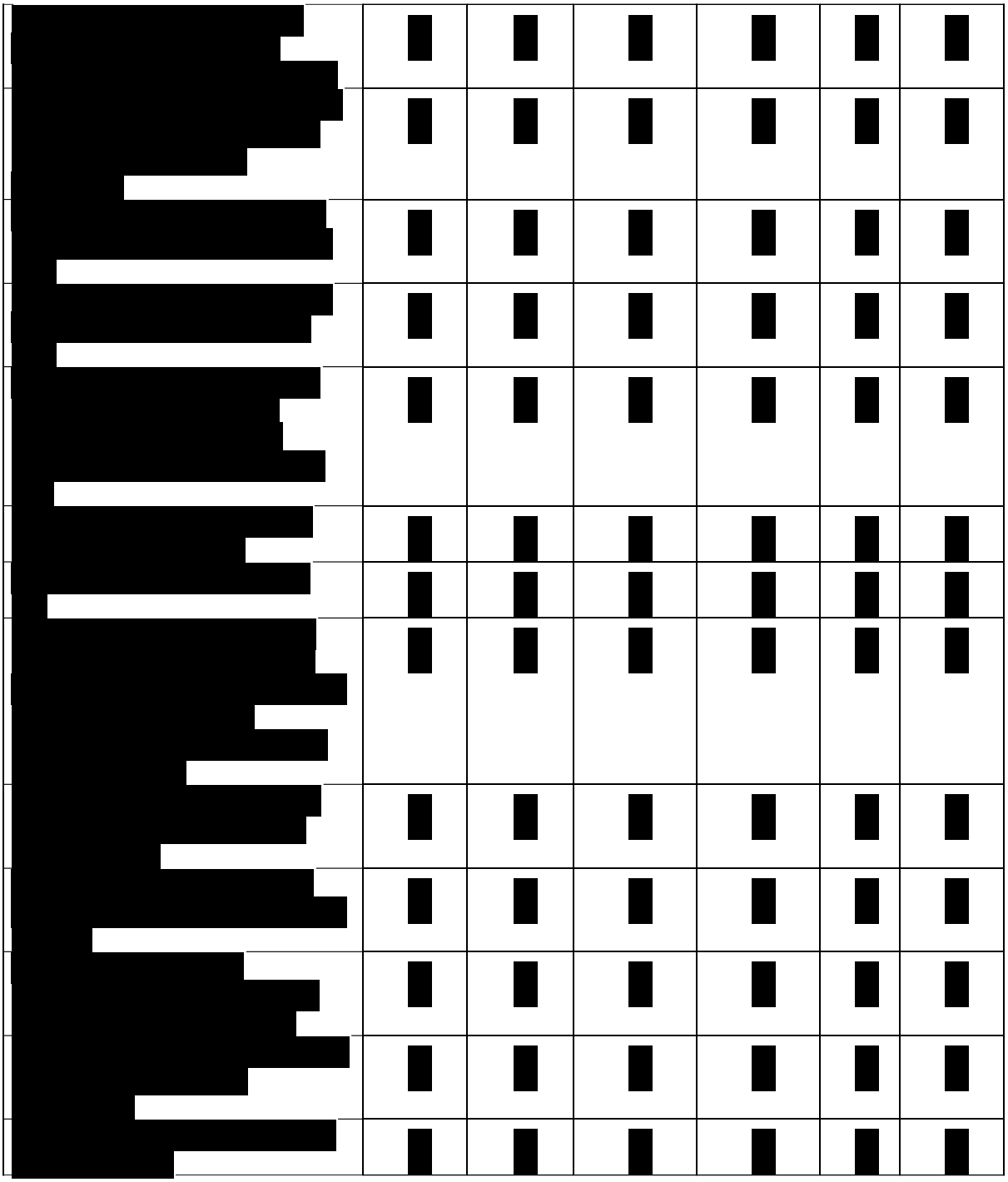

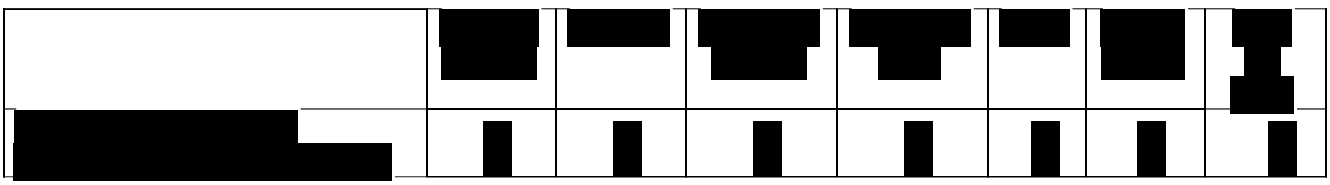

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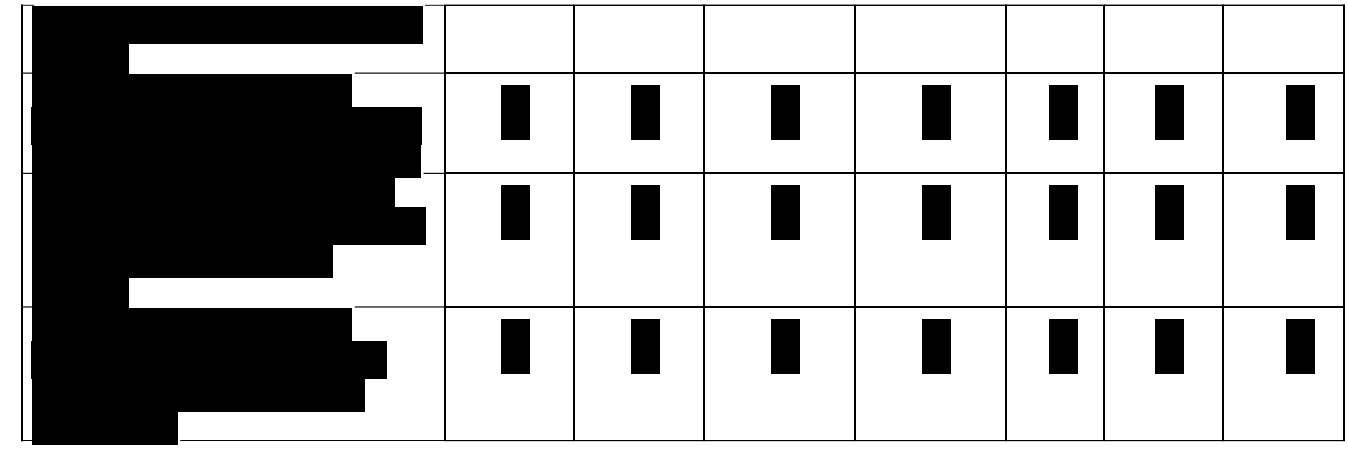

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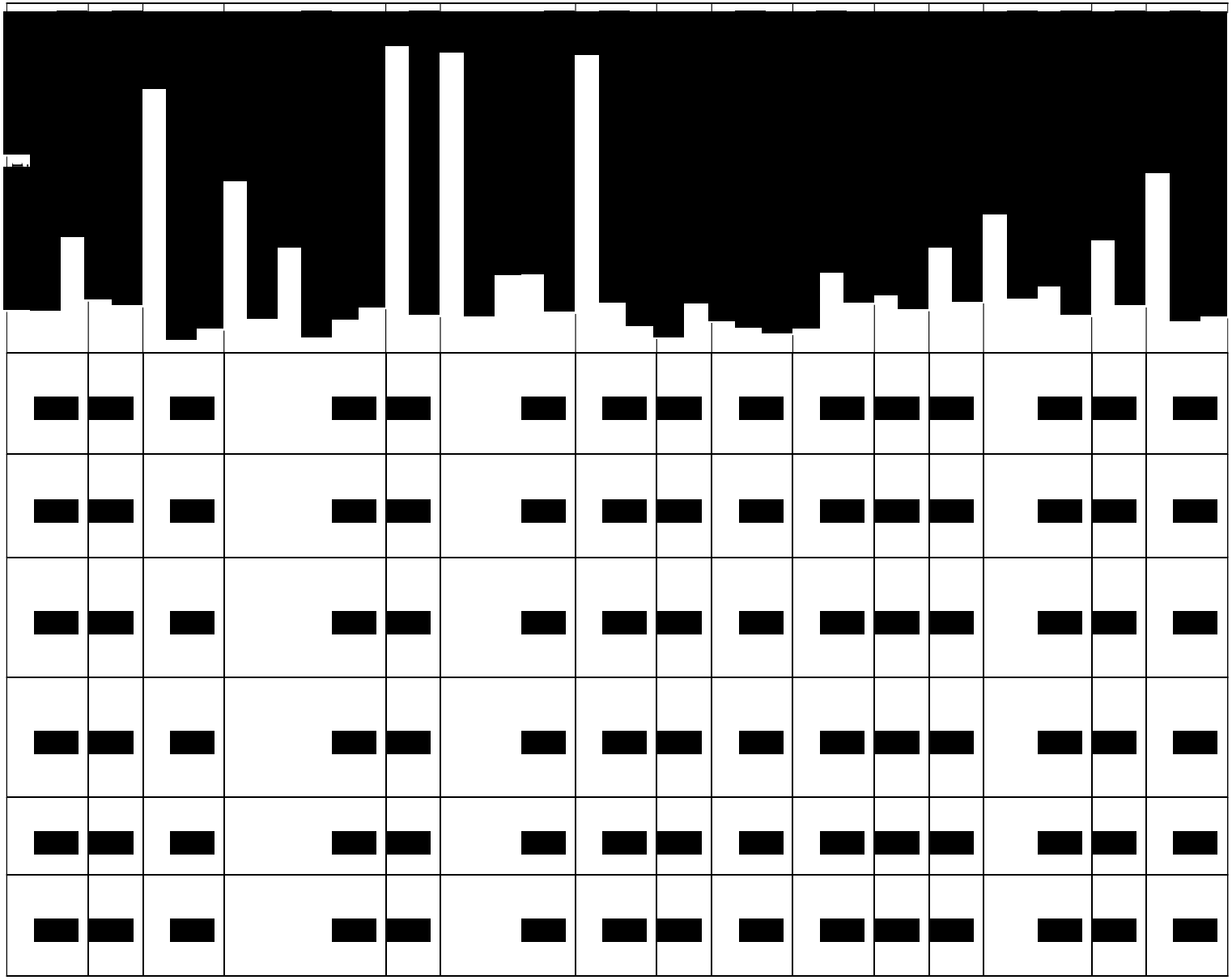

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Clinical Study Protocol Appendix G

Drug Substance Medi0382

Study Code D5670C00004

CSP Appendix G

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