Clinical Study Protocol

Drug Substance	AZD1656
Study Code	D1020C00016
Edition Number	1

A 4-month treatment, Randomized, Double-blind, Placebo-Controlled, Multi-centre, Parallel-Group Phase 2 study to Evaluate Efficacy, Safety and Tolerability of Different Dosing Regimens of AZD1656 as Monotherapy in Japanese Type 2 Diabetes Mellitus Patients

Sponsor:

AstraZeneca K.K., 1-88, 1-chome, Ohyodo-naka, Kita-ku, Osaka 531-0076, Japan

The following Amendment(s) and Administrative Changes have been made to this protocol since the date of preparation:

Amendment No.	Date of Amendment	Local Amendment No:	Date of Local Amendment

Administrative Change No.	Date of Administrative Change	Local Administrative Change No.	Date of Local Administrative Change

PROTOCOL SYNOPSIS

A 4-month treatment, Randomized, Double-blind, Placebo-Controlled, Multi-centre, Parallel-Group Phase 2 study to Evaluate Efficacy, Safety and Tolerability of Different Dosing Regimens of AZD1656 as Monotherapy in Japanese Type 2 Diabetes Mellitus Patients

Principal Investigator

The names of the investigators are described in Supplement A, "Investigators and Study Administrative Structure".

Study centre(s) and number of subjects planned

Study Centres: Approximately 6 centres are planned for participation

Number of Subjects: 220 randomised Japanese subjects

Study period		Phase of development
Estimated date of first subject enrolled	May 2010	Phase 2
Estimated date of last subject completed	June 2011	

Objectives

Primary objective

- To compare the effect on glucose control of 3 different AZD1656 dosing regimens with placebo in Japanese type 2 diabetes mellitus (T2DM) patients, as evaluated by the change in HbA1c from baseline to the end of treatment at 4 months.

Secondary objectives

- To investigate the safety and tolerability of AZD1656 compared to placebo by assessments of adverse events (AE) occurring during the study (including hypoglycaemic events), blood pressure (BP), pulse, physical examination, body weight, waist circumference, safety laboratory variables (including plasma glucose) and electrocardiogram (ECG)

- To characterise the population pharmacokinetic (PK) and pharmacodynamic (PD) properties of AZD1656 in Japanese T2DM patients by utilisation of non-linear mixed effects modelling methodology

- To evaluate other variables of glucose control (fasting plasma glucose [FPG], insulin, C-peptide and number of responders in terms of HbA1c ≤ 7% and ≤ 6.5%, respectively) after 4 months in Japanese T2DM patients receiving AZD1656 compared to placebo

- To evaluate other cardiovascular (CV) risk factors, such as total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, triglycerides and high-sensitivity C-reactive protein (hs-CRP), after 4 months in Japanese T2DM patients receiving AZD1656 compared to placebo

Study design

4-month treatment, randomized, double-blind, placebo-controlled, multi-centre, parallel-group phase II study

Target subject population

Japanese T2DM patients (naïve or treated with one or two oral anti-diabetic drugs (OAD) but not adequately controlled)

Investigational product, dosage and mode of administration

Two tablets AZD1656 orally in the morning just before breakfast and two tablets AZD1656 in the evening just before dinner, i.e. four tablets per day in total.

10 mg dose :	AZD1656 5 mg 1 tablet + AZD1656 placebo 1 tablet, twice daily
20 mg dose :	AZD1656 5 mg 2 tablets, twice daily
40 mg dose :	AZD1656 20 mg 1 tablet + AZD1656 placebo 1 tablet, twice daily
80 mg dose :	AZD1656 20 mg 2 tablets, twice daily
140 mg dose :	AZD1656 20 mg 1 tablet + AZD1656 50 mg 1 tablet, twice daily
200 mg dose :	AZD1656 50 mg 2 tablets, twice daily

Comparator, dosage and mode of administration

Two tablets AZD1656 placebo orally in the morning just before breakfast and two tablets AZD1656 placebo in the evening just before dinner, i.e. four tablets per day in total.

Placebo dose :	AZD1656 Placebo 2 tablets, twice daily

Duration of treatment

This study consists of a 2-week single-blind placebo run-in period, a 4-month double-blinded treatment period and a 2-week follow-up period. Patients with one or two oral anti-diabetic drugs (OAD) should have a 6-week wash-out period before the 2-week placebo run-in period.

Outcome variable(s):

Primary outcome variables

- HbA1c

Secondary outcome variables

- AEs, blood pressure (BP), pulse, physical examination, body weight, waist circumference, laboratory values, electrocardiogram (ECG)
- The time-course of drug concentrations for AZD1656 and its active metabolite AZD5658 in plasma.
- Fasting plasma glucose (FPG) and numbers of patients with an HbA1c ≤6.5% and ≤7%, respectively, at visit 11
- Insulin and C-peptide
- Total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, triglycerides and high-sensitivity C-Reactive protein (hs-CRP)

Statistical methods

Efficacy: A hierarchical closed testing procedure will be adopted for the efficacy analyses. Treatment group comparisons will be tested in dose span order whereby comparisons with placebo will commence with the highest dose regimen (randomized patient on 40 mg daily titrated to maximum of 200 mg daily) tested first, next dose regimen 20 mg daily titrated to maximum of 140 mg daily, and finally dose regimen 10 mg daily titrated to maximum of 80 mg daily. Estimates of the treatment effect and corresponding 2-sided 95% confidence intervals will be presented together with the p-values for the treatment effect. For the primary analysis, tests will be performed at the 5% level of significance.

Primary analysis: the change from baseline to month 4 in HbA1c will be analysed based on ANCOVA model including treatment group (placebo, low, middle and high dosing regimen) as fixed effect and baseline as covariates. The primary analysis will be on the last observation carried forward and will be based on the full analysis set.

Secondary analyses: for the continuous secondary efficacy variables(fasting plasma glucose, insulin, C-peptide), an analysis of covariance will be performed as for the primary analysis. The categorical efficacy variables including HbA1c responders and hypoglycaemia incidence (see definition in Section 3.1.5) will be compared across treatment groups utilising a chi-square test. Analyses of the secondary variables will be conducted on the full analysis set (last observation carried forward) only unless otherwise stated.

Safety: All adverse events will be categorised by body system organ class and preferred term using MedDRA dictionary, and be listed for each patient. In the safety analysis set, adverse events will be reported as frequencies in each treatment group.

Haematology and clinical chemistry data will be listed for each patient and summarised for each treatment group at each visit. Shift tables will also be presented.

Summary of value and change from baseline for electrocardiogram, vital signs, weight and waist measurements will be presented. In addition, summary and shift tables for physical examination will be provided. All data will be presented in listings. Summary of adverse events of special interest, hypoglycaemic events and need for additional glucose lowering treatment will also be presented.

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

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

Abbreviation or special term	Explanation
AE	Adverse event (see definition in Section 6.4.1)
ALT	Alanine Aminotransferase
AST	Asparate Aminotransferase
BP	Blood pressure
CRF	Case Report Form (electronic/paper)
hs-CRP	high-sensitivity C-reactive protein
CSR	Clinical Study Report
CV	Cardiovascular
CV%	Coefficient of Variation
DAE	Discontinuation of Investigational Product due to Adverse Event
DCCT	Diabetes Control and Complications Trial
ECG	Electrocardiogram
FAS	Full analysis set
FPG	Fasting plasma glucose
FSH	Follicle stimulating hormone
GCP	Good Clinical Practice
GFR	Glomerular filtration rate
GK	Glucokinase
GKA	Glucosekinase Activator
GMP	Good Manufacturing Practice
HbA1c	Glycosylated hemoglobin, Hemoglobin A1c
ICH	International Conference on Harmonisation
IP	Investigational Product
IRB	Institutional review board
IWRS	Interactive Web Response System
LH	Luteinizing hormone
LLOQ	Lower Limit of Quantification
LOCF	Last Observation Carried Forward

Abbreviation or special term	Explanation
MAD	Multiple ascending dose
MDRD	Modification of Diet in Renal Disease
MedDRA	Medical Dictionary for Regulatory Activities
NYHA	New York Heart Association
OAD	Oral anti-diabetic drug
OAE	Other Significant Adverse Event (see definition in Section 11.2.3)
PD	Pharmacodynamic(s)
PK	Pharmacokinetic(s)
PP	Per-protocol
SAD	Single ascending dose
SAE	Serious adverse event (see definition in Section 6.4.2).
SMPG	Self monitored plasma glucose
T2DM	Type 2 Diabetes Mellitus
ULN	Upper limit normal
ULOQ	Upper Limit of Quantification
WBDC	Web Based Data Capture

1. INTRODUCTION

1.1 Background

The aim of this study is to evaluate the efficacy, safety, and tolerability of different dosing regimens of AZD1656, a glucokinase activator, after 4 months monotherapy compared to placebo in Japanese type 2 diabetes mellitus (T2DM) patients.

Currently, there are 5 different classes of oral antidiabetic drugs available on the market: sulphonylureas (SU), biguanides (metformin), alpha glucosidase inhibitors, thiazolidinediones and just recently dipeptidyl peptidase-4 (DPP-4) inhibitors have been launched in worldwide. Despite different mechanisms of action, with sometimes potent glucose lowering effects, current agents do not provide optimal treatment for T2DM. Each of the existing therapies is associated with adverse effects on T2DM itself (eg, weight gain and β-cell dysfunction) and/or has adverse effects that limit use. There is therefore a rationale to develop oral products with new mechanisms of action and more favourable benefit/risk profiles.

Glucokinase (GK) is present in the liver and in pancreatic β-cells and catalyses the conversion of glucose to glucose-6-phosphate. GK can be regarded as a glucose sensor and is rate limiting for glucose uptake and utilisation in pancreatic β-cells, where it plays a major role in regulating insulin secretion. GK is also present in liver parenchymal cells (hepatocytes), where it regulates hepatic glucose utilisation. Defects in these 2 processes significantly contribute to the development of hyperglycaemia in T2DM. AZD1656 is a new potent glucose kinase activator (GKA), which, due to its dual-compartment mode of action, has the potential to provide superior glycaemic control relative to existing oral agents. There are as yet no products targeting activation of GK on the market.

AZD1656 has, in pre-clinical studies, been shown to be a potent activator of rat and human GK in vitro. In western phase 1 and 2a studies including both healthy volunteers and T2DM patients, AZD1656 has been well tolerated and no safety signal has been identified. A glucose-lowering effect has been demonstrated when given as monotherapy, on top of insulin and on top of metformin during up to 4 weeks of treatment. In Japanese phase 1 studies, single ascending dose (SAD) study with Japanese healthy volunteers and multiple ascending dose (MAD) study with Japanese T2DM patients, AZD1656 has been well tolerated and a glucose-lowering effect has been demonstrated when given as monotherapy. The results merit further clinical development of AZD1656 as monotherapy for the treatment of Japanese T2DM patients.

1.2 Research hypothesis

The hypothesis tested in this study is that AZD1656 monotherapy is superior to placebo in terms of reduction in HbA1c from baseline to the end of treatment at 4 months.

1.3 Rationale for conducting this study

This study is a dose finding study in Japanese T2DM patients to evaluate the efficacy and safety profile of AZD1656 monotherapy in Japanese T2DM patients in order to select the optimal dosing regimen(s) of AZD1656 to be used in the confirmatory phase III programme. In addition, in order to support the planning of the phase III programme, the effects of AZD1656 monotherapy on cardiovascular risk factors will be evaluated, and the pharmacokinetics (PK) of AZD1656 in Japanese T2DM patients will be determined, with the potential influence of covariates on PK (e.g. gender and renal function).

1.4 Benefit/risk and ethical assessment

AZD1656 is a GKA to be developed as a glucose-lowering agent for the treatment of T2DM patients. Due to its novel, potentially dual compartment, mode of action AZD1656 is expected to deliver anti-hyperglycaemic efficacy through increased glucose-dependent insulin secretion and increased hepatic glucose uptake. Therefore, AZD1656 has the potential to provide improved glycaemic control to existing oral agents.

1.4.1 Safety information from Phase I and IIa studies

In the almost completed phase I and IIa clinical studies, approximately 250 subjects (male and non-fertile females) have been exposed to AZD1656 up to 28 days duration. These studies include evaluation of AZD1656 as monotherapy (7 to 80 mg bd), as add-on to metformin (up to 50 mg bd) and as add-on to insulin glargine (up to 150 mg bd) in T2DM patients. Single doses of AZD1656 (2 to 180 mg) have been given to healthy volunteers during euglycaemic clamp conditions. A glucose-lowering effect have been observed in healthy volunteers as well as in monotherapy, add-on to metformin and add-on to insulin in T2DM patients.

AZD1656 has been well tolerated and no safety concerns have been raised during Phase I-IIa. There have been no treatment related changes in safety laboratory variables including muscle biomarkers and liver function tests. Except for the intended pharmacological effect (reduced blood glucose), there was no apparent difference between AZD1656-treated and placebo-treated subjects regarding AEs. No safety signals were identified regarding vital signs or ECG. Two (2) subjects experienced serious adverse events (SAEs) following exposure to AZD1656: 1 male subject was diagnosed with atrial fibrillation on day 3 in study D1020C00019 (at normal glucose levels on AZD1656 25 mg bd on top of metformin), and 1 subject had an episode of asymptomatic non-sustained, 16-beat ventricular tachycardia post hypoglycaemic clamp in study D1020C00018 (80 mg on top of metformin). One SAE was reported in a subject not exposed to AZD1656 (atrial fibrillation).

In the completed Japanese phase I studies, the SAD study D1020C00003 where AZD1656 (up to 180 mg) was administered to Japanese healthy volunteers and the MAD study D1020C00004 where AZD1656 (up to 80 mg bd, i.e., daily dose of 160 mg) to Japanese T2DM patients, AZD1656 has been well tolerated without any safety concerns.

In the three 28-day repeated dosing studies (with AZD1656 as monotherapy, as add-on to metformin, and as add-on to insulin), the most common AEs were headache and low blood

glucose. Pain in extremities was reported by 7 subjects on AZD1656, these consist of reports of localized pain (including pain at intravenous site), and there were no laboratory indications (i.e., in AST and CK) of muscle damage.

Few hypoglycaemic events have been reported and only rarely with plasma glucose below 3 mmol/L (54 mg/dL). The events were either asymptomatic (detected in scheduled measurement) or associated with mild symptoms, and in all cases manageable by the patients. All events with low plasma glucose have responded rapidly to carbohydrate intake.

The hypothalamic-regulated counter regulatory response to experimentally induced hypoglycaemia in healthy volunteers regarding the hormones epinephrine, norepinephrine, growth hormone and cortisol after a single oral dose of AZD1656 (80 mg) was similar to that after insulin treatment. Similar hypoglycaemic symptoms were reported after AZD1656 as compared to insulin alone in this experimental study. Injections of glucagon have been demonstrated to rapidly normalise glucose levels after experimentally induced hypoglycaemia in T2DM patients treated with AZD1656.

Regarding the pharmacodynamic response and pharmacokinetic data in clinical pharmacological studies and information from non-clinical studies, see the current Investigator's Brochure.

1.4.2 Safety monitoring in the study

Safety will be carefully monitored in this study. During the titration period, low plasma glucose levels and hypoglycaemia will be avoided by a careful stepwise increase of AZD1656 during monitoring of plasma glucose and visits to the clinic on a weekly basis. Patients will receive glucometers and are being asked to check their plasma glucose on a daily basis and in case of symptoms suggestive of hypoglycaemia. AZD1656 will be given just before meals to prevent hypoglycemic events. Furthermore, frequent visits are scheduled to the clinic for monitoring of safety laboratory variables (including liver function tests and muscle enzymes) and adverse events will be collected with special focus on hypoglycaemic events.

Criteria for rescue treatment in case of hyperglycaemia are included in this study to ensure safe glucose levels in all arms during the randomized treatment period.

All participants may benefit from the life-style advice included in the study and the intensified glucose monitoring. The chance of receiving active treatment is 3 out of 4.

The clinical findings to date give confidence that the known risks can be mitigated, and that the proposed 4-month trial can be conducted without undue risk to patient safety (provided that patients' safety is monitored in accordance with this clinical study protocol) and meets the standard of ethics and patient safety.

2. STUDY OBJECTIVES

2.1 Primary objective

- To compare the effect on glucose control of 3 different AZD1656 dosing regimens with placebo in Japanese T2DM patients, as evaluated by the change in HbA1c from baseline to the end of treatment at 4 months.

2.2 Secondary objectives

- To investigate the safety and tolerability of AZD1656 compared to placebo by assessments of adverse events (AE) occurring during the study (including hypoglycaemic events), blood pressure (BP), pulse, physical examination, body weight, waist circumference, safety laboratory variables (including plasma glucose) and electrocardiogram (ECG)

- To characterise the population pharmacokinetic (PK) and pharmacodynamic (PD) properties of AZD1656 in Japanese T2DM patients by utilisation of non-linear mixed effects modelling methodology

- To evaluate other variables of glucose control (fasting plasma glucose [FPG], insulin, C-peptide and number of responders in terms of HbA1C $\leq$ 7% and $\leq$ 6.5%, respectively) after 4 months in Japanese T2DM patients receiving AZD1656 compared to placebo.

- To evaluate other cardiovascular (CV) risk factors, such as total cholesterol, low-density lipoprotein cholesterol (LDL), high-density lipoprotein cholesterol (HDL), triglycerides and high-sensitivity C-Reactive protein (hs-CRP), after 4 months in Japanese T2DM patients receiving AZD1656 compared to placebo.

2.3 Safety objective

See Section 2.2.

2.4 Exploratory objectives – Not applicable

3. STUDY PLAN AND PROCEDURES

This Clinical Study Protocol has been subject to a peer review according to AstraZeneca standard procedures.

3.1 Overall study design and flow chart

This will be a 4-month treatment, randomized, double-blind, placebo-controlled, multi-centre, parallel-group phase II study to evaluate efficacy, safety and tolerability of different dose regimens of AZD1656 as monotherapy in approximately 220 Japanese T2DM patients (naïve

or treated with one or two oral anti-diabetic drugs [OAD] but not adequately controlled). Patients with up to 2 OADs within the last 24 weeks before enrolment visit (Visit1) will be allowed to participate in the study, where the patients should have the wash-out and placebo run-in period. The definition of a "naïve" patient is a patient who has not been treated with anti-diabetic drugs within the last 24 weeks before enrolment visit (Visit1). Naïve patients must be randmised to maximum 20% of the population.

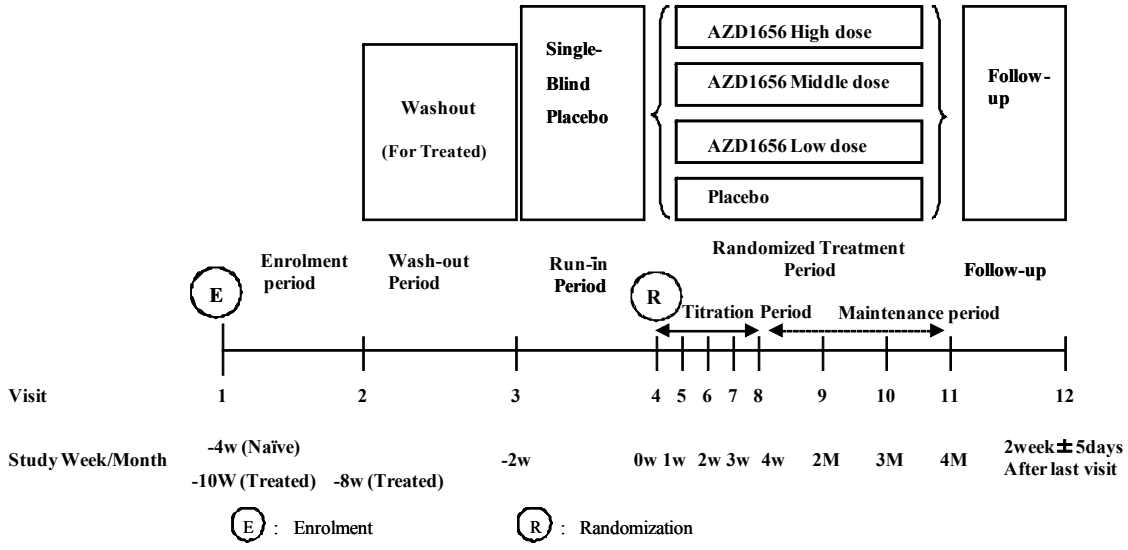
The study consists of 4 parallel arms with 55 patients in each arm. Patients will be randomized to 1 of 3 different dose regimens of AZD1656, or placebo.

AZD1656 or placebo will be given twice daily just before a meal. The dose of AZD1656 or placebo will be stepwise increased, based on glucose response, using the dose steps described below.

High: 40 – 80 – 140 – 200mg (daily dose):
Middle: 20 – 40 – 80 – 140mg (daily dose):
Low: 10 – 20 – 40 – 80mg (daily dose):

The study flow chart is presented in Figure 1.

Figure 1 Study Flow Chart



Enrolment (Visit 1), Wash-out (Visit 2) & Placebo Run-in period (Visit 3):

Patients are required to be treatment naïve with HbA1c ≥ 7.5 % but ≤ 10% (Diabetes Control and Complications Trial [DCCT]), or required to be treated with one or two OADs with HbA1c ≥ 7.5 % but ≤ 9.5% (DCCT). They should meet all inclusion and none of the exclusion criteria. The naïve patients will enter the 2-week Single-blind Placebo Run-in period directly, while patients treated with one or two OADs (treated patients) will have a 6-week wash-out period before entering the Single-blind Placebo Run-in period.

The following enrolment assessment will be performed at Visit 1: demography, relevant medical and surgical history, nicotine/alcohol use, test for Hepatitis B and C, physical examination, ECG, vital signs (BP and pulse), weight and height, concomitant medications.

A safety laboratory screen will be done by central lab. Additional blood samples will be taken to measure FPG, HbA1c, Insulin, and C-peptide. For women in the perimenopausal period, the postmenopausal stage will be confirmed by hormonal tests (Follicle stimulating hormone [FSH] and Luteinizing hormone [LH]).

At Visit2, only performed in treated patients, FPG will be checked at the clinic with a glucometer and if <240 mg/dL (13.3 mmol/L) and patient fulfills also the other eligibility criteria, patients will stop their anti-diabetic drugs. At Visit3 and Visit4, applicable to all patients, FPG will be checked at the clinic (using a glucometer for immediate analysis). If FPG ≥ 240 mg/dL (13.3 mmol/L), the patient will not be randomized.

Patients will be given a Patient Diary at Visit 3 and receive glucometers for self-monitored plasma glucose (SMPG) at Visit 2 for treated patients or at Visit3 for naïve patients.

Between Visit 2 and 3, treated patients will be requested to check their FPG once a week and in case they have symptoms of hyperglycaemia (e.g. thirst and increased urine volumes), see also Section 3.1.1.

Between Visit 3 and 4, applicable to all patients, at least a fasting morning plasma glucose and a bed-time plasmaglucose assessment are needed on a daily basis. Within 3 days before Visit 4, a 7-point glucose assessment will be required at home.

Advice will be given for diet and life style during the wash-out period for treated patients and during the single-blind placebo run-in period for naïve patients.

All patients will be given a single blind placebo tablets during the single-blind placebo run-in period. Patient must have taken at least 75 % of the placebo tablets during the single-blind placebo run-in period.

Randomised Treatment Period

Titration period:

Eligible patients will be randomized to study medication at Visit 4. Patients will be fasting and undergo a physical examination, a safety laboratory screen, ECG, vital signs (BP and pulse), weight, waist circumference and concomitant medications. Diary will be reviewed and advice will be given for diet and life style during the visit. Additional blood samples will be taken to measure FPG, HbA1c, Insulin, C-peptide and hs-CRP.

During the first 4 weeks after randomisation, the dose of AZD1656 will be increased stepwise on a weekly basis, based on glucose response, in a blinded fashion. FPG will be analysed locally at the clinic (using a glucometer for immediate analysis) and the result will be used for the dose decision. On Visits 5, 6 and 7 the dose of blinded treatment will be increased if the

fasting morning plasma glucose analysed at the clinic at the specific visit is > 110mg/dL (6.1 mmol/L) and no other condition opposes a dose increase (e.g. risk for hypoglycaemic events) since last visit according to investigator's judgement. Once the dose of blinded treatment with AZD1656/placebo is established, patients will continue on the dose achieved for the rest of the study, unless reduction is needed due to hypoglycaemia, as judged by the investigator. Dose reduction is permitted during the titration period and only once per individual. Once the FPG goal is reached and the dose increase stopped, no further attempt to increase the dose of AZD1656/placebo should be made no matter if the FPG are higher than the pre-defined goal on later visits.

There will be a simulated dose increase in the placebo arm with AZD1656.

The following assessments will be done: Diary review and advice in diet and lifestyle (Visit 5, 6, 7 and 8), PK blood sampling (Visit 5 and 8), physical examination (Visit 5,6, 7 and 8), safety laboratory screen (Visit 5, 6, 7 and 8), lipids test (Visit 5, 6, 7 and 8),ECG (Visit 5 and 8), vital signs (Visit 5,6, 7 and 8), weight (Visit 8) and concomitant medications. Additional blood samples will be taken at Visit 8 to measure HbA1c, Insulin, C-peptide and hs-CRP. Drug accountability will be recorded and new study medication will be dispensed to cover the need for the coming week.

Between Visit 4 and 8, at least a fasting morning plasma glucose and a bed-time plasma glucose assessment are needed on a daily basis. The patients need to do a 7-point glucose assessment at home within 3 days before Visits 5, 6, 7 and 8 and register the results in the Patient Diary.

Maintenance period:

Patient will come for visits each month starting from 1 month after randomisation (Visit 8) until 4 months after randomisation (Visit 11). Patients will come in fasting and undergo a physical examination, a safety laboratory screen(Visit 9, 10 and 11), ECG(Visit 9, 10 and 11), vital signs (BP and pulse) (Visit 9, 10 and 11), weight (Visit 10 and 11), waist circumference (Visit 11), PK blood sampling (Visit 10 and 11) and concomitant medications. Diary will be reviewed and advice will be given for diet and life style during all visits. HbA1c, FPG and lipids will be taken at all visits. Additional blood samples will be taken at Visit 11 to measure Insulin, C-peptide and hs-CRP. All left over study medications needs be recorded. The investigator will also record if any AE occurred since the last visit with special attention to any symptoms of hypoglycemia.

Hypoglycemic events jeopardizing patient’s safety, according to the investigator, will lead to discontinuation of study participation, since dose reduction is not allowed during the maintenance period.

After Visit 8, patients do not have to check plasma glucose daily at home. The patients need to do a 7-point glucose assessment at home within 5 days before Visit 9 and 10 and register the results in the Patient Diary.

Follow-up period:

The patient will be scheduled in two weeks (±5 days) after the last visit to a final visit. Any ongoing AEs will be followed up as long as medically indicated. Patients will come in fasting and undergo a physical examination, a safety laboratory screen, ECG, vital signs (BP and pulse), weight and advice for diet and life style will be given. Blood sample will be taken to measure FPG.

Unscheduled visit

Extra visits may be necessary for safety reasons. These visits will be recorded in the eCRF as unscheduled visits, necessary safety samples sent to the central lab and AE/SAE section completed as deemed appropriate by the Investigator.

The study assessments are described in the Study plan, Table 1.

Table 1 Study plan

Activity	Enrolment period	Wash-out period	Run-in period	Randomized treatment period								Follow-up period
Visit number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**
Study week / month	**W –4(naïve) W -10 (treated)**	**W –8 (treated)**	**W -2**	**W0**	**W1**	**W2**	**W3**	**W4**	**M2**	**M3**	**M4**	**2 weeks ± 5 days after last visit**
Study day	**-28(+7)(naïve) -70(+7)(treated)**	**-56(±2) (treated)**	**-14(±2)**	**0**	**7 (±2)**	**14 (±2)**	**21 (±2)**	**28 (±2)**	**60 (±5)**	**90 (±5)**	**120 (±5)**	
Informed Consent [a]	X											
Inclusion/exclusion criteria	X	X	X	X								
Demography and nicotine/alcohol use	X										X [b]	
Medical/surgical history	X											
Physical examination	X			X	X	X	X	X	X	X	X	X
Randomisation				X								
12-lead ECG	X			X	X			X	X	X	X	X
Height	X											
Test for Hepatitis B and C	X											
FSH, LH (women only) [c]	X											
Safety blood sampling	X			X	X [d]	X [d]	X [d]	X	X	X	X	X
Safety urine sampling	X			X	X	X	X	X	X	X	X	X
Vital signs (pulse, BP)	X			X	X	X	X	X	X	X	X	X
Weight	X			X				X		X	X	X
Waist circumference				X							X	
FPG [e]	X	X	X	X	X	X	X	X	X	X	X	X
HbA1c	X			X				X	X	X	X	
Efficacy blood samples (Insulin, C-peptide, lipids and hs-CRP)	X [fe]			X	X [g]	X [g]	X [g]	X	X [g]	X [g]	X	

Table 1 Study plan

Activity	**Enrolment period**	**Wash-out period**	**Run-in period**	**Randomized treatment period**								**Follow-up period**
Visit number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**
Study week / month	**W –4(naïve) W -10 (treated)**	**W –8 (treated)**	**W -2**	**W0**	**W1**	**W2**	**W3**	**W4**	**M2**	**M3**	**M4**	**2 weeks ± 5 days after last visit**
Study day	**-28(+7)(naïve) -70(+7)(treated)**	**-56(±2) (treated)**	**-14(±2)**	**0**	**7 (±2)**	**14 (±2)**	**21 (±2)**	**28 (±2)**	**60 (±5)**	**90 (±5)**	**120 (±5)**	
SMPG [h]		X	X	X	X	X	X	X	X	X	X	
Distribution and review of Patient Diary			d	d/r	d/r	d/r	d/r	d/r	d/r	d/r	r	
PK blood sampling					X[i]			X[i]		X[i]	X[j]	
Advice in diet and lifestyle		X	X	X	X	X	X	X	X	X	X	X
Dispense of single-blind placebo for Run-in			X									
Drug accountability of single-blind placebo for Run-in				X								
Dispense of blinded IP (AZD1656 or placebo)				X	X	X	X	X	X	X		
Drug accountability of IP (AZD1656 or placebo)					X	X	X	X	X	X	X	
Concomitant medication	X	X	X	X	X	X	X	X	X	X	X	X
AE / SAE collection [k]	X	X	X	X	X	X	X	X	X	X	X	X

d: distribution, r: review, d/r: distribution and review

a IC should be obtained within 14 days before any study specific procedures performed.
b Nicotine use only.
c See Inclusion criteria No.2
d Excluding p-lactate and cystatin-C.
e FPG will be analysed using a glucometer immediately locally at the clinic. A venous sample will be sent to the central laboratory.
f No lipid status or hs-CRP at enrolment visit (Visit 1)
g lipid test only
h Self-monitoring of plasma glucose at home, see Section 3.1.1.
i One blood sample for PK analysis before morning dose.
j PK samples will be taken before morning dose, post-dose at 1 (±0.5), 3 (±1) and 5 (±1) hours. Each sample should be separated by at least 1 hour.
k All AEs will be collected from the time of start of the single-blind placebo run-in period(Visit3) until the end of the study (including follow-up visit). SAEs will be collected from the time of informed consent provision.

3.1.1 SMPG measurements

All patients will be asked to check their plasma glucose at home on a regular basis during the study from Visit 2 (treated patients only) or from Visit 3 (both treated and naive). Between Visit 2 and 3, patients previously on OAD will be requested to check their FPG once a week. If a patient has FPG ≥240 mg/dL (13.3 mmol/L) at home by SMPG during the washed-out period and the placebo run-in period, he/she should contact the investigator for further guidance. Depending on the SMPG results, the investigator can decide if the patient must be discontinued from the study or can continue until the next visit. Patients will also be instructed to measure plasma glucose if they experience symptoms of hypoglycaemia or hyperglycaemia and register plasma glucose results and event-related information in the Patient Diary.

Patients should consult the investigator if an SMPG is < 54 mg/dL (3.0 mmol/L) at any time during the study. After randomisation, patients should consult the investigator if FPG is 200 mg/dL (11.1 mmol/L) or higher at home at two consecutive mornings, see also Section 5.6.1 for Hyperglycemia rescue treatment.

The Patient Diary will be reviewed by the investigator at each visit after it has been distributed.

Between Visit3 and 4, and during the titration weeks, at least 1 fasting morning plasma glucose and 1 bed-time plasma glucose assessment are needed on a daily basis. Within 3 days before Visit4, 5, 6, 7 and 8, a 7-point glucose assessment will be required at home.

After the titration period, ie, after Visit 8, plasma glucose assessments will not be required on a daily basis. However, patients are requested to collect a 7-point glucose assessment within a 5-day window before Visits 9 and 10 and register the results in the Patient Diary.

Patient need to be fasting except for water from 10:00 pm the night before 7-point SMPG .

The 7-point assessment should include the following time points:

- Fasting before breakfast
- 2 hours after breakfast
- Before lunch
- 2 hours after lunch
- Before dinner
- 2 hours after dinner
- At bed-time

3.1.2 Titration overview

During the first 4 weeks after randomisation, the dose of AZD1656 will be increased stepwise on a weekly basis in a blinded fashion. On Visits 5, 6 and 7 the dose of blinded treatment will be increased if the fasting morning plasma glucose analysed at the clinic (using a glucometer for immediate analysis) at the specific visit is >110 mg/dL (6.1 mmol/L) and no conditions (e.g. hypoglycaemic risk) opposes a dose increase according to investigator's judgment.

Once the dose of blinded treatment with AZD1656/placebo is established, patients will continue on the dose achieved for the rest of the study.

Dose reduction is permitted during the titration period and only once per individual. If the investigators judges as the necessity of the dose reduction once more, the patient should be discontinued from the study.

There will be a simulated dose increase in the placebo arm with AZD1656.

Figure 2 Dosing overview during titration

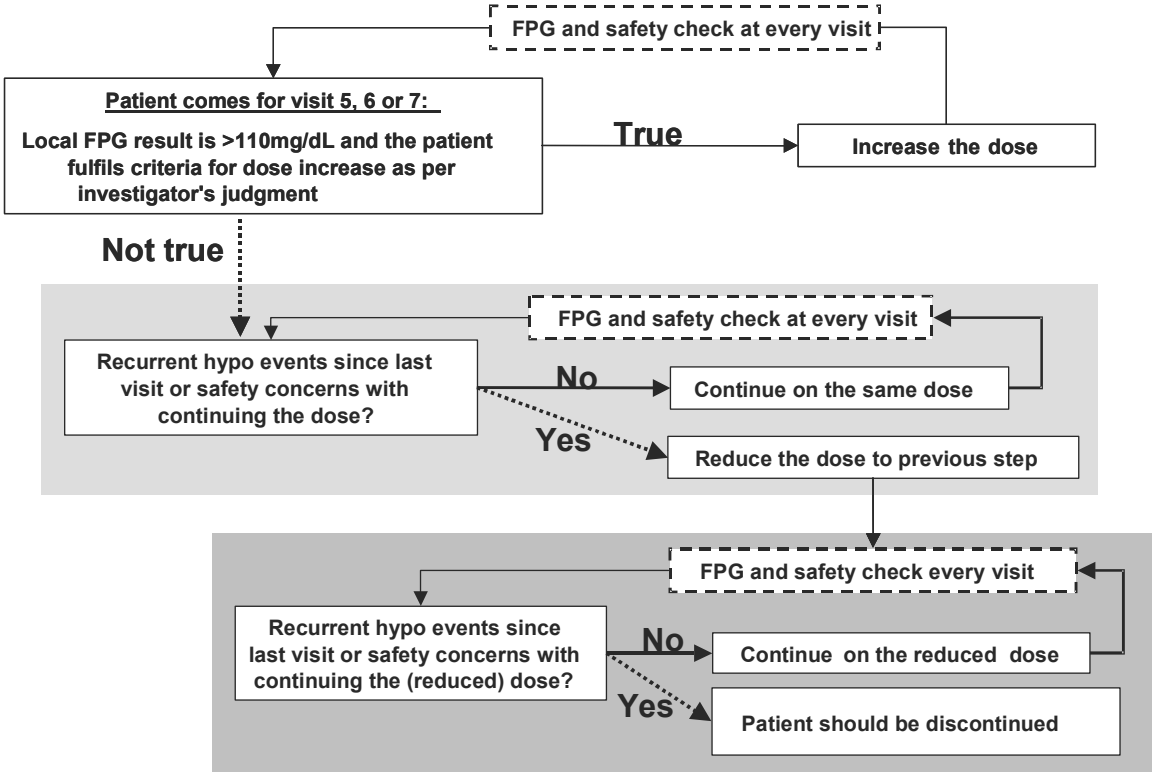


Table 2 Schematic overview of available dose step (daily doses) of AZD1656 during the initial titration period

Randomized treatment	Visit 4 0 (baseline)	Visit 5 After 1 week	Visit 6 After 2 weeks	Visit 7 After 3 weeks
AZD1656 arm higher dose span	40 mg (20mg bid)	80 mg (40mg bid)	140 mg (70mg bid)	200 mg (100mg bid)
AZD1656 arm middle dose span	20 mg (10mg bid)	40 mg (20mg bid)	80 mg (40mg bid)	140 mg (70 mg bid)
AZD1656 arm lower dose span	10 mg (5mg bid)	20 mg (10mg bid)	40 mg (20mg bid)	80 mg (40mg bid)
Placebo arm	Placebo	Placebo	Placebo	Placebo

3.1.3 PK sampling

One blood sample for PK analysis will be taken prior to the morning dose at Week 1 (Visit 5), Week 4 (Visit 8) and Month 3 (Visit 10). During Month 4 (Visit 11), blood samples for PK analysis will be taken before morning dose, post-dose at 1 (±0.5), 3 (±1) and 5 (±1) hours. Each sample should be separated by at least 1 hour. At Visit 11, patients should take food immediately after dosing.

3.1.4 Hyperglycemia during study and rescue treatment

After randomisation, hyperglycemia will be defined as follows:

- FPG equal or greater than 270 mg/dL (15mmol/L) from baseline up to 4-week visit (Visit 8)
- FPG equal or greater than 240 mg/dL (13.3 mmol/L) after the 4-week visit up to the 3-month visit (Visit 10)
- FPG equal or greater than 200 mg/dL (11.1 mmol/L) or HbA1c greater than 8.0 % at any time after the 3-month visit (Visit 10)

During the randomised treatment period, patients with confirmed fasting hyperglycemia which are defined above on at least two consecutive assessments (either SMPG measurements or at the clinic) or HbA1c should receive rescue treatment with alpha glucosidase inhibitors. The type and brand of drug, as well as doses used, will be according to local clinical practice and the drug will be procured by the study site. If patients still remain hyperglycemia, which is defined as the above, despite using rescue treatment, the patients should be discontinued. Initiation and subsequent dose changes of any hyperglycaemia rescue treatment must be recorded in the appropriate sections of the case report form (CRF).

3.1.5 Low glucose levels during study

Patients will be asked to register all events with plasma glucose <54 mg/dL (3.0 mmol/L) in their SMPG diary and in addition all events with symptoms suggestive of hypoglycemia with or without a current plasma glucose value. All patients will be instructed to contact the investigator in case of plasma glucose <54 mg/dL (3.0 mmol/L) with or without symptoms or if external assistance was needed during a hypoglycemic event regardless of glucose level.

The investigator must continuously evaluate if study participation is safe for the individual patient and if recurrent hypoglycaemia despite dose reduction, if applicable, the patient may have to be discontinued from study.

3.1.6 Adjudication of cardiovascular events

An Adjudication Committee will be appointed to evaluate all deaths and suspected cardiovascular events from the time point of randomisation until study completion and perform an event categorisation. The adjudication procedure will be defined in a specific adjudication charter and will include events of death, myocardial infarction/acute coronary syndrome, stroke, events of cardiac heart failure and arrhythmia. This evaluation will be performed on blinded data. See the document “Cardiovascular Event committee Charter” in detail.

3.2 Rationale for study design, doses and control groups

A randomized, double-blind, placebo-controlled, multi-centre, parallel-group study design is standard in dose finding studies and is considered the best choice to achieve the objectives of the study, from both safety and efficacy perspectives. The study is designed to demonstrate superior efficacy versus placebo; a placebo control arm in the trial will enable placebo corrected analysis of safety and efficacy.

In order to minimize the risk for patients, alpha glucosidase inhibitors, which have different mode of action from AZD1656 with regard to lowering blood glucose, will be used as rescue treatment in case of hyperglycaemia. The availability of rescue treatment in case of hyperglycaemia will ensure safe glucose control in all patients, regardless of randomisation, during the study.

AZD1656 stimulates insulin secretion and, in order to mitigate the risk for hypoglycaemia, the dose of this drug will be increased stepwise based on the glucose response during the initial titration period. A stepwise dose increase is in line with anticipated future use of AZD1656. The titration design is also adopted in the ongoing global Phase IIb study (D1020C00009). The patient safety will be secured by monitoring the blood glucose level. In addition, patients will check their plasma glucose level at home and they will be instructed to contact the investigator in case they have inappropriate glucose level defined in this protocol.

Considering this initial titration period, a total treatment period of 4 months has been selected with the aim to ensure appropriate duration of the maintenance period to generate robust safety and efficacy data to support a Phase III programme.

The doses in this study are based on PK, pharmacodynamic and safety and tolerability data collected in Western and Japanese studies. In addition, pharmacokinetic data is similar and overlapping in Japanese and Western studies in healthy volunteers as well as patients (D1020C00001-D1020C00004). The suggested dose range in this study, 10-200 mg/day, is the same as in the global Phase IIb study (D1020C00009).

The starting dose of the three dose regimens (10, 20 and 40 mg/day) were evaluated safe when given as start doses in the Japanese MAD study (D1020C00004). The lowest top dose during maintenance period (80 mg/day) is a dose with expected clinically significant glucose lowering effect, based on data seen in the Japanese MAD study (D1020C00004). The mid top dose, 140 mg/day, is below the highest dose studied in the Japanese MAD study (160 mg/day) and is chosen to investigate a dose between the two top doses in the low and high dose arms. This dose, 160 mg/day, was well tolerated and did not raise any safety concerns. With regard to highest top dose (200 mg/day) this dose level is above the highest dose studied in the Japanese MAD study but well below the highest dose studied in the phase 2a in the Western population. In study D1020C00014 where AZD1656 was studied on top of insulin, following titration, doses of 300mg/day AZD1656 was studied for 7 days. This dose was well tolerated and did not raise any safety concerns. As described above, the suggested top dose in this study, 200 mg/day, is the same as the top dose in the highest dose arm in the ongoing global Phase IIb study (D1020C00009).

Considering the data collected from the studies so far, titration of AZD1656 and frequent safety monitoring including glucose measurements the suggested dosing regimens are justified and can be conducted without undue risk to patient safety.

4. SUBJECT SELECTION CRITERIA

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

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.

4.1 Inclusion criteria

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

1. Provision of written informed consent prior to any study specific procedures
2. Japanese male or women of non-childbearing potential (postmenopausal, and/or have undergone hysterectomy and/or bilateral oophorectomy or salpingectomy/tubal ligation) aged ≥20. Women will be defined as postmenopausal if last menstruation period was >1 year ago and serum FSH and LH are within the postmenopausal range, or if age >50 years and with last menstruation period >2 years ago.
3. Body mass index between ≥19 and ≤42 kg/m^2

4. Clinical diagnosis of T2DM
5. Naïve patients with HbA1c ≥ 7.5% but ≤ 10% at enrolment visit (Visit1) (HbA1c value according to international DCCT standard and obtained from the central laboratory used in the study). Naive patients are defined as not having recieved any anti-diabetic drugs for the last 24 weeks before enrolment visit (Visit1)
   or
   Patients treated with one or two oral anti-hyperglycaemic agent(s) with HbA1c ≥ 7.5% but ≤ 9.5% at enrolment visit (Visit1) (HbA1c value according to international DCCT standard and obtained from the central laboratory used in the study)
   Naïve patients must be randomized to maximum 20% of the population.
6. Patients must have FPG <240 mg/dL (13.3 mmol/L) analysed locally at the clinic by using a glucometer for immediate analysis at start of wash-out period (Visit 2, applicable to patients on OADs only), at start of single-blind placebo run-in period (Visit 3, applicable to all patients) and at randomisation (Visit4, applicable to all patients)
7. Patient must have taken at least 75% of the placebo tablets during the placebo run-in period".

4.2 Exclusion criteria

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

1. Clinical diagnosis of Type 1 diabetes
2. Positive test for Hepatitis B surface antigen or antibodies to Hepatitis C virus at enrolment visit (Visit 1), obtained from the central laboratory used in the study, or suffering from HIV.
3. Participation in weight loss programme (other than the lifestyle advice normally given to T2DM patients) or use of weight loss drugs (OTC or prescriptions) within the last 3 months prior to enrolment visit (Visit 1).
4. Unwilling or unable to perform self-monitoring of plasma glucose at home according to protocol
5. Significant cardiovascular event within the last 6 months prior to enrolment visit (Visit 1) (eg, myocardial infarction/acute coronary syndrome, revascularisation procedure, stroke or transient ischemic event) or heart failure NYHA class III-IV.
6. Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) laboratory results >3 x ULN at enrolment visit (Visit 1), obtained from the central laboratory used in the study.
7. Haemoglobin laboratory results <11.5 g/dL for men, and <10.5 g/dL for women at enrolment visit (Visit 1), obtained from the central laboratory used in the study.
8. History of psychiatric or somatic disease/condition (eg, gastrointestinal disease) that may interfere with the objectives of the study, as judged by the investigator
9. History or ongoing symptoms/signs of severe allergy/hypersensitivity as judged by the investigator

10. History of malignancy within the last 5 years prior to enrolment visit (Visit 1), excluding successful treatment of basal or squamous cell skin carcinoma or in-situ carcinoma of the cervix
11. Impaired renal function in terms of GFR<60 ml/min at enrolment visit (Visit 1), based on Modification of Diet in Renal Disease (MDRD) calculation using the creatinine result obtained from central laboratory used in the study .
12. Past or present alcohol or drug abuse within the last 5 years prior to enrolment visit (Visit 1).
13. SBP >160 mmHg or DBP >95 mmHg at enrolment visit (Visit1)
14. Proliferative retinopathy or other significant diabetes complications
15. Use of warfarin, amiodarone and rifampicin within 3 months prior to enrolment visit (Visit 1) and use of potent CYP450 inhibitors such as (but not limited to) ketoconazole and macrolide antibiotics within 14 days before randomisation visit (Visit 4)
16. Use of anabolic steroids and systemic treatment with glucosteroids within 3 months before enrolment visit (Visit 1). Inhalation steroid treatment allowed.
17. Blood loss in excess of 400 mL within the last 3 months prior to enrolment visit(Visit1).
18. Participation in another clinical trial and/or intake of another investigational drug within the last 30 days (or at least five $t_{1/2}$ of the drug if longer than 30 days) prior to enrolment visit(Visit1).
19. Prior exposure to GKAs.
20. Involvement in the planning and conduct of the study or staff at the investigational site
21. Any other condition prohibiting the patient from participating in the study according to the protocol as judged by the investigator
22. Not willing to use αGI for rescue medicine

Procedures for withdrawal of incorrectly enrolled subjects see Section 5.3.

5. STUDY CONDUCT

5.1 Restrictions during the study

Patients will have to comply with the following restrictions:

1. Abstain from blood and plasma donation during the study and up to 3 months after completion of the study
2. Fast, except for water, at least 10 hours prior to study visit including enrolment visit (Visit 1). During the randomised treatment period, patients should not take the IP morning dose until after arrival at clinic and after blood samples have been collected. IP must be taken just prior to meal/breakfast.

3. Patients must not participate in any weight-loss programme, other than the life-style advice given according to CSP, and should not initiate pharmacological weight-loss treatment during the study.
4. Patients should perform 7-point glucose assessments within a 3-day window before Visits 4, 5, 6, 7 and 8, and within a 5-day window before Visits 9 and 10. Results to be recorded in an SMPG diary.
5. In case of event of suspected hypoglycemia, patients should record the details of the event, including plasma glucose values if possible, in their Patient diary.
6. Male patients must refrain from fathering a child during the study and for 3 months after the dose of study drug. They should not donate sperm and ensure that their partners of child bearing potential use a reliable method of contraception as well as themselves using a barrier method for this period. Acceptable methods used by female partners of child bearing potential include the oral contraceptive pill, hormonal implants, intra-uterine devices (IUDs) or diaphragms with spermicide. Female partners should use this additional contraception for 3 months after the last dose of study drug.

5.2 Subject enrolment and randomisation

The Principle Investigator, or appropriate delegate, will be required to enter information regarding each patient's study visit into Interactive Web Response System (IWRS). During Visit1, the patient identifier information and visit date information will be entered. After Visit1, the site will be requested to enter the E-code, visit number and additional information. Information regarding use of IWRS will be provided as study manual.

5.2.1 Procedures for enrolment/randomisation

Procedures for enrolment

The Principal Investigator 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 Sections 4.1 and 4.2

Procedures for randomisation

The Principle Investigator will:

1. Determine patient eligibility (See Sections 4.1 and 4.2).
2. Assign eligible patients with a unique randomisation code (patient number) through IWRS. (Randomisation codes will be assigned strictly sequentially as subjects become eligible for randomisation.)

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

5.3 Procedures for handling subjects incorrectly enrolled or randomised

Subjects who fail to meet the inclusion/exclusion criteria should not, under any circumstances, be enrolled or randomised. There can be no exceptions to this rule.

Where subjects that do not meet the selection criteria, are randomised in error or incorrectly started on treatment, or where subjects subsequently fail to meet the study criteria post initiation, a discussion should occur between the AstraZeneca Study Delivery Team Physician and the Investigator regarding whether to continue or discontinue the subject from treatment.

The AstraZeneca Study Delivery Team Physician is to ensure all such decisions are appropriately documented. In situations where an agreement cannot be reached, the subject should have their study therapy stopped.

5.4 Blinding and procedures for unblinding the study

5.4.1 Methods for ensuring blinding

All packaging and labelling will be done in such a way as to ensure blinding. AZD1656 tablets will be identical in appearance, smell and taste to the matching placebo.

The investigator(s) sponsor's personnel and subjects will be blinded to treatment allocation throughout the study.

5.4.2 Methods for unblinding the study

Individual treatment codes, indicating the treatment randomisation for each randomised subject, will be available to the investigator(s) or pharmacists, and the personnel who are independent to the study evaluation at the Patient Safety Department, AstraZeneca from the IWRS.

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 subject to the AstraZeneca staff.

AstraZeneca retains the right to break the code for SAEs that are unexpected and are suspected to be causally related to an investigational product and that potentially require expedited reporting to regulatory authorities. 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.

5.5 Treatments

5.5.1 Identity of investigational product(s)

AZD1656 and placebo will be administrated as white, round tablets. The tablets will contain AZD1656 corresponding to the strength 5mg, 20mg, 50mg of the active compound

respectively or placebo. The tablets will be packed into blister cards to achieve the intended dose. Each dose of AZD1656 will be composed of 2 tablets. The patient will take half of the daily dose in the morning and half of the daily dose in the evening just before a meal.

A blister card of AZD1656 dose 10, 20, 40, 80, 140, 200 mg or placebo will be created.

The number of blisters to be distributed for patients receiving AZD1656 is presented in Table 3.

Table 3 Number of blisters per visit

Visit	2	3	4	5	6	7	8	9
Number of blisters on AZD1656	-	1	1	1	1	4	4	4

The packaging will be carried out in accordance with Good Manufacturing Practice (GMP).

Table 4 Product Information

Investigational product	Dosage form and strength	Manufacturer
AZD1656	Tablets 5mg	AstraZeneca
AZD1656	Tablets 20mg	AstraZeneca
AZD1656	Tablets 50mg	AstraZeneca
AZD1656 placebo	Tablets	AstraZeneca

5.5.2 Doses and treatment regimens

Two tablets AZD1656 orally in the morning just before breakfast and two tablets AZD1656 in the evening just before dinner, i.e. four tablets per day in total.

- 10mg dose : AZD1656 5mg 1tablet + AZD1656 placebo 1tablet, twice daily
- 20mg dose : AZD1656 5mg 2tablets, twice daily
- 40mg dose : AZD1656 20mg 1tablet + AZD1656 placebo 1tablet, twice daily
- 80mg dose : AZD1656 20mg 2tablets, twice daily
- 140mg dose : AZD1656 20mg 1tablet + AZD1656 50mg 1tablet, twice daily
- 200mg dose : AZD1656 50mg 2tablets, twice daily

Two tablets AZD1656 placebo orally in the morning just before breakfast and two tablets AZD1656 placebo in the evening just before dinner, i.e. four tablets per day in total.

- Placebo dose : AZD1656 Placebo 2tablets, twice daily

5.5.3 Labelling

Labels will be prepared in accordance with Good Manufacturing Practice (GMP) and local regulatory guidelines. The labels will fulfil GMP Annex 13 requirements for labelling. Label text will be translated into local language.

Each wallet will be labelled with "For clinical study use".

Details of labelling and packaging of the study drug will be described in a separate document, 'Procedure of storage conditions for investigational product'.

5.5.4 Storage

All study drugs should be kept in a secure place under appropriate storage conditions. A description of the appropriate storage conditions is specified in the IP label on wallets and the document 'Procedure of storage conditions for investigational product'.

The investigator will instruct the patient about storage requirements for study medication.

5.6 Concomitant and post-study treatment(s)

Other concomitant medication or therapy will be allowed during the study, from the time of signing informed consent to the follow-up visit and recorded in the appropriate section of the CRF, except for warfarin, amiodarone, rifampicin and potent CYP450 inhibitors such as (but not limited to) ketoconazole and macrolide antibiotics.

Changes in concomitant medication should be avoided during study participation, with the exception of situations defined in this protocol, but medication, which is considered necessary for the patient's safety and well-being, may be given at the discretion of the investigator, who must decide if the patient should remain in study or need to be dismissed from study due to patient's safety or interference with study objectives. The administration of all medication must be recorded in the appropriate sections of CRF with trade names, dosages and dates of starting and ending of medication.

5.6.1 Hyperglycaemia during study and rescue treatment

No other anti-diabetic treatment than defined will be allowed. However, alpha glucosidase inhibitor could be received as hyperglycaemia rescue treatment. The type and brand of drug, as well as doses used, will be according to local clinical practice and the drug will be procured by the study site. In addition, occasional use of insulin in case of acute illness is allowed. Such occasional insulin use is limited to maximally 7 continuous days on 1 occasion.

5.7 Treatment compliance

The administration of all study drugs (including investigational products) should be recorded in the appropriate sections of the Case Report Form.

Treatment compliance will be assessed by tablet count. To be eligible for randomisation, patients must have taken at least 75 % of their placebo tablets during the run-in period. In the statistical analysis, acceptable compliance is defined as having taken at least 75% of the IP doses during the randomized treatment period. Treatment compliance will be calculated as follows:

$$\textbf{Compliance} = \frac{\text{number of tablets dispensed - number of tablets returned}}{\text{(date of last dose – date of first dose +1) x number of tablets}}$$

The number of tablets in the calculation is the number of tablets that patients should have received each day, as per protocol.

5.7.1 Accountability

Study drug will not be distributed to the study site until the contract is concluded between the study site and AstraZeneca. The Investigational Product Storage Manager is responsible for managing the study drug from receipt by the institution until the return of all unused study drug to AstraZeneca. AstraZeneca will provide the study documents 'Procedures for drug accountability' and 'Procedures for drug storage' which describes the specific requirements. The investigator(s) is responsible for ensuring that the subject has returned all unused study drug.

5.8 Discontinuation of investigational product

Subjects may be discontinued from investigational product (IP) in the following situations:

1. Voluntary discontinuation by the subject. The patient is at any time free to discontinue treatment, without prejudice to further treatment.
2. Adverse Event (including laboratory abnormality or intercurrent illness) which, in the opinion of the investigators, indicates that continued participation in the study is not in the best interest of the subject.
3. Severe non-compliance to study protocol as judged by the investigator and/or AstraZeneca
4. Risk to patients as judged by the investigator and/or AZ
5. Patient lost to follow-up.
6. Incorrect enrolment, ie, the subject does not meet the required inclusion/exclusion criteria for the study
7. Incorrectly randomized subjects, where appropriate following discussion between investigator and study team physician.

5.8.1 Development of study specific discontinuation criteria.

Subjects meeting any of the study specific discontinuation criteria listed below must be discontinued from the study:

1. Patient uses amiodarone, warfarin, rimfampicin or potent CYP450 inhibitors, such as, but not limited to, ketokonazole and macrolide antibiotics during the study.

2. Patients who despite dose reduction of IP once, experiences more than one hypoglycaemic event with need for external assistance due to impaired consciousness, or with other hypoglycaemic event(s) resulting in safety concerns with continued IP treatment.
3. Patients with remaining hyperglycemia despite maximum tolerable dose of rescue drug.
4. Patient who meeting hyperglycaemia criteria, but with condition(s) contraindicating the use of a-GI, such as but not limited to liver function abnormality, shock, chronic gastro-intestinal disease and renal failure.
5. Increase in plasma CK levels to more than 10 x ULN on two consecutive measurements that cannot be ascribed to a benign condition or situation.
6. ALT or AST more than 3 x ULN and total bilirubin more than 2 x ULN, see Appendix E.
7. Patient with ALT or AST > 5 x ULN, see Appendix E.
8. Patient with ALT or AST >3 x ULN and clinical signs or symptoms indicating liver dysfunction, see Appendix E.

5.8.2 Procedures for discontinuation of a subject from investigational product

A subject that discontinues will always be asked about the reason(s) for discontinuation and the presence of any adverse events. The Principal Investigator/sub-investigator will perform the best possible observation(s), test(s) and evaluation(s) as well as give appropriate medication and all possible measures for the safety of the subject. They will also immediately inform AstraZeneca of the withdrawal. Adverse events will be followed up (See Sections 6.4.3 and 6.4.4); diary cards and study drug should be returned by the subject.

All randomised subjects who do not complete the treatment period will complete the end of treatment visit (Visit 11) study procedures as soon as possible but at the latest within 7 days after discontinuation of study drug. All randomised subjects will enter the 2-week follow-up period.

For patients discontinuing due to liver enzyme criteria, special evaluation will be performed, see Appendix E.

5.9 Withdrawal from study

Subjects are at any time free to withdraw from study (investigational product and assessments), without prejudice to further treatment (withdrawal of consent). Such subjects will always be asked about the reason(s) and the presence of any adverse events. If possible, they will be seen and assessed by an investigator. Adverse events will be followed up (See Sections 6.4.3 and 6.4.4); diary cards and all study drugs should be returned by the subject.

Withdrawn subjects will not be replaced.

6. COLLECTION OF STUDY VARIABLES

6.1 Recording of data

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 electronic Case Report Forms as specified in the study protocol and in accordance with the instructions provided.

The investigator ensures the accuracy, completeness and timeliness of the data recorded and of the provision of answers to data queries. The investigator will sign the completed electronic Case Report Forms. A copy of the completed electronic Case Report Forms will be archived at the study site.

The Principal Investigator/sub-investigator will record data on the observations, tests and assessments specified in the protocol on the electronic CRFs provided by AstraZeneca. The CRF will be accompanied with 'Instructions for the Investigator', which should be followed. These instructions provide guidance for the recording of study data in the CRF including how to change data incorrectly recorded.

6.2 Data collection

For full details please see the study plan (Table 1).

6.3 Efficacy

6.3.1 Efficacy variables related to glucose control

6.3.1.1 HbA1c

Samples for HbA1c analysis will be collected at the enrolment visit (Visit 1), the randomisation visit (Visit 4), and monthly after the titration period (from Visit 8), see Table 1.

6.3.1.2 FPG

Samples for fasting plasma glucose will be collected and analysed immediately at the clinic by using a glucometer or similar device at every visit, see Table 1. At each visit, a venous sample for analysis of FPG will also be sent to the central laboratory. The FPG samples, both the 1 analysed immediately at the clinic by using a glucometer or similar device and the 1 for the central laboratory, should be taken when the patient is fasting, and before the IP is administered.

6.3.1.3 Insulin, C-peptide

The levels of fasting insulin and C-peptide will be analysed also at time points defined in Table 1.

6.3.2 Assessment of lipid status and marker of inflammation

Samples for analysis of total cholesterol, HDL, LDL, triglyceride and hs-CRP will be collected at time points defined in Table 1.

6.4 Safety

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

6.4.1 Definition of adverse events

An adverse event is the development of an undesirable medical condition or the deterioration of a pre-existing medical condition following or during exposure to a pharmaceutical product, whether or not considered causally related to the product. An undesirable medical condition can be symptoms (eg, nausea, chest pain), signs (eg, tachycardia, enlarged liver) or the abnormal results of an investigation (eg, laboratory findings, electrocardiogram). In clinical studies, an AE can include an undesirable medical condition occurring at any time, including run-in or washout periods, even if no study treatment has been administered.

The term AE is used to include both serious and non-serious AEs.

6.4.2 Definitions of serious adverse event

A serious adverse event is an AE occurring during any study period (ie, from the enrolment visit until the follow-up period), that fulfils one or more of the following criteria:

- Results in death
- Is immediately life-threatening
- Requires in-patient hospitalisation or prolongation of existing hospitalisation (including hospitalisation for tests related to adverse events), except hospitalisation that has been planned before enrolment
- 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 a SAE, see Appendix B to the Clinical Study Protocol.

6.4.3 Recording of adverse events

Time period for collection of adverse events

Adverse Events will be collected from the single blind placebo run-in period (Visit 3) until the end of the study (including the follow-up period).

SAE will be collected from the time of informed consent provision

Follow-up of unresolved adverse events

Any AEs that are unresolved at Visit 12 or at the end of 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.

Variables

The following variables will be collect 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 Investigational Product (yes or no)
- action taken with regard to investigational product
- outcome.
- Whether the AE is a hypoglycaemic symptom or not

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

- Date AE met criteria for serious AE
- Date Investigator became aware of serious AE
- AE is serious due to
- Date of hospitalisation
- Date of discharge

- Probable cause of death
- Date of death
- Autopsy performed
- Causality assessment in relation to Study procedure(s)
- Causality assessment in relation to Other medication
- Description of AE.

The intensity rating is defined as:

- mild (awareness of sign or symptom, but easily tolerated)
- moderate (discomfort sufficient to cause interference with normal activities)
- severe (incapacitating, with inability to perform normal activities)

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 6.4.2. 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 a SAE. On the other hand, a stroke that results in only a limited degree of disability may be considered a mild stroke but would be a SAE.

Causality collection

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

For SAEs causal relationship will also be assessed for other medication and study procedures. Note that for SAEs that could be associated with any study procedure the causal relationship is implied as 'yes'.

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

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 personnel: *'Have you had any health problems since the previous visit/you*

were last asked?', or revealed by observation will be collected and recorded in the CRF. When collecting AEs, the recording of diagnoses is preferred (when possible) to recording a list of signs and symptoms. However, if a diagnosis is known and there are other signs or symptoms that are not generally part of the diagnosis, the diagnosis and each sign or symptom will be recorded separately.

For hypoglycemic events, only symptoms should be added as AE, the hypoglycemic event will be classified from the data entered into the specific hypoglycemia module.

Adverse Events based on examinations and tests

The results from protocol mandated laboratory tests and vital signs will be summarised in the clinical study report. Deterioration as compared to baseline in protocol-mandated measurements should therefore only be reported as AEs if they fulfil any of the SAE criteria or are the reason for discontinuation of treatment with the investigational product.

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

Assessment of hypoglycaemic events

From Visit 3 the patient will be asked to document details of hypoglycaemic episodes in a diary. At each visit the investigator must review any such entries with the patient and a corresponding module in the CRF should be completed based on the investigator's medical interpretation of the event. Any symptoms described for a hypoglycaemic episode will be reported as AE.

6.4.4 Reporting of serious adverse events

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

If any SAE occurs in the course of the study, then investigators or other site personnel inform appropriate AstraZeneca representatives within one day ie, immediately but **no later than the end of the next business day** 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 one calendar day** of initial receipt for fatal and life threatening events **and within five calendar days** of initial receipt for all other SAEs.

For fatal or life-threatening adverse events where important or relevant information is missing, active follow-up is undertaken immediately. Investigators or other site personnel inform AstraZeneca representatives of any follow-up information on a previously reported SAE within one calendar day ie, immediately but **no later than the end of the next business day** 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 personnel reports a SAE to the appropriate AstraZeneca representative by telephone.

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

6.4.5 Laboratory safety assessment

Blood and urine samples for determination of clinical chemistry, haematology, and urinalysis will be taken at the times indicated in the Study Plan (see Table 1).

The following laboratory variables will be measured:

Table 5 Measurement of Laboratory Variables

Haematology	B-Red blood cell count, B-Haemoglobin, B-Hematocrit, B-Leukocyte count, B-Leukocyte differential count (in percentage), B-platelet count
Clinical Chemistry	S-Albumin, S-ALT, S-AST, S-Alkaline phosphatase, S-Bilirubin total, S - Calcium total, S-Creatinine, S-g-GT, S-Potassium, S-Sodium, S-Creatine kinase, P-Lactate [a], Cystatin C [a], FSH [b], LH [b]
Hepatitis Screen Panel	Hepatitis B viral antibody IgM, Hepatitis B surface antigen, Hepatitis C virus antibody.
Urinalysis [c]	U-Hb, U-Protein, U-Glucose

a P-lactate and cyctatin-c are excluded at Visit 5, 6 and 7.
b FSH and LH are taken at enrolment in some women to confirm postmenopausal state.
c Urine samples will be analysed at the central lab.

For blood volume see Section 7.1

6.4.6 Physical examination

At time points defined in Table 1, A physical examination will be performed and include an assessment of the following: general appearance, skin, respiratory, cardiovascular and abdomen, musculo-skeletal, neurological systems, neck, lymph nodes and thyroid.

6.4.7 ECG

At time points defined in Table 1, ECGs will be recorded in the supine position after the patients has rested in this position for 5minutes and assessed locally.

ECGs should be standard 12-lead ECG with a lead II rhythm strip and a paper speed of 25mm/second, covering at least 5 complexes.

The ECG print-outs will be reviewed at the visit by the investigator. The results will be entered as normal or abnormal or specified if abnormal in the eCRF by the investigator.

All original ECGs must be stored in the patient's medical record as source documentation.

6.4.8 Vital sign

6.4.8.1 Pulse and blood pressure

Pulse rate, systolic BP and diastolic BP in supine will be assessed using the equipment used in the normal practice after the patients has been sitting at rest for 5 minutes.

6.4.9 SMPG measurements

All patients will receive life-style advice and glucometers from Visit 2 (treated patients) or Visit 3 (naïve patients) and will be asked to check their plasma glucose on a regular basis at home during the study, registering the results in a Patient Diary. The diary will be utilised from Visit 3.

Between Visit 2 and 3, patients previously on OAD will be requested to check their FPG once a week. If a patient has FPG ≥240 mg/dL (13.3 mmol/L) at home by SMPG during the washed-out period and the placebo run-in period, he/she should contact the investigator for further guidance. Depending on the SMPG results, the investigator can decide if the patient must be discontinued from the study or can continue until the next visit.

Between Visit 3 and 4, and during the titration weeks, at least 1 fasting morning plasma glucose and 1 bed-time plasma glucose assessment are needed on a daily basis and within 3 days prior to each of Visit 4, 5, 6, 7 and 8, a 7-point glucose assessment should be completed and results registered in the Patient Diary. During the maintenance period, after Visit 8 and onwards, plasma glucose checks are not required on a daily bases at home, but patients are requested to collect a 7-point glucose assessment within a 5-day window before each visit to the clinic (ie, before Visits 9 and 10).

Patients will be carefully instructed to register any episode with symptoms suspected being related to low plasma glucose levels. The Patient Diary will be reviewed by the investigator at each study visit and episodes considered as hypoglycaemic events will be transferred into the CRF. The 7-point assessment should include the following time points:

- Fasting before breakfast.
- 2 hours after breakfast.

- Before lunch.
- 2 hours after lunch.
- Before dinner.
- 2 hours after dinner.
- At bed-time.

During the titration period, the decision to increase the dose will be based on SMPG data and the FPG measured at the clinical visit (see Section 3.1). The study staff will transfer any hypoglycaemic event from the Patient Diary to the eCRF. The morning and bedtime glucose results and any additional glucose checks requested by the investigator will not be transferred to the eCRF, those measurements are used for the investigator's safety monitoring of the patient.

6.4.10 Other safety assessments

Weight measurements should be taken pre-dose in the fasting state in the morning after a visit to the lavatory. Patients are only allowed to wear light clothing (ie, t-shirt and underwear) during the measurement and each patient should use the same scale during all measurements.

Height will be measurement at the enrolment visit (Visit 1) only and will not be recorded/monitored at any subsequent visits.

Waist circumference will be measured in centimetres (cm) at the level midway between the most caudal part of the lateral costal arch and the iliac crest at the end of a normal expiration.

6.5 Patient reported outcomes (PRO) - Not applicable

6.6 Pharmacokinetics

6.6.1 Collection of samples

Blood samples (2 mL) for trough concentration determination of AZD1656 and its metabolite AZD5658 in plasma will be drawn before morning dose at Week1 (±2 days), Week 4 (±2 days), Month 3 (±5 days) and Month 4 (±5 days), ie at Visits 5, 8, 10 and 11. In addition, samples will be taken on day 120 (±5 days), ie Visit 11, post-dose at 1 (±0.5), 3 (±1) and 5 (±1) hours. Each sample should be separated by at least 1 hour. Note, PK sampling will take place in all subjects. All samples from patients given active treatment of AZD1656 will be analysed, but no analysis of AZD1656 and its metabolite AZD5658 is planned in samples from patients allocated to placebo treatment. However, if considered necessary, PK samples from placebo treatment groups may be analysed for determination of AZD1656 and its metabolite AZD5658.

The patients will be instructed to record the exact time of morning and evening dose intake the day before each study visit including PK sampling. The times will be recorded by the patient

on a diary card and transferred to the eCRF by the site personnel. The exact time of dose intake in the morning at Visit11 and times for breakfast intake will be recorded in the eCRF by the site personnel. Subjects will have breakfast immediately after the IP intake. The actual blood sampling time will be entered into the lab requisition form on all occasions and transferred to the eCRF by the site personnel.

Plasma samples should be stored at -20ºC and analysed within the timeframe after collection for which the stability in the samples has been validated and found acceptable. Results from samples stored longer than the period stated will not be reported.

Samples will be shipped to the central laboratory during the course of the study. For more details of labelling, storage and shipment see Appendix D and the laboratory manual.

For blood volume see Section 7.1.

6.6.2 Determination of drug concentration

Samples for determination of AZD1656 and it's metabolite AZD5658 in plasma will be analysed by York Bioanalytical Solutions, U.K. on behalf of AstraZeneca R&D, Mölndal using liquid chromatography with mass spectrometric detection after solid phase extraction. The lower limit of quantification (LLOQ) of AZD1656 and AZD5658 in plasma is 5 nmol/L. The methods will be referred to in the CSR.

6.7 Pharmacodynamics

6.7.1 Collection of pharmacodynamic markers

See Section 6.3.1 for efficacy variables related to glucose control.

6.8 Pharmacogenetics – Not applicable

6.9 Health economics – Not applicable

7. BIOLOGICAL SAMPLING PROCEDURES

7.1 Volume of blood

The total volume of blood that will be drawn from each subject in this study is as follows:

Table 6 Volume of blood to be drawn from each subject

Visit	1	2	3	4	5	6	7	8	9	10	11	12	Total
Assessment													
Haematology	2			2	2	2	2	2	2	2	2	2	20
Clinical chemistry[a]	17			11	4	4	4	11	8	8	11	6	84
HbA1c	2			2				2	2	2	2		12
FPG	2	(2[b])	2	2	2	2	2	2	2	2	2	2	22(24[b])
PK					2			2		2	8		14
Total	23	(2[b])	2	17	10	8	8	19	14	16	25	10	152(154[b])

a Including Insulin, C-peptide, hs-CRP, p-lactate, Hepatitis screening panel and lipids.
b Treated patients only

7.2 Handling, storage and destruction of biological samples

The samples will be used up or disposed of after analyses.

7.2.1 Clinical chemistry/ haematology samples

Samples will be disposed after the clinical study report has been finalised.

7.2.2 Pharmacokinetic samples

Samples will be disposed after the clinical study report has been finalised.

7.3 Labelling and shipment of biohazard 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 C '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.

7.4 Chain of custody of biological samples

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

The Principal Investigator 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 AstraZeneca biobank system during the entire life cycle.

7.5 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 subjects' withdrawal of informed consent to the use of donated samples is notified immediately to AstraZeneca
- Ensures that biological samples from that subject, if stored at the study site, are immediately identified, disposed of /destroyed, and the action documented
- Ensures the laboratory(ies) holding the samples is/are informed about the withdrawn consent immediately and that samples are disposed/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 central laboratory(ies) 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.

8. ETHICAL AND REGULATORY REQUIREMENTS

8.1 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/Good Clinical Practice, applicable regulatory requirements and the AstraZeneca policy on Bioethics and Human Biological Samples.

The applicable regulatory requirements in Japan are 'Good Clinical Practice for Trials on Drugs (MHLW Ordinance No. 28, 27 March 1997, partially revised by MHLW Ordinance and their related notifications.

8.2 Subject data protection

The Master Informed Consent Form will explain that: Study data will be stored in a computer database, maintaining confidentiality in accordance with national data legislation. Subject data will be maintaining confidentiality in accordance with national data legislation. For data verification purposes, authorised representatives of AstraZeneca, a regulatory authority, an Ethics Committee may require direct access to parts of the hospital or practice records relevant to the study, including subjects' medical history. All data computer processed by AstraZeneca will be identified by study code and enrolment code (E-code).

8.3 Ethics and regulatory review

An Ethics Committee should approve the final study protocol, including the final version of the Informed Consent Form and any other written information and/or materials to be provided to the subjects. The Head of the study site will ensure the distribution of these documents to the applicable Ethics Committee, and to the study site staff.

The head of the study site should submit a notification of direction/determination as well as a copy of the IRB written approval to AstraZeneca before enrolment of any subject should into the study.

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

AstraZeneca should approve any modifications to the Informed Consent Form that are needed to meet local requirements.

The protocol should be re-approved by the IRB annually. The Principal Investigator should submit progress reports to the IRB via the head of the study site at the time of the protocol re-approval.

Before enrolment of any subject into the study, the final study protocol, including the final version of the Informed Consent Form, 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, including SUSARs (Suspected Unexpected Serious Adverse Reactions), where relevant.

The Head of the study site should submit a written report to the IRB providing the details of all safety relative information reported by AstraZeneca.

8.4 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 they are free to discontinue from the study at any time
- Ensure that each subject is given the opportunity to ask questions and allowed time to consider the information provided
- Ensure each subject provides signed and dated informed consent before conducting any procedure specifically for the study
- Ensure the original, signed Informed Consent Form(s) is/are stored in the Investigator's Study File
- Ensure a copy of the signed Informed Consent Form 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 informed consent form that is approved by an Ethics Committee.

If any new information on the study medication becomes available which may influence the decision of the subject to continue the study, the investigator(s) should inform the subject of such information immediately, record this in a written form, and confirm with the subject if he or she wishes to continue the participation in the study. In addition, if the investigator(s) deem it necessary to revise the Informed Consent Form, they should revise it immediately (Refer to Section 8.5). The investigator(s) should re-explain the subjects using updated Informed Consent Form even if although the subjects have already been informed of the new information verbally. Written informed consent to continue participation in the study should be provided separately.

8.5 Changes to the protocol and informed consent form

Study procedures will not be changed without the mutual agreement of the Principal Investigator and AstraZeneca. If it is necessary for the study protocol to be amended, the amendment should be submitted to the Head of the Study Site and be approved by its IRB. If applicable, AstraZeneca should submit a notification to the regulatory authority before it is implemented. If a protocol amendment requires a change to a particular centre's Informed Consent Form, then AstraZeneca and the centre's IRB should be notified. Approval of the revised Informed Consent Form by AstraZeneca and by the IRB is required before the revised form is used. If an administrative change is required, such a change should be notified to or approved by each IRB according to local requirements.

8.6 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 protocol, Good Clinical Practice (GCP), guidelines of the International Conference on Harmonisation (ICH), and any applicable regulatory requirements. The investigator will contact AstraZeneca immediately if contacted by a regulatory agency about an inspection at the centre.

All study data may undergo a reliability review and onsite-GCP inspection by the regulatory authorities.

9. STUDY MANAGEMENT BY ASTRAZENECA

9.1 Pre-study activities

Before the first subject is entered into the study, it is necessary for a representative of AstraZeneca to visit the investigational study site to:

- Determine the adequacy of the facilities
- Determine availability of appropriate subjects for the study
- Discuss with the investigator(s) (and other personnel involved with the study) their responsibilities with regard to protocol adherence, and the responsibilities of AstraZeneca or its representatives. This will be documented in a Clinical Study Agreement between AstraZeneca and the investigator.

9.2 Training of study site personnel

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 and the WBDC system(s) utilised.

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

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

9.3 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 protocol, that data are being accurately and timely recorded in the CRFs, that biological samples are handled in accordance with the Laboratory Manual and that study drug accountability checks are being performed
- Perform source data verification (a comparison of the data in the CRFs 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 needs information and advice about the study conduct.

9.3.1 Source data

Source data are any data generated as a result of the subject's inclusion in the study (including run-in and/or follow up related to the study) and includes all related medical examinations and other records.

Original data recorded on the CRFs and regarded as source data are as follows.

- Reason for therapy or medication
- Any Comments on CRF
- Evaluation for inclusion/exclusion criteria on CRIT
- Adverse Event (Yes/No, Maximum intensity, Serious, Treatment required, Outcome, Causality)
- Description of AE on Serious Adverse Event form
- Main reason for premature discontinuation

9.3.2 Direct access to source data in Japan

The Head of the institution and the Principal Investigator/sub-investigator will cooperate for monitoring and audit by AstraZeneca, and accept inspection by the IRB or regulatory authorities. All study documents such as raw data will be open for direct access to source data at the request of the monitor and the auditor of AstraZeneca, the IRB, or regulatory authorities.

The monitor(s) will verify data from the CRFs against source data before collecting the CRFs to ensure accuracy and completeness of documentation, and assure that the Principal Investigator/sub-investigator has submitted the CRFs to AstraZeneca. If the investigator wishes to amend the collected CRFs, the monitor will ensure that the Principal Investigator/sub-investigator has documented the amendment in writing (signed and dated) and provided this to AstraZeneca.

9.4 Study agreements

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

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

9.4.1 Archiving of study documents

(i) **Study files.** AstraZeneca will provide the Principal Investigator with a file in which to organise and retain all study-related documents. All study documents (including letters from AstraZeneca) should be retained in this file by the Principal Investigator. The monitor will regularly check the file to ensure that all relevant documents are retained. The contents of the file may be audited/inspected by AstraZeneca's auditor, regulatory authorities, or IRB.

(ii) **Period of record retention**. The study site (and the Principal Investigator) will retain the essential documents specified in the ICH GCP (eg, source document such as medical records, contract, signed consent form). Essential documents should be retained at the study site for at least 15 years following completion of the study, or per regulatory obligations if longer, and thereafter destroyed only after agreement with AstraZeneca. However this is not always applied to those that are not preservable such as blood samples. In the event of any inconsistency between the above-mentioned contents and the contract with the study site, the contract shall prevail. These documents should be retained for a longer period however if needed by AstraZeneca, and the specific period and method of retention will be separately discussed between the study site and AstraZeneca. AstraZeneca should notify the

head of the study site in writing when the study related records are no longer needed. The records should be managed by a responsible person appointed by the head of the study site.

9.4.2 Deviation from the clinical study protocol in Japan

The investigator(s) must not deviate from or make any changes to the protocol without documented agreement between the principal investigator and AstraZeneca K.K. or the IRB approval based on its deliberations. However, this shall not apply to cases where the deviation or change is necessary to avoid an immediate hazard to the patients or for other compelling medical reasons, or where the changes involve only logistical or administrative aspects of the clinical trial (e.g. changes to the organisation/structure of the sponsor, the name/department name of the medical institution, the address or phone number of the medical institution or the sponsor, the job title of the investigator, and monitors).

The investigator(s) should document any deviation from the protocol regardless of their reasons. Only when the protocol was not followed in order to avoid an immediate hazard to the patients or for other medically compelling reason, the investigator should prepare and submit the records explaining the reasons thereof to the sponsor, and retain a copy of the records.

The investigator(s) may deviate from or make a change to the protocol without documented agreement between the principal investigator and AstraZeneca K.K. or the IRB approval, only in the event of a medical emergency, e.g. it is only way to avoid an immediate hazard to the patients. In such case, the principal investigator must notify details of the deviation or change, the reason, and a proposed revision in the protocol if required, to AstraZeneca K.K. and the head of the study site and IRB via the head of the study site as soon as possible, in order to obtain their approval. A certificate of approval by the head of the study site as well as AstraZeneca K.K. should be obtained via the head of the study site.

9.5 Study timetable and end of study

Planned duration of the study:

Study period: May 2010 – June 2011

Registration period: May 2010 – October 2010

Discontinuation or suspension of the whole study programme

If AstraZeneca decides to prematurely terminate or suspend the study, the Principal Investigator, the head of the institution, and regulatory authorities should receive written notification of the reasons for the premature termination or suspension.

The Principal Investigator/sub-investigator will immediately notify the decision to the subjects, give appropriate medical treatment; take necessary measures, and record treatment or measures provided on the source documents.

Completion of the study

Upon terminating the study, the Principal Investigator will report in writing the completion of the study as well as the summary of the results to the head of the study site in accordance with the institution's rules. The head of the study site, who is informed of the termination by the investigator, will provide a written notification of the results to the IRB and AstraZeneca.

10. DATA MANAGEMENT BY ASTRAZENECA

Data management will be performed by AstraZeneca Data Management Centre staff.

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 Medical Dictionary for Regulatory Activities (MedDRA). Medications will be classified according to the AstraZeneca Drug Dictionary. All 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 Data Management Plan. Quality control procedures will be applied to each stage of data handling to ensure that all data are reliable and have been processed correctly.

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.

Data associated with biological samples will be transferred to laboratories internal or external to AstraZeneca.

11. EVALUATION AND CALCULATION OF VARIABLES BY ASTRAZENECA

11.1 Calculation or derivation of efficacy variable(s)

If the assessment (CRF or lab data) is collected more than once for the same visit/time-point, the first assessment will be used in the analysis. If the assessment is outside the visit window then it will still be considered of interest and won't be excluded from the analysis.

For the lab parameters (C-peptide, LDL, HDL, trygliceride, etc.), value reported as <LLOQ will be analysed as LLOQ/2, value reported as > upper limit of quantification (ULOQ) will be analysed as ULOQ.

Change from baseline will be computed as the value at each visit post-baseline – baseline result. Baseline value will be defined as the last non-missing value before first dose of treatment. If the value is missing at the randomisation visit, the enrolment (screening) result will be used.

Percentage will be based on the number of patient in the respective analysis set.

11.2 Calculation or derivation of safety variable(s)

11.2.1 Events of hypoglycemia

Events of hypoglycaemia will be categorised into 1 of the following main categories, based on the investigator reported data:

- Major hypoglycaemia: Hypoglycaemic episode where the patient absolutely needed help from another person to recover, due to impaired consciousness or altered behaviour. There should also be documented prompt recovery after treatment with glucose or glucagon, and pre-treatment plasma glucose should be <54 mg/dL (3.0 mmol/L) or missing.

- Minor hypoglycaemia: Hypoglycaemic episode that the patient was able to manage by self-administration. There should also be a documented plasma glucose <54 mg/dL (3.0 mmol/L) before treatment or an asymptomatic plasma glucose measurement below 54 mg/dL (3.0 mmol/L) .

- Episode suggestive of hypoglycaemia: Any hypoglycaemic episode that the patient was able to manage by self-administration but where pre-treatment plasma glucose is either missing or >54 mg/dL (3.0 mmol/L).

11.2.2 Calculation of the Glomerular Filtration Rate

The GFR will be calculated using MDRD:

GFR (mL/min per $1.73m^2$) = 186 x (SCr)-1.154 x (Age) –0.203 x (1 if male / 0.742 if female)

where SCr = serum creatinine concentration in mg/dL, age is in years, and weight is in kg.

See Appendix F.

11.2.3 Other significant adverse events (OAE)

During the evaluation of the AE data, an AstraZeneca medically qualified expert will review the list of AEs that were not reported as SAEs and DAEs. Based on the expert's judgement, significant adverse events of particular clinical importance may, after consultation with the Global Patient Safety Physician, be considered OAEs and reported as such in the Clinical Study Report. A similar review of laboratory/vital signs/ECG data will be performed for identification of OAEs.

Examples of these are marked haematological and other laboratory abnormalities, and certain events that lead to intervention (other than those already classified as serious), dose reduction or significant additional treatment.

11.3 Calculation or derivation of patient reported outcome variables – Not applicable

11.4 Calculation or derivation of pharmacokinetic variables

Not applicable, see Section 11.5.2.

11.5 Calculation or derivation of pharmacodynamic variable(s)

11.5.1 Calculation or derivation of the relationship between pharmacokinetic and pharmacodynamic variables

Not applicable, see Section 11.5.2.

11.5.2 Population analysis of pharmacokinetic/pharmacodynamic variables

If necessary, population PK/PD modelling of the data will be performed at AstraZeneca R&D, using non linear mixed effects regression in NONMEM. If necessary, a semi-mechanistic drug-disease model, describing the interplay between drug concentrations, glucose, HbA1c and insulin levels as well as their time-course, will be applied and fit to data to estimate mean population PK/PD parameters with associated between- and within-patient variability. Also, the influence of patient-specific covariates such as gender, age, body weight, creatinine clearance and disease status on the PK and PD parameters may be investigated. A population PK/PD analysis plan will be written prior to clean file. The modelling results will be provided in a separate population PK/PD report.

11.6 Calculation or derivation of pharmacogenetic variables – Not aplicable

11.7 Calculation or derivation of health economic variables – Not applicable

12. STATISTICAL METHODS AND SAMPLE SIZE DETERMINATION BY ASTRAZENECA

12.1 Description of analysis sets

12.1.1 Full analysis set

All randomized patients with at least 1 dose administered, and with at least 1 post baseline efficacy data, will be included in the Full Analysis Set (FAS).

Patients will be analysed according to the randomized treatment, irrespective of the treatment received.

This will be the primary analysis set used for all efficacy analysis variables.

12.1.2 Per-Protocol analysis set

The Per-Protocol (PP) analysis set will consist of the patients in the FAS who do not violate any major entry condition and do not violate the protocol between randomisation and study completion. Major deviations from the protocol procedures include:

- Violation of inclusion/exclusion criteria.
- Disallowed concomitant medication.
- Missing key efficacy data. (ie, HbA1c at 4 months).
- Patient is not compliant

This will be the secondary efficacy analysis set and will be applied to all key efficacy analysis variables.

12.1.3 Safety analysis set

All patients who receive at least 1 dose of randomized investigational product, and for whom any post-dose data are available will be included in the safety analysis set. Safety result will be grouped according to actual dosing regimen received, regardless of randomized dosing regimen group.

12.1.4 PK and PD analysis set

Data from all included patients receiving at least 1 dose, contributing with at least 1 PK or PD measurement and providing reliable time-points for sampling and dose intakes, will be used for PK/PD analysis.

12.2 Methods of statistical analyses

Descriptive statistics includes n, mean, standard deviation, min, median, and max, and for variables log-transformed in the analysis, also geometric mean and coefficient of variation (CV%), for quantitative variables, and frequencies for qualitative variables.

The statistical analysis will be performed using SAS® version 8.2 or later.

12.2.1 Data Handling Considerations

Last observation carried forward methods (LOCF) will be used for any missing efficacy data; baseline data will not be carried forward. Analyses based on LOCF data will only be performed using the FAS.

12.2.2 Multiple Treatment Comparisons

For conclusion a hierarchical closed testing procedure will be adopted for the primary efficacy analyses. Treatment group comparisons will be tested in dose span order whereby

comparisons with placebo will commence with the highest dose regimen (randomized patient on 40mg daily titrated to maximum of 200mg daily) tested first, next dose regimen 20mg (daily titrated to maximum of 140mg daily) and finally dose regimen (10mg daily titrated to maximum of 80mg daily). All tests will be performed at the 5% level of significance.

12.2.3 Demographic, baseline and background characteristics

All variables will be presented with descriptive statistics within each treatment group.

12.2.4 Concomitant Medication

Concomitant medication is defined as a medication that is taken prior or after the first day of study treatment.

For incomplete or partial concomitant medication start and/or stop dates, where it is not possible to classify the concomitant medication as before or during, using available date information, it will be assumed that the concomitant medication was taken during double blind treatment.

Concomitant medication will be summarised by treatment group for the Safety analysis set using drug class and preferred term. Patients will only be counted once within a drug class, and once for a medication.

All medication, taken both prior to and during the double blind treatment period, will be included in the supportive data listing. A flag will be added to indicate where a medication was taken prior to the start of double blind treatment.

12.2.5 Compliance and Study Drug Exposure

The compliance of study drug and study drug exposure (defied as date of last dose - date of first dose + 1) will be summarised by treatment group and across all patients in the safety analysis set.

12.2.6 Efficacy Analysis

Individual data will be listed. Where appropriate, descriptive statistics or table of frequencies will be presented by treatment group.

12.2.6.1 Primary variable

An analysis of covariance (ANCOVA) will be performed on the change in HbA1c from baseline to the end of treatment at 4 months, with treatment as a fixed factor and the corresponding baseline HbA1c as a covariate. Estimates of the treatment effect and corresponding 95% confidence intervals based on the ANCOVA model will be presented together with the p-values for the treatment effect.

The FAS will be applied as the primary analysis set on the LOCF approach whereby for missing assessments (visits), the last observation will be carried forward. Baseline values will not be carried forward .

The PP analysis set based on Observed Case will be applied as supportive analyses to the FAS.

The following additional sensitivity analyses will be performed on the primary variable:

- Observed Case analyses will be performed on the FAS whereby missing intermediate assessments (visits) will be excluded.

- If the primary analyses are significant, an additional analysis adjusting for centre effects will be conducted. The primary efficacy variable will be analysed applying the ANCOVA model including additional covariate for centre on both the FAS and PP analysis sets.

- Further exploratory and subgroup investigations will be performed on the primary variable considering effects of other factors including gender. Exploratory analysis methodology will be detailed further in the statistical analysis plan.

12.2.6.2 Secondary variables

Analyses of the following secondary variables will be conducted on the FAS (LOCF) only unless otherwise stated.

- Proportion of patient responders with HbA1c $\leq$ 7% after 4 months.

- Proportion of patient responders with HbA1c $\leq$ 6.5% after 4 months.

- FPG levels after 4 months

- Cardiovascular risk factors, such as total cholesterol, LDL, HDL, triglycerides and hs-CRP, after 4 months.

For the continuous secondary efficacy variables (FPG), an ANCOVA will be performed as for the primary analysis.

The categorical efficacy variables including HbA1c responders and hypoglycaemia incidence will be compared across treatment groups applying χ^2-test methodology.

The remaining secondary efficacy variables are deemed exploratory. Statistical comparisons will be performed at the 5% level of significance on the FAS (LOCF) only:

- All of the above secondary variables and the change from baseline for HbA1c will also be summarised and analysed at other scheduled visits eg, Week 4, Month 2, Month 3 as applicable.

12.2.7 Safety Analysis

Safety variables will be summarised by treatment group using the safety analysis set and the safety analysis set excluding post rescue treatment.

12.2.7.1 Adverse events

Individual AEs will be listed per patient and sorted by treatment group. Number of patients with adverse events (AEs), serious adverse events, adverse events leading to discontinuation of IP and other significant adverse events (OAEs) will be summarised by treatment group. AEs will also be summarised by System Organ Class (SOC) and preferred term (PT) for each treatment group. AE will be considered to be treatment emergent if the onset date occurs, on or after the date of the first date of a randomised treatment period and up to and including 1 day after the last dose is taken (or the last day of the period, if a non-IP period). A separate SOC/PT table will summarize the AEs that have been marked as hypoglycaemic symptoms.

12.2.7.2 Plasma glucose measurements

Number of fasting plasma glucose measurements in pre-defined ranges (as defined in Sections 3.1.4 and 3.1.5) will be summarised.

12.2.7.3 Vital signs

Vital signs will be summarised at each visit and also for change from baseline for each treatment group.

12.2.7.4 ECG

ECG abnormalities will be summarised at each visit for each treatment group.

12.2.7.5 Clinical laboratory data

For quantitative variables, the descriptive statistics of observed values and change from baseline at each time point will be presented. For qualitative variables, shift tables will be produced for each treatment group.

Laboratory abnormalities will be flagged and listed, as appropriate.

Graphical presentations will be used as appropriate.

12.2.8 PK/ PD Analysis

If necessary, PK parameter estimates will be estimated using the NONMEM software. Parameter estimates expressing population mean, between-subject variability and random variability will be presented with their associated precision in a separate population PK/PD report. The PK/PD analysis and the report will be performed by AstraZeneca.

12.3 Determination of sample size

Based on previous experiences in studies with Japanese diabetic patients, the standard deviation for change in HbA1c is expected to be about 1.1%.

A sample size of 53 patients in each group will have 90% power to detect a difference of 0.7 between AZD1656 and placebo treatment arms at 4 months, assuming that the common standard deviation is 1.1 using a 2-group t-test with a 5% 2-sided significance level. Allowing

for an approximate 5% drop-out rate from the primary analysis, a minimum of 55 patients will be randomized to receive study medication in each treatment group.

12.4 Data monitoring committee – Not applicable

13. IMPORTANT MEDICAL PROCEDURES TO BE FOLLOWED BY THE INVESTIGATOR

13.1 Medical emergencies and AstraZeneca contacts

The Principal Investigator is responsible for ensuring that procedures and expertise are available to handle medical emergencies during the study. **A medical emergency usually constitutes an SAE and is to be reported as such, see Section 6.4.4**

In the case of a medical emergency the investigator may contact the Study Delivery Team Leader. If the Study Delivery Team Leader is not available, contact the Study Delivery Team Physician/other physician at the AstraZeneca.

Name	Role in the study	Address & telephone number

13.2 Overdose

In case of known or suspected overdose, symptomatic treatment as well as monitoring of vital functions, should be performed according to routine clinical practice. Plasma glucose should always be monitored and low levels of glucose treated with oral or iv glucose to counteract hypoglycaemia as prolonged episodes of hypoglycaemia may have detrimental effects on CNS, peripheral nerves and other tissues.

In order to collect more information concerning excessive doses of AZD1656 a suspected drug intake of more than 4 tablets of AZD1656/placebo at one occasion or a total daily intake

of more than 6 tablets of AZD1656/placebo needs to be reported to AZ as an overdose, regardless of clinical consequences.

- An overdose with associated AEs is recorded as the AE diagnosis/symptoms on the relevant AE modules in the CRF and on the Overdose CRF module.

- An overdose without associated symptoms is only reported on the Overdose CRF module.

If an overdose on an AstraZeneca study drug occurs in the course of the study, then investigators or other site personnel inform appropriate AstraZeneca representatives **within one day**, ie, immediately but no later than **the end of the next business day** of when he or she becomes aware of it.

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

For overdoses associated with SAE, standard reporting timelines apply, see Section 6.4.4. For other overdoses, reporting should be done within 30 days.

13.3 Pregnancy

Women of childbearing potential are not allowed to be included in this study and male patients must refrain from fathering a child, including sperm donation, during the study and 3 months following the last dose. If the investigator receives information that a pregnancy has occurred during the study (including pregnancy in the partner of a male patient) despite these restrictions, AstraZeneca should be informed.

14. LIST OF REFERENCES – NOT APPLICABLE

Clinical Study Protocol Appendix A

Drug Substance	AZD1656
Study Code	D1020C00016
Edition Number	1
Protocol Dated	

Appendix A
Signatures

ASTRAZENECA SIGNATURE(S)

A 4-month treatment, Randomized, Double-blind, Placebo-Controlled, Multi-centre, Parallel-Group Phase 2 study to Evaluate Efficacy, Safety and Tolerability of Different Dosing Regimens of AZD1656 as Monotherapy in Japanese Type 2 Diabetes Mellitus Patients

---

This Clinical Study Protocol has been subjected to an internal AstraZeneca peer review.

I agree to the terms of this study protocol.

ASTRAZENECA SIGNATURE(S)

A 4-month treatment, Randomized, Double-blind, Placebo-Controlled, Multi-centre, Parallel-Group Phase 2 study to Evaluate Efficacy, Safety and Tolerability of Different Dosing Regimens of AZD1656 as Monotherapy in Japanese Type 2 Diabetes Mellitus Patients

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This Clinical Study Protocol has been subjected to an internal AstraZeneca peer review.

I agree to the terms of this study protocol.

Clinical Study Protocol Appendix B

Drug Substance	AZD1656
Study Code	D1020C00016
Edition Number	1

Appendix B
Additional Safety Information

FURTHER GUIDANCE ON THE DEFINITION OF A SERIOUS ADVERSE EVENT (SAE)

Life threatening

'Life-threatening' means that the subject was at immediate risk of death from the AE as it occurred or it is suspected that use or continued use of the product would result in the subject's death. 'Life-threatening' does not mean that had an AE occurred in a more severe form it might have caused death (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 judgement should be exercised in deciding whether a case is serious in situations where important medical events may not be immediately life threatening or result in death, hospitalisation, disability or incapacity but may jeopardize the subject or may require medical 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 judgement must be used.

Examples of such events are:

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

A GUIDE TO INTERPRETING THE CAUSALITY QUESTION

The following factors should be considered 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?

- Dechallenge 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.

- Rechallenge experience. Did the AE reoccur if the suspected drug was reintroduced after having been stopped? AstraZeneca would not normally recommend or support a rechallenge.

- Laboratory tests. A specific laboratory investigation (if performed) has confirmed the relationship?

A "reasonable possibility" could be considered to exist for an AE where one or more of these factors exist.

In contrast, there would not be a "reasonable possibility" of causality if none of the above criteria apply or where there is evidence of exposure and a reasonable time course but any dechallenge (if performed) is negative or ambiguous or there is another more likely cause of the AE.

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?

Ambiguous cases should be considered as being a "reasonable possibility" of a causal relationship unless further evidence becomes available to refute this. Causal relationship in cases where the disease under study has deteriorated due to lack of effect should be classified as no reasonable possibility.

Clinical Study Protocol Appendix C

Drug Substance	AZD1656
Study Code	D1020C00016
Edition Number	1

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

LABELLING AND SHIPMENT OF BIOHAZARD SAMPLES

International Airline Transportation Association (IATA) classifies biohazardous agents into 3 categories **(http://www.iata.org/whatwedo/cargo/dangerous_goods/infectious_substances.htm).** For transport purposes the classification of infectious substances according to risk groups was removed from the Dangerous Goods Regulations (DGR) 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 (HIV) types 1 and 2. They are assigned the following UN number and proper shipping name:

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

Exempt - all other materials with minimal risk of containing pathogens

- Clinical trial samples will fall into Category B or exempt under IATA regulations
- Clinical trial samples will routinely be packed and transported at ambient temperature in IATA 650 compliant packaging **(http://www.iata.org/whatwedo/cargo/dangerous_goods/infectious_substances.htm)**
- **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.

Clinical Study Protocol Appendix D

Drug Substance	AZD1656
Study Code	D1020C00016
Edition Number	1

Appendix D
Instruction For Sampling, Handling, Storage and Shipment of Pharmacokinetic Samples

1. TYPES OF SAMPLE

In this study, blood samples will be collected and transported to the bioanalytical laboratory in UK to analyse the concentration of AZD1656 and AZD5658 in plasma.

Any biological samples identified as Infectious Category A materials (see IATA 6.2 Regulations Guidance in Appendix C) are not allowed to be shipped (see Section 7.3 in the study protocol).

2. SAMPLING AND HANDLING

2.1 Sample Device

Disposable needles and disposable tubes shall be used. Needles and catheters will be prepared at each study centre, and sampling tubes will be prepared by AstraZeneca K.K. Blood samples (2.0 ml) for determination of AZD1656 and AZD5658 in plasma will be collected in 2.0 mL tubes containing K3-EDTA as anticoagulant.

2.2 Blood Sampling

After applying a tourniquet, venous blood is taken with a disposable needle. If a catheter is used without using an obturator, the first mL of blood on each sampling occasion must be discarded. 2.0 mL of blood is collected in the sampling tube and K3-EDTA and blood are mixed carefully and left in room temperature.

The blood samples will be centrifuged at approximately 4°C for 10 minutes at a Relative Centrifugal Force (RCF) of about 1500 g within 30 minutes of the sample collection. Following centrifugation, the plasma (approx 0.56 mL) will be transferred with a fresh pipette into a 1.8 mL polypropylene tube (Nunc Cryo Tube ™, cat no 375418). The plasma samples must be immediately frozen at -20°C in upright position.

2.3 Labelling

On each sample tube the label with pre-printed information (i.e. study code, randomisation code, visit [day],sample type, protocol scheduled time including the unique sample identification etc.) will be attached. The label can only be used for the intended sample and the pre-printed information must not be changed.

3. SHIPMENT

Samples will be packed in the dedicated package supplied by AstraZeneca K.K., and the appropriate requisition forms must be completed by the investigators or delegates.

Samples will be shipped by Mitsubishi Chemical Medience Corporation via its agreed courier to the laboratory. Where possible, the samples would be shipped in batches and would be coordinated to arrive within working hours of the receiving laboratory site.

Details of sample packing, documentation and shipping conditions are specified in the laboratory manual. Samples must be transported on dry ice.

3.1 Bioanalytical laboratory

York Bioanalytical Solutions

Clinical Study Protocol Appendix E

Drug Substance	AZD1656
Study Code	D1020C00016
Edition Number	1

Appendix E
Liver Enzyme Criteria Special Evaluation

1. LIVER ENZYME CRITERIA SPECIAL EVALUATION

Handling of patients with elevated liver transaminases

The investigator will be alerted from the central laboratory regarding patients developing Alanine aminotransferase (ALT) or Aspartate aminotransferase (AST) > 3 x Upper limit normal (ULN) during the study ie, all values above > 3 x ULN with no upper limit will be alerted. How to handle these patients is described in detail in this section.

The patients must be brought back to the clinic for an unscheduled visit without any delay, but not later than 72 hrs after the test results have been received, for confirmatory laboratory testing.

All patients, regardless of whether they stop or continue the intake of Investigational Product (IP), must be closely monitored with repeated laboratory liver tests every third day or more frequently if judged necessary by the investigator until the liver tests begin to improve. Thereafter liver tests will be performed at an interval decided to be appropriate by the investigator. All patients must be followed until the liver tests have returned to baseline or until a firm explanation (diagnosis) to the elevated liver transaminases has been established.

Beside confirmation laboratory test to for monitoring of increased transaminases should include test of ALT, AST, alkaline phosphatase (ALP), bilirubin (BIL), conjugated BIL, creatine kinase (CK).

Patients who can continue the intake of IP

Patients with ALT or AST > 3 x ULN but ≤ 5 x ULN and no clinical signs or symptoms indicating liver dysfunction can, at the discretion of the investigator, continue the intake of IP with close monitoring. The patients must be brought back to the clinic for an unscheduled visit without any delay, but not later than 72 hrs after the test results have been received, for specific evaluation of the underlying cause for the ALT or AST elevation and confirmatory laboratory testing.

A medical history focused on risk factors for liver injury (alcohol consumption, exposure to toxic agents, infections, medications and drug use including herbal remedies etc) should be obtained, evaluation of recent symptoms (Adverse events [AEs]) and physical examination should be done and all relevant information should be captured in appropriate electronic Case Report Form (eCRF) modules.

Confirmatory laboratory testing should be done and more frequent monitoring of liver tests should be initiated.

Patients who stop intake of IP

Patients with the following findings should immediately be contacted and instructed to stop intake of IP:

- ALT or AST > 5 x ULN
- ALT or AST >3 x ULN in combination with BIL >2 x ULN
- ALT or AST >3 x ULN with clinical signs or symptoms indicating liver dysfunction (such as nausea, fatigue, right upper quadrant pain or tenderness, fever, rash or eosinophilia).

The patients must be brought back to the clinic for an unscheduled visit without any delay, but not later than 72 hrs after the test results have been received, for specific evaluation of the underlying cause of the ALT or AST elevation and confirmatory laboratory testing.

A medical history focused on risk factors for liver injury (alcohol consumption, exposure to toxic agents, infections, medications and drug use including herbal remedies etc) should be obtained, evaluation of recent symptoms (AEs) and physical examination should be done and all relevant information should be captured in appropriate eCRF modules.

Confirmatory laboratory testing should be done and more frequent monitoring of liver tests should be initiated.

In addition, the following blood samples for differential diagnosis purposes should be taken in all patients who stop intake of IP:

- Liver function: INR
- Viral hepatitis: anti-HAV-IgM, HBsAg, anti-HBc-IgM, anti-HCV, HCV RNA, EBV VCA IgM + EBV-EBNA , anti-CMV-IgM
- Autoimmune hepatitis: ANA, AMA, SMA, IgG, IgM, IgA
- Hereditary disorders: S-Iron and TIBC, S-Ferritin, ceruloplasmin, α1-antitrypsin.

Imaging techniques and additional examinations can be done if there is a clinical indication as judged by the investigator (eg, ultrasound, CT, liver biopsy). The results of all testing should be entered in the appropriate eCRF modules. It is important that every effort is made to find an explanation for the elevated liver enzymes.

Clinical Study Protocol Appendix F

Drug Substance	AZD1656
Study Code	D1020C00016
Edition Number	1

Appendix F
Serum Creatinine Exclusion

1. SERUM CREATININE EXCLUSION

Table 1 (Serum creatinine (Scr) in mg/dL) is derived from combining:

Serum creatinine values based on subject's age, gender and race which would exclude the subject from the study because the GFR (as calculated by Simplified Modification in Diet and Renal Disease (MDRD) formula (Rigalleau et al 2005, Levey et al 1999)) is ≤ 60 mL/min/1.73 m^2.

Table 1 Serum creatinine

Age (years)	Male Scr (mg/dL)	Female Scr (mg/dL)
18	1.5	1.3
19	1.5	1.3
20	1.5	1.3
21	1.5	1.2
22	1.5	1.2
23	1.5	1.2
24	1.5	1.2
25	1.5	1.2
26	1.5	1.2
27	1.5	1.2
28	1.5	1.2
29	1.5	1.2
30	1.5	1.2
31	1.5	1.2
32	1.5	1.2
33	1.5	1.2
34	1.5	1.1
35	1.5	1.1
36	1.5	1.1
37	1.5	1.1
38	1.4	1.1
39	1.4	1.1
40	1.4	1.1

Table 1 Serum creatinine

Age (years)	Male Scr (mg/dL)	Female Scr (mg/dL)
41	1.4	1.1
42	1.4	1.1
43	1.4	1.1
44	1.4	1.1
45	1.4	1.1
46	1.4	1.1
47	1.4	1.1
48	1.4	1.1
49	1.4	1.1
50	1.4	1.1
51	1.4	1.1
52	1.4	1.1
53	1.4	1.1
54	1.4	1.1
55	1.4	1.1
56	1.4	1.1
57	1.3	1.1
58	1.3	1.1
59	1.3	1.0
60	1.3	1.0
61	1.3	1.0
62	1.3	1.0
63	1.3	1.0
64	1.3	1.0
65	1.3	1.0
66	1.3	1.0
67	1.3	1.0
68	1.3	1.0
69	1.3	1.0
70	1.3	1.0

Table 1 Serum creatinine

Age (years)	Male Scr (mg/dL)	Female Scr (mg/dL)
71	1.3	1.0
72	1.3	1.0
73	1.3	1.0
74	1.3	1.0
75	1.3	1.0
76	1.3	1.0
77	1.3	1.0
78	1.3	1.0
79	1.3	1.0

2. REFERENCE

Rigalleau et al 2005
Rigalleau V, Lasseur C, Perlemoine C, et al. Estimation of Glomerular Filtration Rate in Diabetic Subjects: Cockcroft formula or modification of diet in renal disease study equation. Diabetes Care 2005; 28(4):838-843.

Levey et al 1999
Levey AS, Bosch JP, Breyer J, et al. A more accurate method to estimate glomerular filtration rate from serum Creatinine: A new Prediction Equation. Ann Int Med 1999; 130 (6):461-470.

Clinical Study Protocol: Supplement A

Drug Substance	AZD1656
Study Code	D1020C00016
Supplement Edition Number	1
Supplement	

Supplement A
Investigators and Study Administrative Structure