AstraZeneca

Revised Clinical Study Protocol

Drug Substance	Saxagliptin
Study Code	D1680L00006
Edition Number	1
Date	

A 24-week, Multicentre, Randomised, Double-Blind, Placebo-Controlled Phase IIIb Study to Evaluate the Efficacy and Safety of Saxagliptin in Combination with Metformin and Sulfonylurea in Subjects with Type 2 Diabetes who have Inadequate Glycaemic Control with the Combination of Metformin and Sulfonylurea

Sponsor:

AstraZeneca Singapore Pte Ltd

AstraZeneca Research and Development site representative

The following Amendment(s) and Administrative Changes are included in this revised protocol:

Amendment No.	Date of Amendment	Local Amendment No:	Date of Local Amendment
1			

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

AstraZeneca

PROTOCOL SYNOPSIS

A 24-week, Multicentre, Randomised, Double-blind, Placebo-Controlled Phase IIIb Study to Evaluate the Efficacy and Safety of Saxagliptin in Combination with Metformin and Sulfonylurea in Subjects with Type 2 Diabetes who have Inadequate Glycaemic Control with the Combination of Metformin and Sulfonylurea

International Co-ordinating Investigator or Principal Investigator or National Co-ordinating Investigator

The International Co-ordinating Investigator will be chosen for particular active contribution, active recruitment and for signing the Clinical Study Report.

Study centre(s) and number of subjects planned

Approximately 30 study centres will take part in the study across Australia, Korea, India, Thailand and the United Kingdom. Approximately 275 patients will be enrolled to reach the target of 250 randomised patients.

Study period		Phase of development
Estimated date of first subject enrolled	Q2 2010	IIIb
Estimated date of last subject completed	Q2 2011	IIIb

Objectives

Primary efficacy: The primary efficacy analysis is to compare the difference between saxagliptin 5 mg once daily (od) plus metformin plus sulfonylurea versus placebo plus metformin plus sulfonylurea, in patients with type 2 diabetes, as determined by the change in HbA_{1c} levels from Baseline to Week 24/Endpoint.

Secondary efficacy: 1) Compare change in fasting plasma glucose (FPG) from Baseline to Week 24/Endpoint between the treatment groups; 2) Compare change in postprandial glucose (PPG) (measured 2 hours after breakfast) from Baseline to Week 24/Endpoint between the treatment groups; 3) Compare proportion of patients achieving a therapeutic glycaemic response at Week 24/Endpoint defined as HbA_{1c} <7% between the treatment groups.

Safety: Safety and tolerability will be evaluated by assessment of adverse events (AEs), including hypoglycemic events; laboratory values; changes in renal function by estimation of creatinine clearance (CrCl) (Cockcroft Gault) and urinary albumin:creatinine ratio;

electrocardiogram (ECG); vital signs (pulse and blood pressure); body weight and physical examination.

Other:

1) Change in total cholesterol (TC), low-density lipoprotein-cholesterol (LDL-C), high-density lipoprotein-cholesterol (HDL-C) and triglycerides (TG), from Baseline to Week 24/Endpoint; 2) Change from Baseline to Week 24/Endpoint in the patient reported EuroQoL-5 Dimension (EQ-5D) questionnaire.

Study design

Type 2 diabetes subjects who have inadequate glycaemic control (HbA_{1c} ≥7% and ≤10%), currently on a stable combined dose of metformin extended release (XR) or immediate release (IR) (at maximum tolerated dose [MTD] with minimum dose for enrolment being 1500 mg) and sulfonylurea (at MTD with minimum dose for enrolment being ≥50% of maximum recommended dose) for at least 8 weeks prior to Visit 1, are eligible for enrolment.

Patients will be enrolled and screened in a 2 week period to confirm HbA_{1c} and other eligibility criteria, and undergo diet and exercise counselling. Following screening, patients meeting all the inclusion criteria and none of the exclusion criteria will be randomised to double-blind saxagliptin 5 mg or placebo, as well as diet and exercise counselling for the duration of the study (24 weeks). Following randomisation, patients will continue receiving metformin and sulfonylurea at doses ascertained at enrolment. Saxagliptin/placebo therapy will be administered as add-on therapy.

Target subject population

Males and females, 18 years or over, with type 2 diabetes who have uncontrolled glycaemia (HbA1c levels ≥7% and ≤10%), on a stable combined dose of metformin extended release (XR) or immediate release (IR) (at MTD, with minimum dose for enrolment being 1500mg) and sulfonylurea (at MTD, with minimum dose for enrolment being ≥ 50% of the maximum recommended dose) for at least 8 weeks prior to Visit 1, are eligible for enrolment.

Note: Patients must be on MTD of metformin IR or XR (minimum dose for enrolment is 1500 mg) and on MTD of sulfonylurea (minimum dose for enrolment is 50% of maximum recommended dose).

Investigational product, dosage and mode of administration

Investigational products of the study will be:

- Double-blind saxagliptin 5 mg tablets, administered orally once daily.
- Double-blind matching placebo for saxagliptin 5mg tablets, administered orally once daily

Duration of treatment

The double-blind treatment period will be 24 weeks. Patients will have a 2-week screening period with diet and exercise counselling before the day of randomisation.

Outcome variables:

Primary:

- Change in HbA_{1c} from Baseline to Week 24/Endpoint

Secondary, efficacy:

- Change in FPG from Baseline to Week 24/Endpoint
- Change in PPG (measured 2 hours after breakfast) from Baseline to Week 24/Endpoint
- Proportion of patients achieving a therapeutic glycaemic response at Week 24/Endpoint defined as HbA_{1c} <7%

Secondary, safety and tolerability:

- Safety and tolerability evaluated by assessment of AEs, laboratory values, ECG, vital signs (pulse, blood pressure), body weight, height and physical examination
- Incidences of hypoglycaemic events
- Changes in renal function as measured by CrCl and urinary albumin:creatinine ratio

Other endpoints:

- To compare change in total cholesterol (TC), low-density lipoprotein-cholesterol (LDL-C), high-density lipoprotein-cholesterol (HDL-C) and triglycerides (TG), from Baseline to Week 24/Endpoint
- To compare patient related endpoints using the EQ-5D questionnaire.

Statistical methods

The primary efficacy analysis to compare the difference between saxagliptin and placebo, in patients with type 2 diabetes, as determined by the change in HbA_{1c} levels from Baseline to Week 24/Endpoint, will be performed on the Full Analysis set (FAS) using an analysis of

covariance model with factors for treatment and country as well as Baseline HbA_{1c} as a covariate.

Missing Week 24 values will be replaced using the last observation carried forward (LOCF) after baseline. The LOCF approach means that Week 24/Endpoint analyses will be based on measurements available at Week 24 or the last post-baseline measurement prior to week 24 if no measurement available at the Week 24 timepoint.

A total of 240 patients randomised and treated (120 patients per treatment group), are needed to provide approximately 80% power at a two-sided significance level of 0.05, assuming a true difference of 0.40% and a standard deviation of 1.1%.

Assuming a 4% drop-out rate of patients who are randomised, but do not return for a post-baseline assessment, a total of 250 patients are required to be randomised. Assuming a 10% screen fail rate of patients who are consented and enrolled but are not eligible for randomisation, a total of 275 patients are planned for screening/enrolment.

TABLE OF CONTENTS PAGE

LIST OF TABLES

LIST OF FIGURES

LIST OF APPENDICES

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
ANCOVA	Analysis of covariance
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
AUC	Area under the concentration-time curve
bHCG	Beta human chorionic gonadotropin
BMI	Body mass index
BMS	Bristol-Myers Squibb
BUN	Blood urea nitrogen
CK	Creatine kinase
C_{max}	Maximum plasma concentration of investigational product
CPMP	Committee for Proprietary Medicinal Products (of the European Union)
CrCl	Creatinine clearance
CRO	Contract Research Organisation
CSA	Clinical Study Agreement
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Event
CYP3A4	Cytochrome P450 3A4
DHSI	Digestive Health Status Instrument
DPP4	Dipeptidyl peptidase-4
DTSQ	Diabetes Treatment Satisfaction Questionnaire
EC	Ethics Committee, synonymous to Institutional Review Board (IRB) and Independent Ethics Committee (IEC)
ECG	Electrocardiogram
eCRF	Electronic Case Report Form (paper)
EQ-5D	Euro Quality of Life-5 Dimension
EU	European Union
FA	Full Analysis
FDA	Food and Drug Administration

Abbreviation or special term	Explanation
FPG	Fasting plasma glucose
FSH	Follicle stimulating hormone
GCP	Good Clinical Practice
GERD	Gastroesophageal reflux disease
GFR	Glomerular filtration rate
GLP-1	Glucagon-like peptide-1
GMP	Good Manufacturing Practice
HbA_{1c}	Glycosylated haemoglobin A_{1c}
HDL-C	High-density lipoprotein-cholesterol
HLGT	Higher Level Group Term
HLT	High Level Term
HRT	Hormone replacement therapy
IBS	Irritable bowel syndrome
ICH	International Conference on Harmonisation
International Co-ordinating Investigator	If a study is conducted in several countries the International Co-ordinating Investigator is the investigator co-ordinating the investigators and/or activities internationally.
IR	Immediate release
IVRS	Interactive Voice Response System
LDL-C	Low-density lipoprotein-cholesterol
LLT	Lowest level term
LOCF	Last Observation Carried Forward
Max	Maximum
MDRD	Modification of diet in renal disease
MedDRA	Medical Dictionary for Regulatory Activities
Min	Minimum
MR	Modified release
NOAEL	No-observed-adverse-effect-level
OAE	Other significant adverse event (see definition in Section 11.2.2)
od	Once daily
OGTT	Oral glucose tolerance testing
PP	Per Protocol
PPG	Postprandial glucose
PRO	Patient reported outcomes

Abbreviation or special term	Explanation
PT	Preferred Term
RHD	Recommended human dose
RUCD	Recommended usual clinical dose
SAE	Serious adverse event (see definition in Section 6.4.2).
SAP	Statistical Analysis Plan
SCr	Serum creatinine
SD	Standard deviation
SDTL	Study Delivery Team Leader
SDV	Source data verification
SOC	System Organ Class
SPC	Summary of Product Characteristics
T_4	Levothyroxine
TC	Total cholesterol
TEAE	Treatment-emergent adverse event
TG	Triglycerides
TSH	Thyroid stimulating hormone
ULN	Upper limit of normal
WBDC	Web Based Data Capture
WHO-DD	World Health Organisation Drug Dictionary
XR	Extended release
ZDF	Zucker diabetic fatty

1. INTRODUCTION

1.1 Background

Saxagliptin (BMS-477118) is a highly potent, selective, reversible, competitive inhibitor of human dipeptidyl peptidase-4 (DPP4) and exhibits enzymological properties consistent with long-acting pharmacodynamics. Its major metabolite, BMS-510849, is also a DPP4 inhibitor approximately 2-fold less potent than saxagliptin. Saxagliptin is being developed by Bristol-Myers Squibb (BMS) and AstraZeneca (AZ) for the treatment of type 2 diabetes mellitus.

1.1.1 Nonclinical pharmacokinetics / pharmacodynamics / metabolism

Oral saxagliptin effectively increases the levels of active glucagon-like peptide-1 (GLP-1) elicited by a glucose challenge in normal rats. In insulin-resistant Zucker fa/fa rats and ob/ob mice, saxagliptin significantly enhanced plasma glucose clearance and insulin secretion during oral glucose tolerance testing (OGTT). In chronic dosing studies using the progressively Zucker diabetic fatty (ZDF) rat model, saxagliptin delayed development of fasting hyperglycaemia and significantly improved glucose excursions during OGTT. The metabolism of saxagliptin in human liver microsomes was primarily mediated by cytochrome P450 3A4 (CYP3A4). Renal clearance was the major route of elimination for saxagliptin and BMS-510849 in all species studied.

1.1.2 Nonclinical toxicology

Saxagliptin has been well characterised in a comprehensive drug-safety programme, demonstrating no mutagenicity (based on weight of evidence), carcinogenicity, immunotoxicity, teratogenicity, or effects on fertility or safety pharmacology assessments. In dogs, saxagliptin primarily produced gastrointestinal toxicity. Following 12 months of dosing, the no-observed-adverse-effect-level (NOAEL) is 4-fold and 2-fold (based on the area under the concentration-time curve [AUC]) for saxagliptin and its major metabolite (BMS-510849), respectively, compared to a 5 mg recommended human dose (RHD). In cynomolgus monkeys, major target organ changes included reversible erosive and/or ulcerative skin lesions with scab formation and reversible multi-tissue mononuclear-cell infiltrates. The AUC at the NOAEL for these changes was 1-fold to 3-fold the RHD for saxagliptin and BMS-510849. Findings from these studies support the continued clinical development of saxagliptin.

1.1.3 Clinical pharmacology

In clinical pharmacology studies, 620 subjects have received at least one single oral dose (1 mg to 400 mg) of saxagliptin. Saxagliptin is rapidly and completely absorbed after oral administration, with maximum plasma concentration usually attained within 2 hours after dosing. Approximately 24% and 36% of the dose was excreted into the urine as unchanged saxagliptin and BMS-510849, the major pharmacologically active metabolite, respectively.

Saxagliptin may be administered without regard to meals and no dosage adjustment is considered necessary in elderly subjects on the basis of age. Type 2 diabetes, body mass index (BMI), gender, age, race, hepatic impairment, and mild renal insufficiency (creatinine clearance [CrCl] 50 mL/min to 80 mL/min) had no clinically meaningful effects on the pharmacokinetics of saxagliptin or BMS-510849. In subjects with moderate (CrCl 30 mL/min to 50 mL/min) and severe renal impairment (CrCl <30 mL/min), AUC values for saxagliptin and/or BMS-510849 were greater than 2-fold higher than the AUC values in healthy subjects.

Co-administration of saxagliptin with the following drugs had no meaningful effect on the pharmacokinetics of saxagliptin, BMS-510849, or the other drug tested: metformin, glyburide, pioglitazone, digoxin, or simvastatin. Co-administration of saxagliptin and ketoconazole or diltiazem dosed to steady-state resulted in up to 1.6-fold and 2.5-fold increase in saxagliptin maximum plasma concentration (C_{max}) and AUC (INF) values, respectively, and up to an 8-fold decrease in the exposure to BMS-510849 (Study CV181005). However, the systemic exposures to the total active moieties of saxagliptin (saxagliptin plus BMS-510849 corrected for relative differences in potency of DPP4 inhibition) were not meaningfully altered by diltiazem or ketoconazole. Co-administration of saxagliptin with gastric acid controllers such as aluminum and magnesium hydroxides plus simethicone, famotidine or omeprazole did not meaningfully alter the pharmacokinetics of saxagliptin or BMS-510849.

Single, daily oral doses of 1 mg to 400 mg saxagliptin potently inhibited DPP4 activity (>80% at doses ≥2.5 mg) in a dose-dependent manner whilst elevating active GLP-1 plasma concentrations (1.5-fold to 2.5-fold).

1.1.4 Efficacy

The results from the eight clinical studies in the saxagliptin Phase IIb and III programme in over 4600 subjects combined with the results from clinical pharmacology studies support the oral dose of saxagliptin 5 mg once daily (od) in a wide range of subjects with type 2 diabetes, as either monotherapy, add-on combination therapy with metformin, a thiazolidinedione, or a sulfonylurea, or initial combination therapy with metformin.

In the Phase IIb dose-ranging study, administration of saxagliptin 5 mg was associated with significant inhibition of plasma DPP4 activity at the trough of the dosing interval as well as clinically meaningful decreases in HbA_{1c}, fasting serum glucose and postprandial serum glucose. The results from the short-term periods of the Phase III studies confirmed clinically meaningful benefits of saxagliptin 5 mg on HbA_{1c}, as well as fasting plasma glucose (FPG), postprandial glucose, insulin, C-peptide, and glucagon levels. A greater percentage of subjects treated with saxagliptin achieved target glycaemic goals including HbA_{1c} levels <7% compared to subjects treated with placebo or active comparator. The saxagliptin 5 mg groups generally achieved greater reductions from Baseline in HbA_{1c} than the saxagliptin 2.5 mg groups. There was no consistent evidence for an incremental efficacy benefit for 10 mg saxagliptin beyond that seen for the 5 mg dose. Sustained reductions in HbA_{1c} relative to control were observed at all doses tested after 102 weeks of saxagliptin treatment in the monotherapy (CV181011) and add-on combination therapy with metformin (CV181014) studies.

Saxagliptin treatment consistently demonstrated a beneficial antihyperglycaemic effect across subgroups of demographic and baseline diabetic characteristics.

1.1.5 Safety

Saxagliptin administered orally was safe and well tolerated at doses of up to 400 mg od for 2 weeks, 100 mg od for 6 weeks, 40 mg od for 12 weeks, and at doses of 2.5, 5, and 10 mg od for up to 102 weeks. In an extensive Phase IIb/III programme, the majority of reported adverse events (AEs) were of mild intensity and did not require discontinuation of treatment. The safety profile was generally consistent when saxagliptin was given as monotherapy, as add-on combination treatment to metformin, sulfonylurea, or thiazolidinedione, and as initial therapy in combination with metformin. Although the rate of certain AEs was higher in subjects who received saxagliptin 10 mg compared with those who received 2.5 mg and 5 mg, saxagliptin 10 mg was also safe and well tolerated, providing a safety margin for the saxagliptin 5 mg dose.

Treatment with saxagliptin led to rates of hypoglycaemia that were generally similar compared to placebo. This is consistent with the mechanism of action of DPP4 inhibitors, which exert their insulinotropic effects on the β-cell in a glucose-dependent manner. In the add-on to sulfonylurea study, the rate of hypoglycaemia was numerically higher in subjects who received 2.5 mg or 5 mg of saxagliptin added on to an intermediate dose of glyburide compared with the up-titration of glyburide monotherapy plus placebo.

The frequency of skin-related AEs was generally comparable between subjects who received saxagliptin 5 mg and placebo. In non-clinical toxicology studies where saxagliptin was administered to cynomolgus monkeys, reversible erosive and/or ulcerative skin lesions with scab formation were observed. Overall, evaluation of the Phase III clinical data has not revealed any signals that correlate to the skin findings in the monkey.

The proportion of subjects with AEs of localised oedema, an event of special interest given reports of symptomatic oedema of the hands and feet in subjects who received another member of the DPP4 inhibitor class, was generally similar in subjects who received saxagliptin and placebo with the exception of the add-on to thiazolidinedione study, where there was a higher rate of events constituting localised oedema compared to placebo in subjects treated with saxagliptin 5 mg. The majority of these events in the saxagliptin 5 mg plus thiazolidinedione group were for pedal oedema with no imbalance seen for events of hand oedema. Across the clinical programme, the majority of events of localised oedema were of mild to moderate intensity and did not lead to study discontinuation.

The frequency of investigator reported AEs of lymphopaenia was similar for subjects who received saxagliptin and placebo. Mean lymphocyte counts remained stable and within normal limits with daily dosing up to 102 weeks in duration. Overall, a small decrease in mean absolute lymphocyte count was observed at a dose of 5 mg saxagliptin and above.

At the saxagliptin 5 mg dose, the mean decrease was approximately 100 cells/μL relative to placebo (from baseline absolute lymphocyte count of approximately 2200 cells/μL), based on

a pooled analysis of the 5 placebo-controlled clinical studies including saxagliptin as monotherapy, and as add-on therapy to metformin, thiazolidinedione and sulfonylurea. While the clinical significance of the decreases in lymphocyte count relative to placebo is not known, the decreases were not associated with clinically relevant AEs.

Results from the Phase III clinical studies demonstrated no clinically meaningful or consistent effect on platelet counts. In the five pooled monotherapy and placebo-controlled combination studies, the frequencies of AEs in the System Organ Class (SOC) Infection and Infestations were comparable in the saxagliptin 2.5 mg, saxagliptin 5 mg, and placebo groups (36.4%, 35.9%, and 34.8% respectively); a higher frequency of AEs was observed in the saxagliptin 10 mg group (40.1%). There was no evidence for an association of saxagliptin treatment with an increased risk of elevated liver function tests or serum creatinine.

In the clinical pharmacology programme, results from a thorough QTc study at daily doses of saxagliptin up to 40 mg od and analyses from other studies at daily doses up to 400 mg od demonstrated an absence of an effect of saxagliptin and BMS-510849 on QTc interval in humans. There were no signs of renal toxicity (i.e., saxagliptin-related changes in serum creatinine or blood urea nitrogen) or hand/foot oedema identified in the saxagliptin clinical pharmacology programme.

For more information, please consult the Investigator's Brochure (Investigator's Brochure).

1.2 Research hypothesis

In subjects on metformin and sulfonylurea who have inadequate glycaemic control, adding saxagliptin 5 mg will more effectively reduce HbA_{1c} than the double-combination plus placebo, and will be well tolerated.

The hypothesis tested is that administration of saxagliptin 5 mg od added on to the maximum tolerated dose (MTD) of metformin in combination with the MTD of sulfonylurea will be more effective in improving glycaemic control, as determined by the change in the HbA_{1c} level from Baseline to Week 24, in patients with type 2 diabetes who have inadequate glycaemic control on the MTD of metformin in combination with MTD of sulfonylurea. The hypothesis was chosen to show a change in the efficacy (HbA_{1c}) and a larger percentage of patients at goal with the addition of saxagliptin to double-combination of metformin and sulfonylurea, with minimal side effects.

In the regulatory guidelines for type 2 diabetes studies (Committee for Proprietary Medicinal Products [CPMP] 2002), HbA_{1c} is the prescribed measure for the determination of glycaemic control and is therefore chosen as the primary variable.

1.3 Rationale for conducting this study

Uncontrolled diabetes patients are treated not by switching medications but by adding on therapies. Double-combination of metformin and sulfonylurea is highly common in Asia Pacific and the United Kingdom, with a high proportion of patients being uncontrolled

and needing a third drug. The addition of saxagliptin to the metformin and sulfonylurea combination could improve the control of diabetes.

There is an unmet need with the current pharmacological treatment of type 2 diabetes. Despite available drugs with different mechanisms of actions, many patients are not reaching glycaemic control goals. Some insulin secretagogues have significant side effects such as hypoglycaemia, weight gain and insulin resistance.

The purpose of this 24-week Phase IIIb clinical study is to determine whether the addition of saxagliptin to a double-combination of metformin and sulfonylurea will provide better glycaemic control, and to compare the safety and tolerability profiles of the two treatment groups (placebo versus saxagliptin as add on therapy to double-combination of metformin and sulfonylurea), in patients with type 2 diabetes.

1.4 Benefit/risk and ethical assessment

For an overall risk/benefit assessment of saxagliptin, see the Investigator's Brochure (Investigator's Brochure).

A total of 5346 subjects were evaluated in the saxagliptin Phase I to III clinical development programme, including 423 in a Phase IIb dose-ranging study and 4250 subjects in Phase III studies. In the development programme, saxagliptin was studied at maximum daily doses of 400 mg (80-fold the Recommended Usual Clinical Dose [RUCD]) for up to 2 weeks, 100 mg (20-fold the RUCD) for up to 6 weeks, 40 mg (8-fold the RUCD) and 20 mg (4-fold the RUCD) for up to 12 weeks, and 10 mg (2-fold the RUCD) for up to 2 years. Saxagliptin doses of 2.5 mg and 5 mg have also been studied for up to 2 years. As of October 2008, the total number of subjects in the Phase IIb/III studies exposed to saxagliptin (2.5 mg, 5 mg, or 10 mg) for ≥50 weeks included 652 subjects treated with saxagliptin monotherapy, 902 subjects treated with saxagliptin in combination with metformin, 407 subjects treated with saxagliptin added on to sulfonylurea, and 275 subjects treated with saxagliptin added on to thiazolidinedione.

In summary, the safety and efficacy data collected to date from clinical studies in healthy volunteers and patients with type 2 diabetes indicate that the clinical safety and efficacy profile of saxagliptin support studies with 5 mg as the usual recommended dose. It is hypothesised that saxagliptin has a comparable safety and tolerability profile compared to metformin with regards to hypoglycaemic events. Studies on the long-term cardiovascular safety profile of saxagliptin are currently ongoing.

Increased incidence of gastrointestinal distress has previously been noted with metformin therapy.

The incidence of hypoglycemia was numerically higher for subjects who received saxagliptin 5 mg when added to an intermediate dose of SU compared with uptitration of SU monotherapy in study CV181040 (add-on combination therapy with glyburide in subjects who have inadequate glycaemic control on submaximal SU dose).

2. STUDY OBJECTIVES

2.1 Primary efficacy objective

The primary efficacy analysis is to compare the difference between saxagliptin 5 mg od plus metformin plus sulfonylurea versus placebo plus metformin plus sulfonylurea, in patients with type 2 diabetes, as determined by the change in HbA_{1c} levels from Baseline to Week 24/Endpoint.

2.2 Secondary efficacy objectives

- Compare change in fasting plasma glucose (FPG) from Baseline to Week 24/Endpoint between the treatment groups;
- Compare change in postprandial glucose (PPG) (measured 2 hours after breakfast) from Baseline to Week 24/Endpoint between the treatment groups;
- Compare proportion of patients achieving a therapeutic glycaemic response at Week 24/Endpoint defined as HbA_{1c} <7% between the treatment groups.

2.3 Safety objectives

Safety and tolerability will be evaluated by assessment of:

- All AEs, including hypoglycaemic events
- Laboratory values
- Changes in renal function by estimation of CrCl (Cockcroft Gault) and urinary albumin:creatinine ratio
- 12-Lead electrocardiogram (ECG)
- Vital signs (pulse and blood pressure)
- Body weight
- Physical examination

2.4 Other objectives

- To compare change in total cholesterol (TC), low-density lipoprotein-cholesterol (LDL-C), high-density lipoprotein-cholesterol (HDL-C) and triglycerides (TG), from Baseline to Week 24/Endpoint
- To compare patient related endpoints using the EuroQoL-5 Dimension (EQ-5D) questionnaire.

3. STUDY PLAN AND PROCEDURES

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

3.1 Overall study design and flow chart

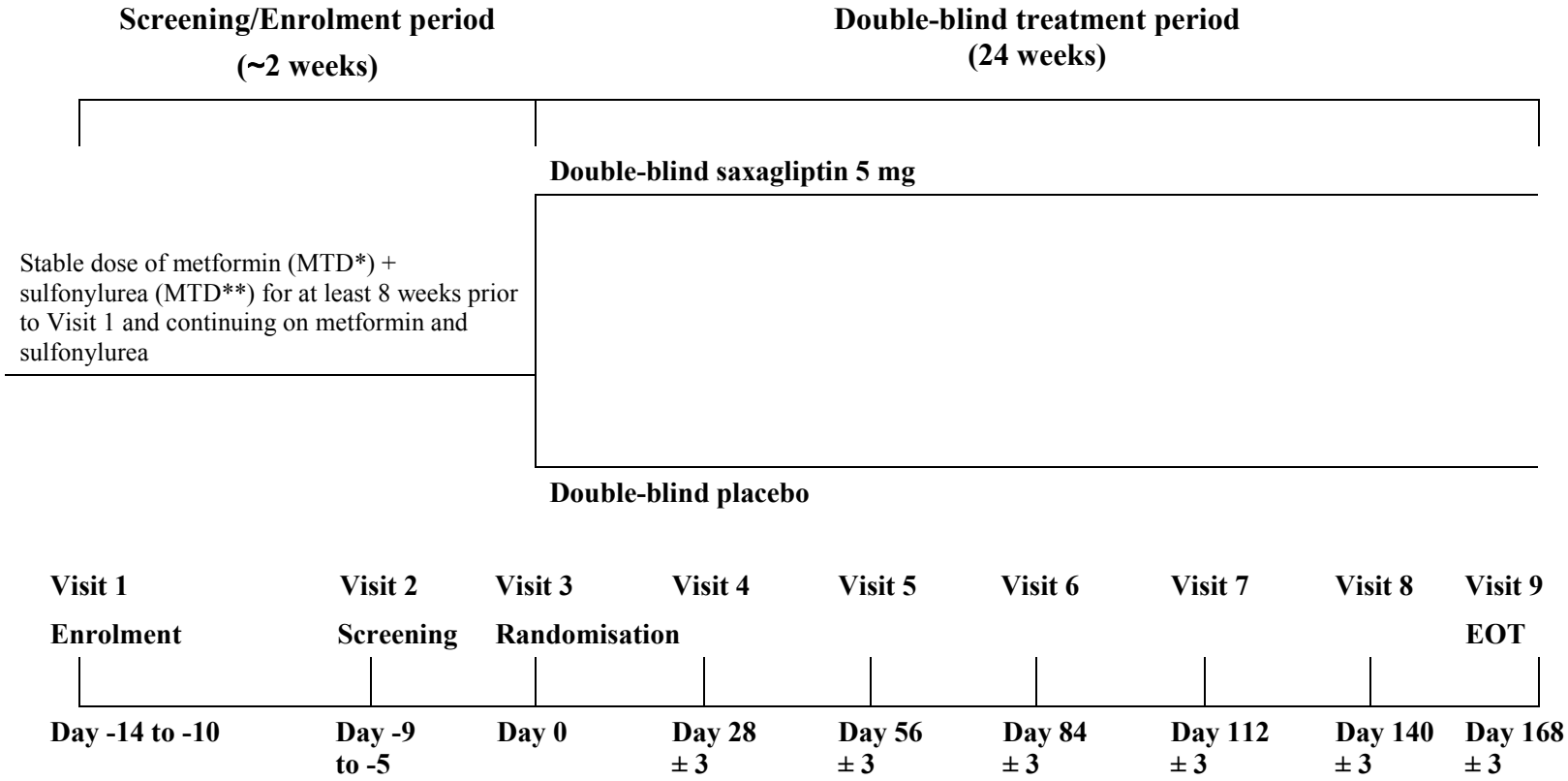
The following information relates to the key elements of the study design and where appropriate, the rationale behind their inclusion.

This study is a 24-week, multicentre, randomised, parallel-group, double-blind, placebo-controlled Phase IIIb study to evaluate the efficacy and safety of saxagliptin as add-on therapy to a stable metformin dose plus sulfonylurea compared to placebo as add-on therapy to a stable metformin dose plus sulfonylurea in patients with type 2 diabetes who have inadequate glycaemic control (HbA1c ≥7% and ≤10%). Patients should be on a stable combined dose of metformin extended release (XR) or immediate release (IR) (at MTD, with minimum dose for enrolment being 1500mg) and sulfonylurea (at MTD, with minimum dose for enrolment being ≥50% of the maximum recommended dose) for at least 8 weeks prior to Visit 1.

This study will be conducted in the Asia Pacific region and the United Kingdom with a recruitment period of approximately 6 months. Approximately 275 patients need to be enrolled in order to reach the target of 250 randomised patients (males and females ≥18 years old with type 2 diabetes). The Overall Study Flow is presented in Figure 1. The Study Plan is presented in Table 1 and specifies the number, timing and routine assessments for the planned visits.

In order to minimise the number of screening failures entering Visit 2 patients will be pre-screened for HbA_{1c} – at Visit 1 (14 days prior to randomisation). Patients whose HbA_{1c} is ≥7% and ≤10%, as confirmed by central laboratory, will undertake safety and other assessments at Visit 2 (7 days prior to randomisation) to confirm remaining eligibility criteria. Diet and exercise counselling will be provided at Visit 2 and again at randomisation. An Informed Consent Form based on all applicable regulatory requirements and laws will be provided to the patients and the study-related procedures and assessments explained. The Informed Consent Form must be signed before any study-related procedures or assessments are performed (e.g. collection of the blood sample for determination of HbA_{1c} at the central laboratory). Values outside the requested HbA_{1c} range is one of the main screening failure reasons and discrepancies between locally and centrally determined values are well known. All patients who are screened should be listed on a patient screening log.

Figure 1 Study flow chart for screening, enrolment period and double-blind treatment period



MTD: Maximum tolerated dose

* Minimum dose of metformin for enrolment = 1500 mg

** Minimum dose for sulfonylurea for enrolment is 50% of the maximum recommended dose:

Note: Patients will continue taking metformin and sulfonylurea at doses ascertained at enrolment, during the double-blind treatment period. Saxagliptin and Placebo will be administered as add-on therapy.

In this study, each patient will be enrolled on a stable combined dose of metformin XR or IR (MTD, with minimum dose for enrolment being 1500mg) and sulfonylurea (MTD, with minimum dose for enrolment being ≥50% of the maximum recommended dose) for at least 8 weeks prior to Visit 1.

.Note: Patients must be on MTD of metformin IR or XR (minimum dose for enrolment being 1500 mg) and on MTD of sulfonylurea (minimum dose for enrolment being 50% of maximum recommended dose).

Following Informed Consent, patients will be pre-screened for HbA_{1c} – at Visit 1, within 14 days prior to randomisation. Patients whose HbA_{1c} is ≥7% and ≤10%, as confirmed by central laboratory, will undertake safety and other assessments at Visit 2 (Day -7) to confirm remaining eligibility criteria. Patients who meet all of the inclusion criteria and none of the exclusion criteria will be randomised at Visit 3 and will commence the 24-week double-blind treatment period.

During the 24-week double-blind treatment period of the study, patients will still receive metformin and sulfonylurea at the dose ascertained during enrolment. In addition, patients will be randomised, at Visit 3, to receive the following:

- Double-blind saxagliptin 5 mg, orally, od or
- Double-blind matching placebo orally, od.

The study will consist of two periods:

Screening/enrolment period

Patients with type 2 diabetes who have inadequate glycaemic control (HbA1c ≥7% and ≤10%) and are currently on a stable combined dose of metformin XR or IR (MTD) and sulfonylurea (MTD) for at least 8 weeks prior to Visit 1 are eligible for enrolment. Blood samples for assessment of inclusion and exclusion criteria will be taken at Visit 1 and Visit 2 and assessed at the central laboratory before randomisation

Randomisation and double-blind treatment period

Patients with HbA_{1c} ≥7% and ≤10%, as confirmed by the central laboratory and who meet all the inclusion and none of the exclusion criteria, will be randomised (1:1) at Visit 3 to one of the following two treatment groups:

- Double-blind saxagliptin (5 mg od) or
- Double-blind matching placebo

At Visit 3, either one tablet of double-blind 5 mg saxagliptin or a matching placebo tablet will be added to the metformin and sulfonylurea (same dose as being used at Visit 1) treatment.

The patient will return every 4 weeks (Visit 4 to Visit 9), and blood glucose measurements made by the patient since the last visit, the gastrointestinal tolerability and the FPG value (performed at the central laboratory) will be assessed.

Matching placebo tablets for saxagliptin will be given as appropriate for the 24-week double-blind treatment period of the study.

Fasting plasma glucose will be measured at the central laboratory every 4 weeks during the double-blind treatment period. The metformin and sulfonylurea doses must remain constant during the 24-week double-blind treatment period (Visit 3 to Visit 9) to ensure a steady state effect of the HbA_{1c} which is the primary endpoint of the study. Sulfonylurea may be down-titrated once in the case of major hypoglycaemic event or recurring minor hypoglycaemic events. (Refer to Section 5.8). Titration (up or down) of study medication during the treatment period (Visit 3 to Visit 9) is prohibited. Blood samples for the assessment of the glycaemic parameters (based on results from the central laboratory) will be taken at each visit to determine if criteria for discontinuation of the investigational product are met. The patients will be instructed to monitor their fasting blood glucose levels at least every other day and to register the values associated with hypoglycaemic events into their patient diary.

During the double-blind treatment period, dietary and lifestyle modification will be re-inforced.

Finally, randomised patients who do not complete the study should complete the procedures described for Visit 9 (End of Study Visit).

Table 1 Study plan for screening, enrolment period and double-blind treatment period

Study period	**Screening / Enrolment**		**Double-blind treatment period**						
Visit label	**Enrolment**	**Screening**	**Randomisation**						
Visit number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9a**
Study Week	**-2**	**-1**	**1**	**4**	**8**	**12**	**16**	**20**	**24**
Study Day	**-14 to -10**	**-9 to -5**	**0**	**28**	**56**	**84**	**112**	**140**	**168**
Visit Window (No. days relative time Visit 3)		**-**		**28±3**	**56±3**	**84±3**	**112±3**	**140±3**	**168±3**
Informed consent	X								
Blood sample for HbA1c	X		X	X	X	X	X	X	X
Demography and medical history		X							
Weight		X	X	X	X	X	X	X	X
Height		X							
Waist circumference			X						X
Inclusion/exclusion criteria	X	X	X						
Physical examination		X							X
Brief physical examination			X	X	X	X	X	X	
Vital signs		X	X	X	X	X	X	X	X
12-lead ECG			X						X
Concomitant medication		X	X	X	X	X	X	X	X
Laboratory assessmentsb		X	X	X	X	X	X	X	X
Pregnancy testc		X	X	X	X	X	X	X	X

Study period	**Screening / Enrolment**		**Double-blind treatment period**						
Visit label	**Enrolment**	**Screening**	**Randomisation**						
Visit number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9a**
Study Week	**-2**	**-1**	**1**	**4**	**8**	**12**	**16**	**20**	**24**
Study Day	**-14 to -10**	**-9 to -5**	**0**	**28**	**56**	**84**	**112**	**140**	**168**
Visit Window (No. days relative time Visit 3)		**-**		**28±3**	**56±3**	**84±3**	**112±3**	**140±3**	**168±3**
Dispense/Return investigational products			X	X	X	X	X	X	X
Dispense/Return glucometer and/or supplies/provide instruction		X	X	X	X	X	X	X	X
Dispense patient diary		X	X	X	X	X	X	X	
Patient diary review for hypoglycaemic events/check glucose values in glucometer			X	X	X	X	X	X	X
Patient reported outcome questionnaired			X						X
Adverse events (AEs)	X	X	X	X	X	X	X	X	X
Drug accountability			X	X	X	X	X	X	X

a. Randomised patients who do not complete the study should complete the procedures described for the end of the double-blind treatment period (Visit 9 [End of Study Visit]).
b. Specification of laboratory parameters is presented in Section 6.3.1 (efficacy) and Section 6.4.5 (safety).
c. Pregnancy test will be performed on all women of childbearing potential.
d. Patient reported outcome questionnaire: Euro Quality of Life-5 Dimension (EQ-5D).

3.2 Rationale for study design, doses and control groups

3.2.1 Study design and regulatory requirement

The purpose of the study is to investigate if treatment with saxagliptin as add-on therapy to a stable combined treatment of metformin and sulfonylurea will be beneficial for patients with type 2 diabetes as compared to placebo in combination with the metformin and sulfonylurea treatment. This Clinical Study Protocol incorporates the main features of the Committee for Proprietary Medicinal Products' guidance for investigations of diabetes (CPMP 2002).

The study will be a double-blind design, to minimise the risk of bias in either direction.

3.2.2 Study doses and control groups

Many patients with type 2 diabetes do not reach glycaemic control goals with a stable combined dose of metformin and sulfonylurea. Uncontrolled diabetes patients are not treated by switching medications but by adding on therapies. The addition of a glucose-lowering agent with a different mechanism of action might show benefits, but might result in gastrointestinal tolerability issues. Double-combination of metformin and sulfonylurea is highly common in Asia Pacific and the United Kingdom, with a high proportion of patients being uncontrolled and needing a third drug. The patients must be on a stable combined treatment of metformin (MTD, with minimum dose being 1500mg) plus sulfonylurea (MTD, with minimum dose at least 50% of the maximum recommended dose) for at least 8 weeks prior to Visit 1.

The addition of saxagliptin to the metformin and sulfonylurea combination could improve control of type 2 diabetes. The dose of saxagliptin used in the study is 5 mg as this is the recommended dose in patients with a CrCl >60 ml/min. The dose of 5 mg was generally associated with maximal efficacy in Phase II and III clinical studies evaluating doses of saxagliptin in the range of 2.5 mg to 40 mg as monotherapy in drug-naive patients with type 2 diabetes. In those studies, maximal decrease in both HbA_{1c} as well as in FPG was seen with 5 mg of saxagliptin. Comparable decreases were seen with 5 mg, 10 mg, 20 mg, and 40 mg saxagliptin.

In the Phase IIb dose-ranging study, administration of saxagliptin 5 mg was associated with significant inhibition of plasma DPP4 activity at the trough of the dosing interval as well as clinically meaningful decreases in HbA_{1c}, FPG and postprandial glucose. The results from the short-term periods of the Phase III studies confirmed clinically meaningful benefits of saxagliptin 5 mg on HbA_{1c}, as well as FPG, postprandial glucose, insulin, C-peptide, and glucagon levels. A greater percentage of subjects treated with saxagliptin achieved target glycaemic goals including HbA_{1c} levels <7%, compared to subjects treated with placebo or an active comparator. The saxagliptin 5 mg groups generally achieved greater reductions from Baseline in HbA_{1c} than the saxagliptin 2.5 mg groups. There was no consistent evidence for an incremental efficacy benefit for 10 mg saxagliptin beyond that seen for the 5 mg dose. In the monotherapy (CV181011) and add-on combination therapy with metformin (CV181014) studies, where data was available for up to 102 weeks, treatment with saxagliptin, at all doses tested, produced sustained reductions in HbA_{1c} relative to control.

3.2.3 Study duration

Patients will be enrolled at Visit 1 (14 days prior to randomisation) and will have HbA_{1c} assessed. Patients with HbA_{1c} ≥7% and ≤10%, as confirmed by the central laboratory, will undergo safety and other assessments at Visit 2 (7 days prior to randomisation) to confirm remaining eligibility criteria before being randomised at Visit 3. The double-blind treatment period is 24 weeks to allow for an optimal dosing period.

Patients included in the study will receive investigational product for 24 weeks as this is usually the case with studies on type 2 diabetes. This duration is required to obtain a steady-state of the HbA_{1c} endpoint as it is a reflection of the glucose control over the past 3 months.

3.2.4 Choice of outcome variables

The HbA_{1c} is the prescribed measure for determination of glycaemic control in a diabetes study and has therefore been chosen as the primary variable. This variable is also recommended in regulatory diabetes guidelines. As a member of DPP4 inhibitors, saxagliptin leads to enhanced glucose dependent insulin secretion with a low risk of hypoglycaemia and few gastrointestinal adverse effects.

3.2.5 Choice of study population

The study will be performed in Asia Pacific and the United Kingdom and the population will be selected in such a manner to balance demands on representation of the future patient population and limit bias caused by confounding factors. .

The HbA_{1c} inclusion criterion at randomisation was selected to include patients with a wide range of glycaemic control. The lower bound of this interval (ie, 7.0%) reflects the most recent ADA and EASD treatment guidelines (ADA 2009; Nathan et al 2009). Although other guidelines recommend treatment to lower HbA_{1c} targets, the results of recent studies suggest that these stricter targets may not be appropriate for all patients. The upper limit of this interval (ie, 10.0%) was chosen because insulin is generally the treatment of choice for patients with HbA_{1c} values above this level. Higher HbA_{1c} levels reflect hyperglycaemia which in the long run exposes patients with diabetes to a very high risk of developing micro- and macrovascular complications. The reduction in HbA_{1c} is therefore chosen as a primary efficacy endpoint.

The limitation regarding patients with renal impairment is based on relative contraindications for treatment with metformin.

The purpose of the remaining inclusion and exclusion criteria is to limit confounding factors that would complicate the interpretation of the results (e.g., corticosteroid-induced type 2 diabetes, haemoglobinopathies that would interfere with the HbA_{1c} analyses) or to exclude patients whose safety could be compromised by participation in the study.

4. SUBJECT SELECTION CRITERIA

Patient population should be selected without bias.

Investigators should keep a record, namely, 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 all the following criteria:

1. Provision of written informed consent prior to the performance of any study-related procedures.

2. Males and females who are ≥18 years of age at the time of obtaining consent at Visit 1.

3. Clinical diagnosis of type 2 diabetes with uncontrolled glycaemia in spite of being on the combination of metformin IR or XR (MTD, minimum dose for enrolment being 1500mg) plus sulfonylurea (at MTD, with minimum dose for enrolment being ≥50% of the maximum recommended dose) daily for at least 8 weeks prior to Visit 1.

4. HbA_{1c} ≥7% and ≤10% obtained at Visit 1 as confirmed by the central laboratory.

5. BMI ≤40 kg/m^2.

1. Females of childbearing potential must be using an adequate method of contraception to avoid pregnancy throughout the study and for up to 4 weeks after the study in such a manner that the risk of pregnancy is minimised, and have a negative urine pregnancy test at Visit 2 and each scheduled study visit thereafter.

   Definitions:

   - **Females of Child Bearing Potential** – women who have experienced menarche but who have not been permanently or surgically sterilised, are not postmenopausal and are capable of procreation.

   - **Females NOT of Child Bearing Potential** - women who have undergone successful surgical sterilisation (hysterectomy, bilateral tubal ligation or bilateral oophorectomy) or who are postmenopausal.

   - **Postmenopausal Women** – women will be considered postmenopausal if they have had amenorrhea ≥12 consecutive months; or women on hormone

replacement therapy (HRT) with documented serum follicle stimulating hormone (FSH) level >35 mIU/mL

4.2 Exclusion criteria

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

1. Any clinically significant abnormality identified on physical examination or laboratory tests that would compromise patient's safety or successful participation in the study as judged by the investigator.

2. Pregnant or breastfeeding females.

3. Symptoms of poorly controlled diabetes including but not limited to marked polyuria and polydipsia with more than 10% weight loss in the 3 months before Visit 1 or other signs and symptoms.

4. History of diabetic ketoacidosis or hyperosmolar non-ketotic coma.

5. Current or prior use within 3 months of Visit 1, of insulin, DPP4 inhibitor, GLP-1 analogues (exenatide or liraglutide), and/or other oral anti-diabetic agents (other than metformin and sulfonylurea)

6. Estimated CrCl <60 ml/min at Visit 2

7. Congestive heart failure defined as New York Heart association (NYHA) class III or IV (see Appendix D) and/or left ventricular ejection fraction of <40%.

8. Active liver disease and/or significant abnormal liver function define as aspartate aminotransferase (AST) >3 x the upper limit of normal (ULN) and/or alanine aminotransferase (ALT) >3 x ULN and/or bilirubin >2.0 mg/dL (> 34 µmol) at Visit 2.

9. Creatine kinase ≥10 x ULN at Visit 2.

10. Treatment with systemic glucocorticoids other than replacement therapy. Inhaled, local injected and topical use of glucocorticoids is allowed.

11. Treatment with CYP3A4 inducers, such as carbamazepine, dexamethasone, phenobarbital, phenytoin, rifampin and St. John's Wort, and/or potent CYP3A4/5 inhibitors, such as delavirdine, indinavir, nelfinavir, ritonavir, clarithromycin, itraconazole, ketoconazole (topical use is allowed), nefazodone, saquinavir and telithromycin.

12. Patients who could have a potential allergy to the investigational product or any of its formulation excipients.

13. Contraindications to therapy as outlined in the metformin and/or sulfonylurea package insert including conditions leading to an increased risk of hypoxemia and lactic acidosis.

14. History of haemoglobinopathies (sickle cell anaemia or thalassemias, sideroblastic anaemia).

15. History of alcohol abuse or illegal drug abuse within the past 12 months prior to Visit 1.

16. Involvement in the planning and conduct of the study (applies to both AstraZeneca and Bristol-Myers Squibb personnel or personnel at the study centre).

17. Participation in an interventional clinical study during the 30 days prior to Visit 1.

18. Donation of blood, plasma or platelets within the 3 months prior to Visit 1.

19. Individuals, in the opinion of the investigator, whose participation in this study may pose a significant risk to the patient and could render the patient unable to successfully complete the study.

20. Suspected or confirmed poor protocol or medication compliance as judged by the investigator.

21. Previous enrolment or randomisation in the present study.

Procedures for withdrawal of incorrectly enrolled subjects are provided in Section 5.3.

5. STUDY CONDUCT

5.1 Restrictions during the study

There are no restrictions on patients participating in this study with regards to diet, smoking or physical activity, other than the inclusion and exclusion criteria listed above. However, patients will be counselled on diet and exercise and should not donate blood, plasma or platelets during the study.

Information on restricted concomitant medications is provided in Sections 5.6.1 and 5.6.2.

5.2 Subject enrolment, randomisation and initiation of investigational product

5.2.1 Screening and enrolment

The Principal Investigator will:

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

2. Assign each potential patient a unique enrolment code, an E-code, consisting of country, study centre, and patient specific numbers.

3. Determine patient eligibility. See Sections 4.1 and 4.2.

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

If a patient has discontinued his/her participation in the study, then he/she cannot re-enter into the study.

5.2.2 Procedures for randomisation

Randomisation to investigational products (1:1) will be done via IWRS/IVRS at Visit 3 in balanced blocks in order to ensure approximate balance between the two treatment arms. The study plans to randomise 250 patients in a 1:1 ratio.

The IWRS/IVRS will sequentially allocate the investigational products through the AstraZeneca prepared randomisation scheme and provide the randomisation number and the appropriate Kit ID from Investigational Product Supply available at the study centre in such a way that probability of allocation to each treatment is balanced across country. The Randomisation numbers will be prepared by the global randomisation administrator at AstraZeneca and made available for IWRS/IVRS use.

The patient should always be provided medication with the Kit ID allocated by the IWRS/IVRS. If a patient at any time during the study conduct receives the incorrect randomised treatment, this must be corrected as soon as discovered. Until resolution, the patient should continue taking study medication, but at the latest until the next scheduled visit.

5.3 Procedures for handling subjects incorrectly enrolled or randomised or initiated on investigational product

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

Patients who are enrolled and fail to meet the inclusion/exclusion criteria, but are not yet randomised should be withdrawn from the study.

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

The AstraZeneca Study Delivery Team Physician is to ensure that all such decisions are appropriately documented. In situations where an agreement could not be reached, the administration of the investigational product should be discontinued.

5.4 Blinding and procedures for unblinding the study

5.4.1 Methods for ensuring blinding

The study treatment period will be double-blind to ensure the blinding of the investigational product during the 24-week double-blind treatment period of the study. The saxagliptin tablets and the matching placebo tablets will be identical in size, colour, smell, and taste and the packaging will be identical.

No member of the study delivery team at AstraZeneca or Bristol-Myers Squibb, personnel at the study centres or at any Contract Research Organisation (CRO) handling data will have access to the randomisation scheme during the conduct of the study. AstraZeneca personnel (or designee) generating the randomisation scheme, the Investigational Products Department at AstraZeneca or their designee, where the information is needed to package study medication, and the drug safety department at Bristol-Myers Squibb and AstraZeneca will be the exception. The information in the randomisation scheme must be kept from other personnel involved in the conduct of the study, and in a secure location until the end of the study.

5.4.2 Methods for unblinding the study

Individual treatment codes, indicating the treatment randomisation for each randomised patient, will be available to the investigator(s) and personnel who are independent to the study evaluation at the Patient Safety Department, AstraZeneca from the IVRS/IWRS. Routines for this will be described in the IVRS/IWRS user manual that will be provided to each centre.

The treatment code should not be broken except in medical emergencies when the appropriate management of the patient requires knowledge of the treatment randomisation. The investigator documents and reports the action to AstraZeneca, without revealing the treatment given to patient to the AstraZeneca staff.

AstraZeneca and Bristol-Myers Squibb 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 patient have been made and documented.

5.5 Treatments

5.5.1 Identity of investigational product(s)

The investigational product will be supplied by Bristol-Myers Squibb Pharmaceutical Research Institute. Investigational product will be packaged in bottles. The saxagliptin/placebo bottles will contain 35 tablets. The tablets may contain lactose, which

may cause discomfort in lactose-intolerant individuals. Primary packaging of the investigational product will be carried out by Bristol-Myers Squibb or their designess, or AstraZeneca or their designee in accordance with Good Manufacturing Practice (GMP).

Investigational product	Dosage form and strength	Manufacturer
Saxagliptin (double-blind)	Plain, yellow, biconvex, round, film coated tablet, 5 mg	Bristol-Myers Squibb
Placebo matching saxagliptin (double-blind)	Plain, yellow, biconvex, round, film coated tablet to match saxagliptin, 5 mg	Bristol-Myers Squibb

5.5.2 Doses and treatment regimens

During the screening period (Visit 1 to Visit 3) each patient will continue receiving a stable combined dose of metformin XR or IR and sulfonylurea at the dose ascertained during enrolment (Visit 1).

Patients will be randomised at Visit 3 to one of the following two treatment groups:

- Double-blind saxagliptin (5 mg od) as add-on therapy to metformin plus sulfonylurea (same dose as being used at Visit 1)

or

- Double-blind placebo matching saxagliptin as add-on therapy to metformin plus sulfonylurea (same dose as being used at Visit 1)

After the randomisation visit (Visit 3), either a double-blind tablet of saxagliptin 5 mg or placebo will be administered in the morning as add-on therapy to the metformin and sulfonylurea.

The patients will return every 4 weeks (Visits 4 to 9) for evaluation of the blood glucose measurements made by him/her since the last visit, the gastrointestinal tolerability and the FPG value (performed at the central laboratory at each visit).

The investigational product or matching placebo as well as metformin and sulfonylurea will be taken orally and together with meals, at approximately the same time of the day during the study period. The doses to be taken in the morning should not be taken before the scheduled visit but after the relevant laboratory specimens have been collected. The investigational products plus metformin and sulfonylurea will be taken at breakfast (standardised breakfast packs provided) which will be provided at the study centres during the scheduled visits. Patients should be instructed to abstain from all food and beverages for 10 hours prior to each scheduled visit; however, drinking water is allowed. In the morning prior to each scheduled visit, acceptable concomitant medications can be taken, but with water only.

The following investigational products and doses will be used during the double-blind treatment period:

- Double-blind saxagliptin oral tablets, 5 mg, od for the 24-week double-blind treatment period
- Matching oral placebo tablets for saxagliptin, 5 mg, od for the 24-week double-blind treatment period

Visit ID	No. of bottles to dispense of saxagliptin 5 mg or matching placebo[a]
Visit 1	N/A
Visit 2	N/A
Visit 3	1 bottle
Visit 4	1 bottle
Visit 5	1 bottle
Visit 6	1 bottle
Visit 7	1 bottle
Visit 8	1 bottle
Visit 9	N/A

[a] Each bottle contains 35 tablets.

5.5.3 Labelling

Labelling of the investigational product will be carried out by AstraZeneca in accordance with current Good Manufacturing Practice (GMP). Booklet labels or single panel 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 the local language if necessary.

The label will include the following information:

- Name of sponsor (AstraZeneca)
- Study drug dosage form, route of administration, and quantity of dosage units

- Study code
- Packaging Lot ID (to identify the contents and packaging operation)
- Enrolment code (will be added by the investigator when investigational product is dispensed)
- Kit ID
- Directions for use (For oral use)
- The name of the investigator, if applicable (will be added by the investigator when investigational product is dispensed)
- The period of use, such as expiry date
- Storage conditions
- "for clinical trial use only"
- "keep out of reach of children"

5.5.4 Storage

All investigational products should be kept in a secure place under appropriate storage conditions. The investigational product label on the bottle specifies the appropriate storage.

5.6 Concomitant and post-study treatment(s)

No post-study treatment will be provided.

5.6.1 General medication

Other medication than described in the Exclusion Criteria Section 4.2 and Discontinuation Criteria Section 5.8, which is considered necessary for the patient's safety and well-being (e.g., to treat illnesses or complaints that occur during the study), may be provided at the discretion of the investigators and recorded in the appropriate sections of the electronic Case Report Form (eCRF). The specific type of medication (trade or generic name), the indication for use, route of administration, total daily dose, start and end dates of medication administration and whether administration is ongoing, should be reported.

5.6.2 Prohibited and restricted medication

For prohibited and restricted medication, see Exclusion Criteria Section 4.2 and Discontinuation Criteria Section 5.8.

5.7 Treatment compliance

The administration of all medication (including all investigational products) should be recorded in the appropriate sections of the eCRF.

Patients will be asked to return all unused investigational products and empty packages and bottles to the study centre at each visit. Compliance will be discussed and assessed at each scheduled visit based on the number of tablets returned at each scheduled visit. The patient's compliance will be assessed by the investigator or delegate and recorded in the eCRF. Patients judged to be non-compliant, defined as patients taking less than 80% or more than 120% of their prescribed dose of investigational products, may continue in the study, but should be counselled on the importance of taking their investigational products as prescribed.

The total daily doses of metformin and sulfonylurea should also be recorded.

5.7.1 Accountability

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

The study centre personnel will account for all investigational products dispensed to and returned by the patient.

The investigational product will be prescribed only by the investigator. Under no circumstances will the investigator allow the investigational product to be used other than as directed by the Clinical Study Protocol without AstraZeneca approval.

Investigational product will only be delivered to the centre when the required regulatory approval has been obtained. Ethics Committee approval may also be required, depending on local regulations. It is the investigator and/or institution's responsibility to establish a system for handling study treatments, including investigational product, so as to ensure that:

- Deliveries of products from AstraZeneca or their designee are correctly received by the investigator or his or her designee;
- Such deliveries are recorded on an appropriate drug log.

The investigator must maintain accurate records accounting for the receipt and for the disposition of the investigational products. This record is in addition to any drug accountability information recorded in the eCRFs. It must be possible to reconcile delivery records with records of usage and returned stocks. Any discrepancies must be accounted for. Certificates of delivery and return should be signed by the investigator or a designated person.

The investigator is responsible for making sure:

- That the investigational product are handled and stored safely and properly (see Section 5.5.4)

- That the investigational product are only dispensed to study patients in accordance with this Clinical Study Protocol.

Patients must return all unused investigational product and empty containers to the investigator.

At the termination of the Clinical Study or at the request of AstraZeneca, the investigator will either return any unused investigational products to AstraZeneca, or destroy investigational products at the study centre depending on local regulations. If the investigational product is destroyed at the study centre, the study centre personnel will account for all unused investigational product and for appropriate destruction. Certificates of delivery, destruction and return must be signed. If the investigational product is returned to AstraZeneca, the study centre personnel or the AstraZeneca monitor will return all unused investigational product to AstraZeneca. Certificates of delivery and return must be signed.

5.8 Discontinuation of investigational product

Patients may be discontinued from investigational product in the following situations:

- Patient decision. The patient is at any time free to discontinue the investigational products, without prejudice to further treatment.
- Safety reasons (AE) as judged by the investigator, AstraZeneca and/or Bristol-Myers Squibb Pharmacovigilance.
- Severe non-compliance to the Clinical Study Protocol as judged by the investigator and/or AstraZeneca.
- Incorrect enrolment.
- Patient lost to follow-up (unable to reach the patient after three documented phone calls, fax, email, or attempts to contact him/her through patient locator agencies [if allowed per national regulation] and having sent one letter by registered/certified mail; all should be documented in the patient's medical records).

Study specific discontinuation criteria are listed below. The FPG, PPG and HbA_{1c} values will be measured at the central laboratory, whilst the patients will also determine their FPG daily using a Glucometer.

1. Use of (need for) additional anti-hyperglycaemic medication other than the investigational product for more than 7 consecutive days. Insulin for up to 7 days during hospitalisation will be allowed as long as the primary reason for hospitalisation is not management of the patient's glycaemic control.
2. Treatment with glucocorticoids equivalent to oral prednisolone >10 mg/day (two temporary periods of higher daily doses but no longer than 7 days each will be allowed).

3. Severe and/or frequent hypoglycaemic events, defined as ≥1 major event or recurring minor events and the possibility of down-titration of sulfonylurea and contributing factors (e.g., excessive physical activity) has been evaluated. Down-titration of sulfonylurea will be permitted once during the treatment period.

4. Patients whose individual treatment codes are broken by the investigator.

5. FPG > 15.0 mmol/L (>270mg/dL) during the double-blind treatment period, between Visit 3 and Visit 6, confirmed at repeated measurement within 5 days (results from central laboratory). If self-monitored FPG > 15.0 mmol/L (>270mg/dL) between Visit 3 and Visit 6, patient to repeat the self-monitoring of FPG within 2 days. If this second FPG is still >15.0 mmol/L (>270mg/dL), the patient should contact the study centre and have this measure confirmed by central laboratory within 5 days for discontinuation.

6. FPG > 12.2 mmol/L (>220mg/dL) during the double-blind treatment period, between Visit 6 and Visit 9, confirmed at repeated measurement within 5 days (results from central laboratory). If self-monitored FPG > 12.2 mmol/L (>220mg/dL) between Visit 6 and Visit 9, to repeat the self-monitoring of FPG within 2 days. If this second FPG is still >12.2 mmol/L (>220mg/dL), the patient should contact the study centre and have this measure confirmed by central laboratory within 5 days for discontinuation.

7. Calculated CrCl <60 ml/min or an increase in serum creatinine of ≥44.2 µmol/L (≥0.5 mg/dL) above the baseline value confirmed at a repeated measurement within 1 week.

8. Serum total bilirubin >34 µmol/L (>2 mg/dL) confirmed at a repeated measurement within 1 week.

9. Increase of ALT and/or AST >3 x ULN and increase of total bilirubin ≥2 x ULN confirmed at a repeated measurement within 1 week.

10. Increase of ALT or AST >5 x ULN confirmed at a repeated measurement within 1 week.

11. A temporary discontinuation of investigational product must occur when the patient receives intravascular administration of iodinated contrast agents. Since intravascular administration of iodinated contrast agents in radiologic studies can lead to renal failure, both metformin and investigational product should be temporarily stopped prior to, or at the time of the test and not re-instituted until at least 48 hours afterwards. Investigational product and metformin should also be temporarily stopped 48 hours before elective surgery with general anaesthesia and should not be resumed earlier than 48 hours afterwards.

5.8.1 .Procedures for discontinuation of a subject from investigational product

A patient that decides to discontinue the investigational product will always be asked about the reason(s) and the presence of any AEs. If possible, they will be seen and assessed by an

investigator(s). Adverse events will be followed up (See Sections 6.4.3 and 6.4.4); diary cards, glucometers, and the investigational product should be returned by the patient.

Randomised patients who do not complete the study should complete the procedures described for Visit 9 (End of Study Visit).

If a patient is withdrawn from the study, see Section 5.9.

5.9 Withdrawal from study

Patients are free to withdraw from study at any time (the investigational product and assessments), without prejudice to further treatment (withdrawal of consent). Such patients should always be asked about the reason(s) and the presence of any AEs. 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, glucometers, and the investigational product should be returned by the patient.

A patient withdrawn from the study 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 eCRF as specified in the Clinical Study Protocol and in accordance with the instructions provided.

The investigator ensures the accuracy, completeness, and timeliness of the data recorded and of the provision of answers to data queries according to the Clinical Study Agreement.

Data must be entered into the WBDC system at the study centre within 72 hours after the scheduled visit (except for SAEs that should be entered within 1 calendar day). Trained study personnel will be responsible for entering data into the WBDC system according to the Instructions for the investigator including the data entry instructions. Data includes observations, tests and assessments specified in the Clinical Study Protocol.

When data have been entered, reviewed, edited and source data verification has been performed by an AstraZeneca representative, the data will be frozen to prevent further editing. The Principal Investigator is responsible for signing the eCRF and this can be delegated to a trained investigator. The eCRF is signed electronically as per the eCRF instructions. A copy of the eCRF data will be archived at the study centre.

Data verification and validation will be performed. The Investigator should answer any external queries raised by AstraZeneca in a timely manner, and query resolutions will be saved in the central database.

Health-related quality of life (EQ-5D) questionnaire will be completed in paper. Data will be entered on the eCRF by trained study personnel.

6.2 Data collection and enrolment

The following data will be collected and recorded in the appropriate sections of the eCRF (refer to the Study Plan, Section 3.1).

- Date of signed informed consent
- Inclusion and exclusion criteria
- Demography: Date of birth, gender and ethnicity
- Timing of laboratory assessments
- Pregnancy test
- Medical history
- Physical examination (see Section 6.4.6) including vital signs, height, weight and waist circumference
- A 12-lead ECG, see Section 6.4.7
- Prior and concomitant medication
- Data from patient reported outcome questionnaires

6.2.1 Follow-up procedures

Randomised patients who do not complete the study should complete the procedures described for Visit 9 (End of Study Visit).

6.3 Efficacy

Baseline is defined as the last non-missing value before the first dose of double-blind treatment on Week 1 (Day 1).

Self-monitoring of plasma glucose should be done in order to reduce the risk of prolonged periods of undetected hyperglycaemia or to confirm hypoglycaemia. Patients will be asked to do self-monitoring of plasma glucose using glucometers provided by AstraZeneca. The patients will receive training on the use of the glucometer, according to the manufacturer's instruction.

6.3.1 Efficacy variables

The laboratory variables that will be measured to assess efficacy and the visits these will be measured are presented in Table 2. These variables will be assessed at the central laboratory.

For information on methods of collection, assessment, labelling, storage and shipment of samples, see the Laboratory Manual.

Table 2 Efficacy laboratory variables

Visit number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**
Study week	**-2**	**-1**	**1**	**4**	**8**	**12**	**16**	**20**	**24**
Study Day	**-14**	**-7**	**1**	**28**	**56**	**84**	**112**	**140**	**168**
HbA1c	X		X	X	X	X	X	X	X
FPGb			X	X	X	X	X	X	X
PPGa			X						X
Insulinb			X						X
C-peptide			X						X
Glucagon			X						X

FPG: Fasting plasma glucose, PPG: Postprandial glucose.
a. Measured 2 hours after breakfast; b. Fasting

Patients should be instructed to abstain from all food and beverages for 10 hours prior to each clinical visit; however, drinking water is allowed. In the morning prior to each visit, acceptable concomitant medications can be taken, but with water only.

The patient should not take any investigational product in the morning before the scheduled visit, but after the relevant laboratory specimens have been collected. The investigational products will be taken at breakfast which will be provided at the study centres during the scheduled visits. Laboratory samples for the PPG will be collected after the patient has had breakfast.

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 AE 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 investigational product. An undesirable medical condition can be symptoms (e.g., nausea, chest pain), signs (e.g., tachycardia, enlarged liver) or the abnormal results of an investigation (e.g., laboratory findings, ECG). 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 SAE is an AE occurring from the time of informed consent (Visit 1) was obtained for the duration of the study, up until the last contact, Visit 9 (End of Study Visit) 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
- Results in persistent or significant disability or incapacity
- Is a congenital abnormality or birth defect
- Is an important medical event that may jeopardise the patient or may require medical intervention to prevent one of the outcomes listed above

In addition, the following events (**regardless of whether or not they meet any of the serious criteria above**) will be collected as SAEs:

- Cancer
- Drug dependency/abuse

Serious AEs related to skin lesions, infection, lymphocytopaenia, thrombocytopaenia and symptomatic hand and foot oedema should be given special attention.

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

For the purposes of regulatory reporting, the following events/medical concepts should be transmitted as described in Section 6.4.4 below in the same timelines as SAEs regardless of whether the reports are classified as serious or non-serious:

- Pancreatitis
- Opportunistic infections (eg, tuberculosis, Herpes zoster, cytomegalovirus, Pneumocystis jirovecii, etc)
- Serum AST or ALT $\geq$ 3 x ULN and serum total bilirubin > 2 x ULN or evidence of jaundice.

6.4.3 Recording of adverse events

6.4.3.1 Time period for collection of adverse events

Adverse events will be collected from the time informed consent was obtained for the duration of the study, up until the last contact, Visit 9 (End of Study Visit).

Serious AEs will be collected from the time of signature of informed consent throughout the study until and including the last contact, Visit 9 (End of Study Visit).

6.4.3.2 Adverse event dictionary

The latest version of the Adverse Event dictionary, Medical Dictionary for Regulatory Activities (MedDRA), will be used for the classification and analysis of AEs entered in the study database. For regulatory reporting, SAEs will be processed at the Bristol-Myers Squibb Pharmacovigilance database and coded using MedDRA.

6.4.3.3 Variables

The following variables will be collected for each AE:

- AE (verbatim)
- The date when the AE started, stopped or was ongoing
- Maximum intensity (if AE changes in intensity, the severest intensity is to be documented in the eCRF, the duration of the AE reported in the eCRF should however describe the total time of occurrence of the AE).
- Whether the AE is serious or not
- Investigator causality rating against the investigational product (Yes or No)
- Action taken with regard to investigational products:
  - Not applicable: For AE occurring during the pre-treatment period as well as during the 30 days follow-up of an AE after last investigational product administration (Visit 9).
  - No change: Investigational product dosing remained the same in spite of AE being present.
  - Temporarily discontinued: Investigational product usage is temporarily discontinued because of the AE, either because the patient chooses to discontinue the investigational product or the physician feels it is in the patient's best interest to temporarily discontinue the investigational product.
  - Permanently discontinued: Investigational product usage is permanently discontinued because of the AE, either because the patient chose to discontinue

the investigational product or the physician feels it is in the patient's best interest to discontinue the investigational product.

- Other: Other countermeasures are required such as an operative procedure.

- AE caused patient's withdrawal from study (Yes or No).
- Outcome:
  - Resolved: The AE is no longer present at any intensity - symptoms have completely abated.
  - Resolving: The AE is abating, but has not completely resolved yet.
  - Not resolved: The AE has not resolved, but is still present with the same intensity.
  - Resolved with sequelae: The AE resolved but has resulted in consecutive symptom(s).
  - Worsened: The AE is still present but at a heightened intensity. The rule of repetition of AE reporting should be applied.
  - Fatal: The AE directly caused or contributed to the patient's death.
  - Unknown: There is no information available on the outcome of the AE.

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

- Date AE met criteria for SAE
- Date investigator became aware of SAE
- Reason for classification as serious
- Date of hospitalisation
- Reason for hospitalization
- 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

If the intensity of an AE changes only the maximum intensity of the event will be recorded. Intensity is defined as one of the following:

- Mild: Awareness of event, but easily tolerated. Symptoms can be ignored and disappear when the patient is distracted. They do not interfere with the patient's daily activities and are not clinical relevant.
- Moderate: Symptoms cause discomfort but are tolerable, they cannot be ignored and affect concentration. Symptoms may interfere with the daily activities and may be clinically relevant.
- Severe: Symptoms affect usual daily activity (inability to carry out usual activity) and are clinically relevant.
- Very Severe: Debilitating, significantly incapacitates patient despite symptomatic therapy.

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.

6.4.3.4 Causality collection

The investigator will assess causal relationship between the investigational product and each AE, and answer 'Yes' or 'No' in the eCRF to the question 'Do you consider that there is a reasonable possibility that the event may have been caused by the investigational products?' If there is any valid reason, even if undetermined or untested, for suspecting a possible cause-and-effect relationship between the investigational products and the occurrence of the AE, then this answer should be 'Yes'. Otherwise, if no valid reason exists for suggesting a possible relationship, then this answer should be 'No'. If more than one AE is identified, a causality assessment should be made for each AE.

For SAEs the 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.

6.4.3.5 Adverse Events based on signs and symptoms

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

6.4.3.6 Adverse events based on examinations and tests

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

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

Deterioration of a laboratory value, which is unequivocally due to disease progression, should not be reported as an AE/SAE.

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

6.4.3.7 Disease progression

Disease progression can be considered as a worsening of a patient's condition attributable to the disease for which the investigational product is being studied. It may be an increase in the severity of the disease under study and/or increases in the symptoms of the disease. Events, which are unequivocally due to disease progression, should not be reported as an AE during the study.

6.4.3.8 Follow-up of unresolved adverse events

Any AEs that are unresolved at the end of the study (Visit 9) or at discontinuation, will be followed up until resolution by the investigator or until the investigator decides that no further follow-up is necessary, but without further recording in the eCRF. AstraZeneca retains the right to request additional information for any patient with ongoing AEs/SAEs at the end of the study, if judged necessary. The requirement to follow-up is not intended to delay database lock or production of the CSR. Both these activities should proceed as planned with ongoing AEs if necessary.

Any follow-up of ongoing SAEs after database lock will be reported to AstraZeneca, who will notify the appropriate Bristol-Myers Squibb Pharmacovigilance contact.

6.4.3.9 Adverse events reported after the end of treatment

Only unsolicited SAEs will be collected for a period of up to 30 days after the last dose of investigational products. All SAEs and associated concomitant medication will be recorded and reported to AstraZeneca who will notify Bristol-Myers Squibb Pharmacovigilance, see Section 13.1.

6.4.3.10 Reporting of hypoglycaemic events

Hypoglycaemic events (see Section 6.4.11) should be reported in a separate 'Hypoglycaemic AE' section in the eCRF.

Hypoglycaemic events should not be recorded in the regular AE section, except if the hypoglycaemic event fulfils the definition for an SAE, when it should be reported in the 'SAE' section in the eCRF.

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 eCRF.

If any SAE occurs in the course of the study, then investigators or other study centre personnel will inform appropriate AstraZeneca representatives within one day, i.e., 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 Bristol-Myers Squibb Global Pharmacovigilance & Epidemiology **within one calendar day** of initial receipt for all SAEs. The AstraZeneca representative will notify the appropriate Bristol-Myers Squibb Pharmacovigilance contact to ensure regulatory compliance.

For fatal or life-threatening AEs where important or relevant information is missing, active follow-up is undertaken immediately. Investigators or other study centre personnel will inform AstraZeneca representatives of any follow-up information on a previously reported SAE within one calendar day, i.e., immediately but **no later than the end of the next business day** of when he or she becomes aware of it.

The reference document for definition of expectedness is the Investigators Brochure for the investigational product and the European Union (EU) Summary of Product Characteristics (SPC) for the active comparator product.

6.4.4.1 Serious adverse event handling using Web Based Data Capture (WBDC)

Serious AE (SAE) information will be entered and submitted into the WBDC system on the relevant eCRF pages. An automated e-mail alert will be sent to the designated AstraZeneca representative who will work with the investigator to ensure that all the necessary information is available in the system within the required time frames. The AstraZeneca representative will send a completed SAE report to the appropriate Bristol-Myers Squibb Pharmacovigilance representative via fax or e-mail.

If the WBDC system is not available, then the investigator or other study centre personnel reports a SAE to the appropriate AstraZeneca representative by telephone. The AstraZeneca representative will advise the investigator/study centre personnel how to proceed.

A paper back-up SAE report should be sent to the AstraZeneca representative, who will notify Bristol-Myers Squibb, recognising that the same reporting time frames still apply. The investigator is responsible for completing the eCRF as soon as the system becomes available again.

6.4.5 Laboratory safety assessment

Blood and urine samples for determination of clinical chemistry, haematology and urinalysis tests will be taken at the times indicated in Table 3. The date and time of sampling will be recorded on the laboratory requisition form. The samples will be processed by the central laboratory and results will be reported back to the study centre within 72 hours.

All samples should be taken by adequately trained study personnel, and performed and handled in accordance with given instructions in the Laboratory Manual. Up to date reference ranges will be provided during the study and laboratory results will be compared to the laboratory standard normal ranges and flagged if they are outside the normal range. The investigator should make an assessment of the available results with regard to clinically significant abnormalities. The laboratory reports should be signed and retained at the study centre as source data for laboratory variables.

For information on how AEs based on laboratory tests should be recorded and reported, see Section 6.4.3.

The complete list of safety laboratory variables is displayed in Table 3.

Table 3 Safety laboratory variables

Visit number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**
Study Week	**-2**	**-1**	**1**	**4**	**8**	**12**	**16**	**20**	**24**
Study Day	**-14**	**-7**	**1**	**28**	**56**	**84**	**112**	**140**	**168**
Haematology									
Haemoglobin		X	X			X			X
Haematocrit		X	X			X			X
Red blood cell count		X	X			X			X
White blood cell count and differential		X	X			X			X
Platelet count		X	X			X			X
Clinical chemistry									
Aspartate aminotransferase (AST)		X	X			X			X
Alanine aminotransferase (ALT)		X	X			X			X
Alkaline phosphatase		X	X			X			X
Creatine kinase (CK)		X	X			X			X
Total bilirubin		X	X			X			X
Total protein		X	X			X			X
Albumin		X	X			X			X
Blood urea nitrogen (BUN)		X	X			X			X
Electrolytes: - Sodium - Potassium - Chloride		X	X			X			X
Serum creatinine (SCr) for estimation CrCl (Cockcroft Gault)		X	X			X			X

Visit number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**
Study Week	**-2**	**-1**	**1**	**4**	**8**	**12**	**16**	**20**	**24**
Study Day	**-14**	**-7**	**1**	**28**	**56**	**84**	**112**	**140**	**168**
Thyroid stimulating hormone (TSH)a			X						
Follicle stimulating hormone (FSH)b			X						
Total Cholesterol			X						X
HDL-C			X						X
LDL-C			X						X
TG			X						X
Urinalyses									
pH		X	X			X			X
Proteinc		X	X			X			X
Glucose		X	X			X			X
Leukocyte esterasec		X	X			X			X
Blood by dipstickc		X	X			X			X
Pregnancy testd		X	X	X	X	X	X	X	X
Albumin:creatinine ratio		X	X			X			X

a. If abnormal, refer to free levothyroxine (T_4).
b. For women on hormone replacement therapy.
c. Microscopy if dipstick positive for blood, leukocyte esterase or protein.
d. Urine beta human chorionic gonadotropin (bHCG) pregnancy test for women of childbearing potential (hCG minimum sensitivity of 25 IU/L) (dipstick analysed at the study centre).

For blood volume collected, see Section 7.1

6.4.6 Physical examination

A physical examination will be performed according to common medical practice at Visit 2 and Visit 9. The physical examination includes an evaluation of general appearance, lymph nodes, thyroid, musculoskeletal system, extremities, cardiovascular system, lungs, abdomen, reflexes and measurement of vital signs. Baseline data is collected at Visit 3, and findings are entered into the eCRF. New findings at the physical examination at Visit 9 are recorded as a change from Baseline.

A brief physical examination will be performed from Visit 3 to Visit 8 and includes an evaluation of general appearance, extremities, cardiovascular system, lungs, abdomen and measurement of vital signs to verify the findings from the physical examination at Baseline (Visit 3).

Any changes since Visit 1 will be recorded as AEs if the change is considered clinically significant by the investigator. For more information on how AEs based on examinations and tests should be recorded and reported, see Section 6.4.3.

6.4.7 ECG

A 12-lead ECG will be taken (supine position, standard ECG with a paper speed of 50 mm/second covering at least 6 sequential beats) after the patient has been lying down resting for at least 5 minutes at Visit 3 and Visit 9. The 12-lead ECG will be evaluated by the investigator and assessed as ‘Normal’ or ‘Abnormal clinically significant’ or ‘Abnormal not clinically significant’ in the eCRF.

For information on how AEs based on examinations and tests should be recorded and reported, see Section 6.4.3.

6.4.8 Vital signs

Vital signs will be assessed at all scheduled visits from Visit 2 to Visit 9 following the Study Plan provided in Section 3.1.

6.4.8.1 Blood pressure and pulse rate

Blood pressure and pulse rate will be measured using a standardised cuff adapted to the size of the patient’s arm after the patient has been sitting and resting for at least 5 minutes and before blood samples are taken.

6.4.9 Weight and height

The patient’s weight will be recorded in kilogram (kg), on a fasting stomach with light clothing and no shoes at Visit 2 and all scheduled visits from Visit 3 to Visit 9. The patient’s height will be recorded in centimetres, without shoes, at Visit 2.

6.4.10 Waist circumference

The waist circumference will be measured in the morning at Visit 3 and again at Visit 9, before breakfast in a standing position at the natural waist (smallest waist circumference). If there is no natural waist, the measurement should be made at the level of the umbilicus.

6.4.11 Hypoglycaemic events

The patient will be asked to self-monitor plasma glucose levels and symptoms suggestive of hypoglycaemia and to register if a finger stick value was obtained and the glucose value in the supplied patient diary.

A hypoglycaemic event can be either:

- An episode with symptoms and confirmed low glucose
- An episode with low glucose
- An episode with symptoms when glucose was not measured

For the evaluation of hypoglycaemic events, special attention will be given to hypoglycaemia as defined in accordance with the CPMP guidance on clinical investigation of medicinal products in the treatment of diabetes mellitus (CPMP 2002), as described below:

- Major hypoglycaemic events, defined as symptomatic events requiring external assistance due to severe impairment in consciousness or behaviour, with plasma glucose level <3.0 mmol/L (<54 mg/dL), and prompt recovery after glucose or glucagon administration.
- Minor hypoglycaemic event, defined as either a symptomatic event with plasma glucose level <3.0 mmol/L (<54 mg/dL), and no need for external assistance, or an asymptomatic blood glucose measurement <3.0 mmol/L (<54 mg/dL).
- Events suggestive for hypoglycaemia, with symptoms that the patient experiences as hypoglycaemia and no confirmative measurement.

Plasma glucose values will be obtained from the central laboratory. Therefore, the corresponding plasma glucose values will be used to define hypoglycaemia, that is, plasma glucose <3.0 mmol/L (<54 mg/dL).

Data to be collected for each hypoglycaemic event:

- Date of start and stop and time of the day for start
- If symptoms are present or not and which symptoms
- If finger-stick value obtained and the plasma glucose value

- Intervention needed for recovery, maximum intensity, action taken, causality and possible contributing factors

The patient diary will be reviewed and data regarding hypoglycaemic events transcribed into the eCRFs at each scheduled visit. A new diary for the next visit period will be handed over to the patient. If a major hypoglycaemic event occurs, or more than one minor event since the last visit, the patient should contact the investigator. For the reporting of hypoglycaemic events/symptoms suggestive of hypoglycaemic events as AEs, see Section 6.4.3.10.

6.5 Patient reported outcome

6.5.1 Patient diary

Patients will be supplied with diaries at Visit 2 to Visit 8 for the 24-week double-blind treatment period. The diaries will be collected at each subsequent visit and kept in the Investigator Study File and a new diary for the next visit period will be handed over to the patient. The patient should be instructed to enter FPG values in the diary section for hypoglycaemic events (see Section 6.4.11).

6.5.1.1 Method of assessment

Glucometer measurements

Patients will be provided with a glucometer at Visit 2 to check their plasma glucose level at home. Patients will be instructed on the use of the glucometer and the recording of their FPG levels in the diary. The FPG level should be self-monitored at least every other day or according to local clinical practices for the duration of the study (Visit 2 to Visit 9).

The glucometer is equipped with a memory which should be reviewed by the study centre at each visit, from Visit 3 to Visit 9.

If self-monitored FPG is above 15 mmol/L (270 mg/dL) between Visit 3 and Visit 6, or if FPG is above 12.2 mmol/L (220 mg/dL) between Visit 6 and Visit 9, the patient is highly recommended to repeat the self-monitoring of FPG within 2 days. If this second FPG is still above 15 mmol/L (270 mg/dL) between Visit 3 and Visit 6, or above 12.2 mmol/L (220 mg/dL) between Visit 6 and Visit 9, the patient should contact the study centre and be scheduled for a FPG measurement at the study centre (analysed by the central laboratory).

Diary for hypoglycaemic events

The patient will be asked to self-monitor plasma glucose levels and symptoms suggestive of hypoglycaemia. If a hypoglycaemic event occurs, the start and stop date, time of the day, plasma glucose values, and the presence of the following symptoms: sweating, shakiness, pounding heart, hunger, confusion, dizziness/lightheadness, drowsiness, nausea and headache should be recorded in the diary. If any other symptoms occur concurrently, these should also be recorded and specified in the diary. The study centre personnel will review the diary at each following visit (Visit 3 to Visit 9) and enter data into the 'Hypoglycaemic adverse event' section in the eCRF.

6.5.2 Patient reported outcome method or questionnaires

Translations of the patient reported outcome (PRO) questionnaires into local languages will be performed according to a linguistic validation process. The patient needs to be able to read and to understand the local language to be able to answer the questionnaires.

The EuroQoL-5Dimension (EQ-5D) (The EuroQoL Group 1990) questionnaire will be administered at Visit 3 and Visit 9 (End of Study Visit) in paper version.

6.5.3 Method of assessment of patient reported outcome questionnaires

6.5.3.1 EuroQoL-5 Dimension Questionnaire

The EQ-5D is a generic, preference-based utility questionnaire and consists of two parts, the EQ-VAS and the EQ-5D index (The EuroQoL Group 1990). The EQ-VAS is a visual analogue scale ranging from 0 = worst possible health to 100 = best possible health. The EQ-5D index is a five dimension questionnaire. The dimensions consist of mobility, self-care, usual activity, pain/discomfort and anxiety/depression. Each item has three levels: 'No problems', 'Some problems' and 'Severe problems'.

The questions will be assessed at Visit 3 and at the end of the 24-week double-blind treatment period (Visit 9). The questions (a visual analogue scale and five dimensions) will take approximately 5 minutes to answer.

6.5.4 Administration of patient reported outcome questionnaires

It is important to administer the questionnaire according to the recommendations relevant for the questionnaire to standardised the processes. The patient should be informed about how important his/her participation is. The patients should complete the questionnaire/questions before any other study-related procedures are performed and before any communication relating to the study with the study centre personnel. The questionnaire should be completed in a quiet place without influence from study centre personnel or accompanied family or friend. The study centre personnel should never help the patient to choose an answer and must be neutral in their response to the patient's questions. The personnel at the study centre are not allowed to interpret or rephrase the questions for the patient. After the patient has completed the questionnaire, the study centre personnel will review the questionnaire for completeness only.

6.6 Pharmacokinetics (Not applicable)

6.7 Pharmacodynamics (Not applicable)

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 patient in this study is as follows:

Table 4 Volume of blood to be drawn from each patient

Assessment		Sample volume (mL)	No. of samples	Total volume (mL)
Safety	Clinical chemistry[a]	10	4	40
	Haematology	4	4	16
Efficacy	HbA1c	2	8	16
	FPG	2	7	14
	PPG	2	2	4
Total				90

a Include sample for efficacy variables insulin, c-peptide and glucagon

7.2 Blood and urine samples

Blood and urine samples for clinical laboratory tests will be obtained by standardised techniques and assessed by the central laboratory.

Sample collection

The central laboratory will provide the study centres with all the appropriate materials for specimen collection and sample processing, packaging, and shipping. A Laboratory Manual for investigators giving detailed instructions will be provided to each study centre prior to the start of the study. The investigator should follow the procedures defined in the Laboratory Manual.

When blood is taken for analysis, patients should have been sitting for at least 5 minutes prior to sampling. A tourniquet may be applied but for no longer than 2 minutes and it should be removed prior to the collection of blood.

Sample labelling

All samples will be labelled with a bar code containing a number which references the study code, study centre number, E-code and visit number. These labels will be prepared and supplied by the central laboratory for all tubes and containers which are used to collect, treat, store or ship aliquots of the samples to the central laboratory. The study centre personnel will record the patient information on the label, as instructed in the Laboratory Manual.

Sample shipment

Shipment of samples will be carried out according to the Laboratory Manual.

7.3 Handling, storage and destruction of biological samples

The samples will be disposed of after analyses.

7.4 Labelling and shipment of biohazard samples

The Principal Investigator will ensure 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 patient unless agreed with AstraZeneca and appropriate labelling, shipment and containment provisions are approved.

7.5 Chain of custody of biological samples

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

The Principal Investigator at each study centre keeps full traceability of collected biological samples from the patients while in storage at the study 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 centres and auditing of external laboratory providers.

7.6 Withdrawal of informed consent for donated biological samples

If a patient withdraws consent for 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, the patient will be withdrawn from further study participation.

The Principal Investigator:

- Ensures patients' withdrawal of informed consent for the use of donated samples is notified immediately to AstraZeneca
- Ensures that biological samples from that patient, if stored at the study centre, are immediately identified, disposed of/destroyed, and the action documented
- Ensures the laboratory(ies) holding the samples is informed about the withdrawn consent immediately and that samples are disposed of/destroyed, the action documented and the signed document returned to the study centre
- Ensures that the patient and AstraZeneca are informed about the sample disposal

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 the International Conference on Harmonisation (ICH) and Good Clinical Practice (GCP) guidelines, applicable regulatory requirements and the AstraZeneca policy on Bioethics and Human Biological Samples.

8.2 Subject data protection

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

8.3 Ethics and regulatory review

An Ethics Committee (EC) should approve the Clinical Study Protocol, including the final version of the Informed Consent Form and any other written information and/or materials to be provided to the patients. The Principal Investigator will ensure the distribution of these documents to the applicable EC, and to the study centre personnel.

The opinion of the EC should be given in writing. The Principal Investigator should submit the written approval to AstraZeneca before enrolment of any patient into the study.

The EC should approve all advertising used to recruit patients for the study.

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

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

Before enrolment of any patient into the study, the final Clinical 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 the regulatory authorities, ECs and Principal Investigators with safety updates/reports according to local requirements.

8.4 Informed consent

The Principal Investigator at each study centre will:

- Ensure each patient is given full and adequate oral and written information about the nature, purpose, possible risk and benefit of the study.
- Ensure each patient is notified that they are free to discontinue from the study at any time.
- Ensure that each patient is given the opportunity to ask questions and allowed time to consider the information provided.
- Ensure each patient 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 patient.
- Ensure that any incentives for patients who participate in the study as well as any provisions for patients harmed as a consequence of study participation are described in the Informed Consent Form that is approved by an EC.

8.5 Changes to the Clinical Study Protocol and Informed Consent Form

Study procedures will not be changed without the mutual agreement of the International Co-ordinating Investigator and AstraZeneca.

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

The amendment should be approved by each EC and if applicable, also the national regulatory authority, before implementation. Local requirements should be followed for revised protocols.

AstraZeneca will distribute any subsequent amendments and new versions of the Clinical Study Protocol to each Principal Investigator. For distribution to the EC see Section 8.3.

If a protocol amendment requires a change to a study centre's Informed Consent Form, AstraZeneca and the study centre's EC should approve the revised Informed Consent Form before the revised form is used.

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

8.6 Audits and inspections

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

9. STUDY MANAGEMENT BY ASTRAZENECA

9.1 Pre-study activities

Before the first patient is entered into the study, it is necessary for a representative of AstraZeneca to visit the study centre to:

- Determine the adequacy of the facilities.
- Determine availability of appropriate patients for the study.
- Discuss with the investigator(s) (and other personnel involved with the study) their responsibilities with regard to Clinical Study 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 centre personnel

Before the first patient is entered into the study, an AstraZeneca representative will review and discuss the requirements of the Clinical Study Protocol and related documents with the study centre personnel and also train them in any study specific procedures and the WBDC system utilised.

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

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

9.3 Monitoring of the study

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

- Provide information and support to the investigator(s).
- Confirm that facilities remain acceptable.
- Confirm that the investigational team is adhering to the Clinical Study Protocol, that data are being accurately and timely recorded in the eCRFs, that biological samples are handled in accordance with the Laboratory Manual and that investigational product accountability checks are being performed.
- Perform source data verification (a comparison of the data in the eCRFs with the patient's medical records at the hospital or practice, and other records relevant to the study) including verification of informed consent of participating patients. This will require direct access to all original records for each patient (e.g., clinic charts).
- Ensure withdrawal of informed consent to the use of the patient's biological samples is reported and biological samples are identified and disposed of/destroyed accordingly, and the action is documented, and reported to the patient.

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

9.3.1 Source data

For location of source data, please refer to the CSA.

9.4 Study agreements

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

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

9.4.1 Archiving of study documents

The Principal Investigator follows the principles outlined in the CSA.

(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 EC.

(ii) **Period of record retention**. The study centre (and the Principal Investigator) will retain the essential documents specified in the ICH GCP (e.g., source documents such as medical records, contract, signed consent forms). Essential documents should be retained at the study centre 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 centre, 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 centre and AstraZeneca. AstraZeneca should notify the head of the study centre 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 centre.

9.5 Study timetable and end of study

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

The study is expected to start in Q2 2010 and to end by Q2 2011.

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

10. DATA MANAGEMENT BY ASTRAZENECA

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

Recording of data, see Section 6.1. Data includes observations, tests and assessments specified in the Clinical Study Protocol. Data entered in the WBDC system will immediately be saved at a central database and changes tracked to provide an audit trail. When data has been entered, reviewed and edited and when Source Data Verification has been performed, the investigator will sign the eCRF. The data will then be frozen to prevent further editing. After final validation has been performed and the study data has been locked, a copy of the database will be provided to the study centre for archiving.

Patient reported outcomes and patient-recorded diary data is collected on paper and will be entered into the WBDC system by study centre personnel.

The data collected through third party sources will be obtained and reconciled against study data.

Data associated with biological samples will be sent to, and analysed by a central laboratory. Data from the central laboratory will be sent to AstraZeneca directly as data sets or text files, and will then be validated to ensure consistency with the clinical data. Any queries on the laboratory data will either be raised and resolved within the WBDC system or sent directly to the central laboratory as relevant.

The data will be verified and 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.

Adverse Events and medical/surgical history will be classified according to the terminology of the latest version of MedDRA. Medications will be classified according to the AstraZeneca Drug Dictionary (AZDD). All coding will be performed by Cognizant Data Management.

Data verification and validation will be performed. Data queries will be raised in the WBDC system for inconsistent, impossible or missing data. The investigator should answer any queries raised by Cognizant Data Management in accordance with the timelines as specified in the CSA, and query resolutions will be saved in the central database. All entries to the study database will be available in an audit trail. Prior to breaking the treatment codes, all decisions on the availability of the data from each individual patient must have been made and documented. 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. Cognizant Data Management will document the date of clean file and database lock.

Following database lock, required amendments to the database due to critical errors will only be allowed with the appropriate supporting documentation. Non-critical errors will not result in amendments to the database but will be captured via the appropriate documentation. A copy (disc or equivalent) of the eCRF will be made available to the study centre after the study database has been locked.

The Data Management Plan will describe in greater detail the methods used to collect, check, and process clinical data. It will also clarify the roles and responsibilities of the various functions and personnel involved in the data management process.

11. EVALUATION AND CALCULATION OF VARIABLES

11.1 Calculation or derivation of efficacy variables

11.1.1 Baseline and Change from Baseline

Baseline is defined as the last non-missing value before the first dose of double-blind treatment on Week 1 (Day 1). Change from Baseline will be calculated as:

Change from Baseline at Week 24/Endpoint = (Value at Week 24/Endpoint – Baseline value).

The Endpoint value for the primary or secondary efficacy parameters will be derived using the last observation of the double-blind randomised treatment period (from first administration of double-blind investigational product to last administration of double-blind investigational product) carried forward.

11.2 Calculation or derivation of safety variables

11.2.1 Derivation or calculation of outcome variables

The mean blood pressure measurements (diastolic and systolic blood pressure) will be computed by AstraZeneca for each patient at each visit. The BMI will be calculated using the formula weight/height^2 (where weight is measured in kg and height in meters) and calculated using the height measured at baseline (Visit 3) will be used.

11.2.2 Other significant adverse events

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 discontinuation due to an AE. Based on the expert's judgement, significant AEs of particular clinical importance may, after consultation with the Global Patient Safety Physician, be considered other significant AEs (OAEs) and reported as such in the CSR.

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

11.3.1 EuroQoL-5 Dimension

The method of assessment of EQ-5D is presented in Section 6.5.3.1.

The EQ-5D is constructed by applying utility weights to each of the levels within each dimension and adding these together. Utility weights are elicited from general population surveys that used one of the available direct utility assessment methods.

The EQ-5D will be completed by the patient at Baseline and at Week 24.

11.4 Calculation or derivation of pharmacokinetic variables (Not applicable)

11.5 Calculation or derivation of pharmacodynamic variable(s) (Not applicable)

11.6 Calculation or derivation of pharmacogenetic variable(s) (Not applicable)

11.7 Calculation or derivation of health economic variables (Not applicable)

12. STATISTICAL METHODS AND SAMPLE SIZE DETERMINATION

A comprehensive Statistical Analysis Plan (SAP) will be prepared before unblinding of the data.

12.1 Description of analysis sets

The following analysis sets will be discussed and finalised at the final blind data review meeting before treatment unblinding (when all patients have completed the Week 24 assessments, data has been cleaned, coding reviewed and approved and SAE reconciliation completed) and are defined as follows. A summary of the number of patients per analysis set will be given and reasons for exclusion of a patient from an analysis set will be listed.

The evaluation of efficacy will be performed using the Full Analysis (FA) set. Safety analyses will be performed on the Safety analysis set.

12.1.1 Consented analysis set

The Consented analysis set will include patients who gave informed consent and were enrolled.

12.1.2 Randomised analysis set

All patients randomised to double-blind treatment at Week 1 (Day 1) will be considered eligible for the Randomised analysis set.

12.1.3 Safety analysis set

The Safety analysis set will include all randomised patients who received at least one dose of double-blind randomised investigational product. Patients who were dispensed the incorrect randomised treatment will be analysed according to actual treatment received.

12.1.4 Full Analysis set

The FA set will include all randomised patients (as randomised) who received at least one dose of investigational product during the 24-week double-blind treatment period and, who have a non-missing baseline value and at least one post-baseline value for at least one efficacy parameter. The intention-to-treat principle will be preserved despite the exclusion of patients who took no investigational product, as the decision of whether or not to begin treatment during the double-blind treatment period could not be influenced by knowledge of the assigned treatment.

12.1.5 Per Protocol analysis set

The Per Protocol (PP) analysis set is defined as a subset of the FA set including patients with no reason for exclusion. A PP analysis on the primary variable will only be performed if more than 10% of the patients in any double-blind treatment are found to significantly violate the terms and conditions of the Clinical Study Protocol. Otherwise, analysis of the primary variable will be restricted to the FA set.

These exclusions from the PP analysis set will include but not be limited to the patients who were:

- Excluded in the FA set
- Non-compliance to the investigational product
- Have insufficient essential efficacy data available, that is, a Baseline and at least one post-baseline (up to and including Week 24) HbA_{1c} value
- Significant protocol deviations

The exclusions from the PP analysis set will be explicitly defined in the SAP before breaking the blind.

12.2 Methods of statistical analyses

12.2.1 Efficacy

The primary objective of this study is to compare the difference between saxagliptin and placebo as add-on therapy to combination metformin and sulfonylurea in the change in HbA_{1c} levels from Baseline to Week 24/Endpoint.

The null hypothesis H0 given below will be tested against the alternative hypothesis HA (α=0.05, two-sided). For saxagliptin the alternative hypothesis states that the difference in the mean change from Baseline to Week 24/Endpoint and placebo is not zero:

$$H0: \mu T - \mu P = 0 \qquad \text{versus} \qquad HA: \mu T - \mu P \neq 0$$

where μT denotes the mean change in HbA_{1c} from Baseline to Week 24/Endpoint in the group of patients treated with saxagliptin (active investigational product, T) and μP the mean change in HbA_{1c} from Baseline to Week 24/Endpoint in the group of patients with placebo (comparator, P).

The change from Baseline to Week 24/Endpoint in HbA_{1c} will be analysed using an analysis of covariance (ANCOVA) model with treatment group and country as factors and Baseline HbA_{1c} as a covariate. Missing Week 24 values will be replaced using the last observation carried forward (LOCF) after baseline. The model will be used to derive a least squares estimate of the treatment difference in mean change with corresponding two-sided 95% confidence interval (CI) and two-sided p-value. Further, two-sided 95% CIs for the mean change within each treatment group will be calculated.

The LOCF approach means that Week 24/Endpoint analyses will be based on measurements available at Week 24 or the last post-baseline measurement prior to Week 24, if no measurement is available at the Week 24 time-point.

Continuous secondary and other relevant variables will be analysed by means of an ANCOVA for change from baseline to Week 24 using treatment group and country as factors and their baseline value as a covariate. By analogy to the primary efficacy variable, the LOCF method will be applied and the model will be used to derive point estimates and two-sided 95% confidence intervals for the mean change within each treatment group as well as for the difference in mean change between the two treatment groups. Nominal two-sided p-values for the difference between the treatment groups will be provided.

Binary response variables will be summarised per treatment group by counts, proportions, and corresponding 95% confidence intervals. Comparisons between the treatment groups will be performed using a logistic regression model with treatment group and country as factors and, if applicable, the baseline value of the associated continuous variable as a covariate. Nominal two-sided p-values for the difference between the treatment groups will be provided. Efficacy will primarily be evaluated using the full analysis set. Analyses based on the PP analysis set will be performed as confirmatory. All analyses of secondary variables are to be interpreted in a strictly exploratory sense.

The time course of all continuous variables will be presented using standard descriptive summary statistics calculated at each scheduled measuring time-point. Moreover, standard descriptive summary statistics will be calculated for the change from baseline to each scheduled measuring time-point after baseline. Measurements at the last individual measuring time-point will be included as a separate time-point, if appropriate. Due to the large number of centres and the expected low number of patients per centre it will not be appropriate to explore centre effects. Tables by country will be provided in order to explore country effects. Where analyses including treatment and country as factors are performed, the corresponding interaction will also be assessed.

12.2.2 Safety

The Safety analysis set will be used for the analysis of the safety and tolerability data.

The number and percent of patients with an AE will be summarised for each treatment group. Changes from baseline to each scheduled time point for each clinical laboratory test, vital signs and ECG will be summarised by treatment group. The number and percent of patients with a predefined marked abnormality in clinical laboratory tests will be summarised by treatment group. In addition, the incidence of hypoglycaemic events will be presented per treatment group. Hypoglycaemic events will also be summarised by major or minor incidence (see Section 6.4.11 for definitions of major and minor). The aforementioned safety analyses will be presented by relevant time point as set out in the Study Flow Chart (see Section 3.1).

12.2.3 Interim analyses

For this study, no interim analysis is planned.

12.3 Determination of sample size

To demonstrate a significant difference between saxagliptin as compared to placebo, as add-on therapy to combination metformin and sulfonylurea, in the change from Baseline to Week 24/Endpoint in HbA_{1c}, a total of 240 patients randomised and treated (120 patients per treatment group), are needed to provide approximately 80% power at a two-sided significance level of 0.05, assuming a true difference of 0.40% and a SD of 1.1%.

Assuming a 4% drop-out rate of patients who are randomised, but do not return for a post-baseline assessment, a total of 250 patients are required to be randomised. Assuming a 10% screen fail rate of patients who are consented and enrolled but are not eligible for randomisation, a total of 275 patients are planned for screening/enrolment.

The sample size for this study was selected to be consistent with the research hypothesis as described in Section 1.2.

12.4 Data monitoring committee

A data monitoring committee will not be used. An Independent Adjudication Committee will be used for adjudication of cardiovascular events, see Section 12.4.1.

12.4.1 Independent Adjudication Committee

An Independent Adjudication Committee, blinded to the treatment of the patient, will classify cardiovascular AEs, such as, but not limited to, death, myocardial infarction, and stroke reported in the study. A separate Adjudication Manual will define and describe the procedure

13. FOR THE HANDLING, REPORTING AND CLASSIFICATION OF THESE EVENTS. IMPORTANT MEDICAL PROCEDURES TO BE FOLLOWED BY THE INVESTIGATOR

13.1 Medical emergencies and AstraZeneca/Bristol-Myers Squibb 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 Marketing Company in Australia.

Name	Role in the study	Address & telephone number

Name	Role in the study	Address & telephone number

Reporting of unsolicited SAE 30 days after end of study treatment, see Section 6.4.3.9.

Overdose

For the purposes of this study, before the blind is broken, an overdose (of active or placebo) is defined as a dose exceeding 8 tablets of saxagliptin for each day. After code break, an overdose is defined as a dose exceeding 40 mg of saxagliptin per day. Should an overdose (accidental or deliberate) occur, it must be reported in accordance with the procedures described below, regardless of whether the overdose was associated with any symptom or not. All symptoms associated with the overdose should be reported as AEs.

- An overdose with associated AEs is recorded as the AE diagnosis/symptoms on the relevant AE pages of the eCRF and on the Overdose eCRF page.
- An overdose without associated symptoms is only reported on the Overdose eCRF page.

For overdoses associated with SAE, standard reporting timelines apply, see Section 6.4.4 . For other overdoses, reporting should be done within 30 days. An Overdose paper form will be used if the WBDC system is not available.

13.2 Pregnancy

All outcomes of pregnancy should be reported to AstraZeneca.

13.2.1 Maternal exposure

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

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

If any pregnancy occurs in the course of the study, then investigators or other study centre personnel will inform appropriate AstraZeneca representatives **within one day** that is, 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 Bristol-Myers Squibb Global Pharmacovigilance & Epidemiology within 1 day for SAEs, see Section 6.4.4 and within 30 days for all other pregnancies.

The same timelines apply when outcome information is available.

14. LIST OF REFERENCES

ADA 2009
American Diabetes Association. Standards of Medical Care in Diabetes – 2009. Diabetes Care 2009;32 (Suppl 1) :S13-S61.

Bradley et al 1994
Bradley C. The Diabetes Treatment Satisfaction Questionnaire: DTSQ. In: Bradley C (Ed), Handbook of Psychology and Diabetes: a guide to psychological measurement in diabetes research and practice. Chur, Switzerland: Harwood Academic Publishers 1994.

Investigator's Brochure
Investigator Brochure, BMS-477118, Saxagliptin. Bristol-Myers Squibb, Research and Development, P.O. Box 4000, Princeton, NJ 08543-4000 and AstraZeneca LP, P.O Box 15437, Wilmington, DE 19850-5437. Version 6 2 July 2008.

Nathan et al 2009
Nathan DM, Buse JB, Davidson MB, Ferrannini E, Holman RR, Sherwin R, Zinman B. Medical management of hyperglycemia in type 2 diabetes: a consensus algorithm for the initiation and adjustment of therapy: a consensus statement from the American Diabetes Association and the European Association for the Study of Diabetes. Diabetologia 2009;52(1):17-30.

Ryden et al 2007
Ryden L, Standl E, Bartnik M, Van den Berghe G, Betteridge J, de Boer MJ et al. Task Force on Diabetes and Cardiovascular Diseases of the European Society of Cardiology (ESC). European Association for the Study of Diabetes (EASD). Guidelines on diabetes, pre-diabetes, and cardiovascular diseases: executive summary. [Journal Article. Practice Guideline] European Heart Journal. 2007;28(1):88-136.

Shaw et al 1998
Shaw M, Talley NJ, Adlis S, Beebe T, Tomshine P, Healey M. Development of a digestive health status instrument: tests of scaling assumptions, structure and reliability in a primary care population. Aliment Pharmacol Ther 1998;12:1067-1078.

Shaw et al 2001
Shaw MJ, Beebe TJ, Adlis SA, Talley NJ. Reliability and validity of the digestive health status instrument in samples of community, primary care, and gastroenterology patients. Aliment Pharmacol Ther 2001;15:981-987.

The EuroQoL Group 1990
The EuroQoL Group: EuroQoL-a new facility for the measurement of health-related quality of life. Health Policy, 1990;16(3):199-208.

AstraZeneca

Clinical Study Protocol Appendix B

Drug Substance	Saxagliptin
Study Code	D1680L00006
Edition Number	1
Date	

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.

AstraZeneca

Clinical Study Protocol Appendix C

Drug Substance	Saxagliptin
Study Code	D1680L00006
Edition Number	1
Date	

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.

AstraZeneca

Clinical Study Protocol Appendix D	
Drug Substance	Saxagliptin
Study Code	D1680L00006
Edition Number	1
Date	

Appendix D
New York Heart Association Classification

1. NEW YORK HEART ASSOCIATION CLASSIFICATION

Classification of Functional Capacity and Objective Assessment

In 1928 the New York Heart Association published a classification of patients with cardiac disease based on clinical severity and prognosis. This classification has been updated in seven subsequent editions of Nomenclature and Criteria for Diagnosis of Diseases of the Heart and Great Vessels (Little, Brown & Co.). The ninth edition, revised by the Criteria Committee of the American Heart Association, New York City Affiliate, was released March 4, 1994. The classifications are summarized below.

Class I. Patients with cardiac disease but without resulting limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea or anginal pain.

Class II. Patients with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea or anginal pain.

Class III. Patients with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes fatigue, palpitation, dyspnea or anginal pain.

Class IV. Patients with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of heart failure or the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort increases.

Source: The Criteria Committee of the New York Heart Association. Nomenclature and Criteria for Diagnosis of Diseases of the Heart and Great Vessels. 9th ed. Boston, Mass: Little, Brown & Co; 1994:253-256.