AstraZeneca

Revised Clinical Study Protocol

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SAVOR

Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus

A Multicentre, Randomised, Double-Blind, Placebo-Controlled Phase IV Trial to Evaluate the Effect of Saxagliptin on the Incidence of Cardiovascular Death, Myocardial Infarction or Ischaemic Stroke in Patients with Type 2 Diabetes

Sponsor: AstraZeneca AB, 151 85 Södertälje, Sweden

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			
2			

Administrative change No.	Date of Administrative Change	Local Administrative change No.	Date of local Administrative Change
1			

AstraZeneca

PROTOCOL SYNOPSIS

SAVOR

Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus

A Multicentre, Randomised, Double-Blind, Placebo-Controlled Phase IV Trial to Evaluate the Effect of Saxagliptin on the Incidence of Cardiovascular Death, Myocardial Infarction or Ischaemic Stroke in Patients with Type 2 Diabetes

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Study centre(s) and number of patients planned

Approximately **900** centres and **16500** patients planned

Study period		**Phase of development**
Estimated date of first patient enrolled	Q2-Q3 2010	IV
Estimated date of last patient completed	**Q3 2014 – Q2 2015**	

Objectives

Primary objectives

Efficacy

The primary efficacy objective is to determine, as a superiority assessment, whether treatment with saxagliptin compared with placebo when added to current background therapy will result in a reduction in the composite endpoint of cardiovascular death, non-fatal myocardial infarction or non-fatal ischaemic stroke, in patients with type 2 diabetes mellitus.

Safety

The primary safety objective of this trial is to establish that the upper bound of the 2-sided 95% confidence interval for the estimated risk ratio comparing the incidence of the composite endpoint of cardiovascular death, non-fatal myocardial infarction or non-fatal ischaemic

stroke, in patients with type 2 diabetes mellitus, observed with saxagliptin to that observed in the placebo group is less than 1.3.

Secondary efficacy objective

The **first** secondary efficacy objective is to determine whether treatment with saxagliptin compared with placebo when added to current background therapy in patients with type 2 diabetes mellitus will result in a reduction of the composite endpoint of cardiovascular death, non-fatal myocardial infarction, non-fatal ischaemic stroke, hospitalisation for heart failure, hospitalisation for unstable angina pectoris or hospitalisation for coronary revascularisation.

The next secondary efficacy objective is to determine whether treatment with saxagliptin compared with placebo when added to current background therapy in patients with type 2 diabetes mellitus will result in a reduction of all-cause mortality.

Other efficacy objectives

Other efficacy objectives are to determine whether treatment with saxagliptin compared with placebo when added to current background therapy in patients with type 2 diabetes mellitus will result in a reduction of:

- Need for increase in dose or addition of new antidiabetic medication
- Initiation of insulin therapy in patients not receiving insulin therapy at baseline
- Hospitalisation for hypoglycaemia
- The individual components of the primary endpoint (cardiovascular death, non-fatal myocardial infarction or non-fatal ischaemic stroke)
- The individual additional components of the secondary efficacy endpoint (hospitalisation for any of the following: heart failure, unstable angina pectoris and coronary revascularisation)
- **The primary composite endpoint (CV death, non-fatal MI or non-fatal ischaemic stroke) during the first year of follow-up and after the first year**
- Retinal laser treatment due to development of and/or deterioration in diabetic retinopathy
- New and/or progression of diabetic nephropathy
- **The composite event of death, doubling of serum creatinine, initiation of chronic dialysis, renal transplant, or a serum creatinine > 6.0 mg/dL (> 530 µmol/L)**

Secondary safety objectives

Safety and tolerability will be evaluated by assessment of overall adverse events and adverse events of special interest. These will include assessment of the long-term effects of saxagliptin on decrease in lymphocyte counts, decrease in thrombocyte counts, severe infections, hypersensitivity reactions, liver abnormalities, bone fractures, pancreatitis, skin reactions and renal abnormalities.

Other safety objectives

Other safety objectives will include assessment of hypoglycaemic events, cancers, peripheral oedema, laboratory tests, pulse, blood pressure, waist circumference and body weight.

Additional objectives

The study will also include health economic and patient reported outcomes objectives as well as exploratory objectives including future biological research, future pharmacogenetic research, and overall glycaemic control.

Study design

This is a multicentre, randomised, double-blind, placebo-controlled Phase IV study to evaluate if treatment with saxagliptin can reduce major adverse cardiovascular events in patients with type 2 diabetes mellitus and to definitively exclude unacceptable cardiovascular toxicity.

Target patient population

Approximately **16500** patients with documented type 2 diabetes mellitus and with either a history of previous cardiovascular events or multiple risk factors for vascular disease including patients with renal failure will be enrolled from sites throughout the world. To reflect a scenario as close to real life as possible, both patients who are treated with glucose-lowering medication (with the exception of incretin-based therapy) and treatment-näive patients will be enrolled.

Investigational product, dosage and mode of administration

Active treatment will comprise the doses of 5 and 2.5 mg based upon a patient's renal function. Patients with a estimated GFR >50 mL/min will be randomised to receive 5 mg saxagliptin or placebo and patients with a estimated GFR ≤50 mL/min will be randomised to receive 2.5 mg saxagliptin or placebo. Saxagliptin is administered orally, once daily.

Comparator, dosage and mode of administration

Matching placebo, as described above, will be used as comparator.

Duration of treatment

The study is cardiovascular event–driven with an anticipated total duration of **4-5** years.

Outcome variable(s)

Primary efficacy variable

The primary efficacy outcome variable of the study is defined as the composite endpoint of cardiovascular death, non-fatal myocardial infarction or non-fatal ischaemic stroke (time to first event).

Primary safety variable

The primary safety outcome variable of the study is defined as the composite endpoint of cardiovascular death, non-fatal myocardial infarction or non-fatal ischaemic stroke (time to first event).

Secondary efficacy variable

The **first** secondary efficacy variable is the composite endpoint of cardiovascular death, non-fatal myocardial infarction, non-fatal ischaemic stroke, hospitalisation for heart failure, hospitalisation for unstable angina pectoris or hospitalisation for coronary revascularisation.

The next secondary efficacy variable is time to any documented death.

Other efficacy variables

Other efficacy variables include:

- Addition of new antidiabetic medication or ≥1 step increase in dose for an oral antidiabetic drug or ≥25% increase in insulin dose which lasts for ≥3 months
- Start of insulin regimen which lasts for ≥3 months
- Hospitalisation for hypoglycaemia
- Cardiovascular death
- Non-fatal myocardial infarction
- Non-fatal ischaemic stroke
- Hospitalisation for heart failure
- Hospitalisation for unstable angina pectoris
- Hospitalisation for coronary revascularisation
- **Primary endpoint composite (CV death, non-fatal MI or non-fatal ischaemic stroke) occurring during the first year of follow-up and after the first year**

- Documented laser treatment due to development of and/or deterioration in diabetic retinopathy

- Diabetic renal disease progression (diabetic nephropathy) as assessed by the following:

  - Reduction from baseline of the microalbumin/creatinine ratio

  - Categorical change from baseline in albuminuria (normoalbuminuria, microalbuminuria, and/or macroalbuminuria)

  - Doubling of serum creatinine levels

  - Initiation of chronic dialysis and/or renal transplant and/or a serum creatinine >6.0 mg/dL (> 530 µmol/L)

- **The composite event of death, doubling of serum creatinine, initiation of chronic dialysis, renal transplant, or a serum creatinine > 6.0 mg/dL (> 530 µmol/L)**

Secondary safety variables

Secondary safety variables includes overall adverse events and adverse events of special interest. These will include assessment of the long-term effects of saxagliptin on decrease in lymphocyte counts, decrease in thrombocyte counts, severe infections, hypersensitivity reactions, liver abnormalities, bone fractures, pancreatitis, skin reactions and renal abnormalities

Other safety variables

Other safety variables will include hypoglycaemic events, cancers, peripheral oedema, pulse, laboratory tests, blood pressure, waist circumference and body weight.

Health economic and patient reported outcomes variables

Hospitalisations and the health-related quality of life questionnaire, the EuroQol-5D, will be measured at baseline, annually, and at the visit after any major adverse cardiovascular event has occurred.

Exploratory variables

Exploratory variables include:

- Future biological research

- Future genetic research

- Change from baseline in glycosylated haemoglobin A1c, fasting plasma glucose, homeostasis model assessment beta cell function and achievement of HbA1c ≤6.5% and <7% (every year and end of the study).

Statistical methods

Demographic and baseline characteristics will be summarised, using frequency distributions and summary statistics based on the intention-to-treat data set, for each treatment group as well as for all patients combined. Key baseline characteristics will be summarised.

The primary efficacy variable is the same as the primary safety variable: the time to first major adverse cardiovascular event.

The primary efficacy endpoint is the time to first major adverse cardiovascular event. The primary safety and efficacy analysis will be based on the intention-to-treat population, using events adjudicated and confirmed by the independent adjudication committee. Secondary time to event variables will be treated similarly.

For the primary and secondary time to event variables, hazard ratios and confidence intervals will be derived from a Cox proportional hazards model stratified by baseline renal impairment category and by CV risk category (established CV disease, multiple risk factors without established CV disease).

A confirmatory sequential test procedure to strongly control the family-wise type I error will be used for the primary objectives and the secondary objective.

Safety variables, including Adverse Events, laboratory results, and vital signs, will be summarized descriptively.

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

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

Abbreviation or special term	Explanation
ACS	Acute coronary syndrome
AE	Adverse event (see definition in Section 6.4.1)
ALT	Alanine aminotransferase (SGPT)
AST	Aspartate aminotransferase (SGOT)
bd	Twice daily
BMS	Bristol-Myers Squibb
BP	Blood pressure
CBC	Complete blood count
CEC	Clinical Event Adjudication Committee
CI	Confidence interval
CRF	Case Report Form (electronic/paper)
CRO	Clinical research organisation
CSR	Clinical Study Report
CV	Cardiovascular
CXCR4	CXC chemokine receptor 4
DMC	Data Monitoring Committee
DPP4	Dipeptidyl peptidase 4
E-code	Enrolment code
ECG	Electrocardiogram
EoT	End of treatment
EQ-5D	EuroQol-5D (health status questionnaire)
EQ-VAS	EuroQol-Visual Analog Scale
FDA	Food and Drug Administration
FPG	Fasting plasma glucose
GCP	Good Clinical Practice
GIP	Glucose-dependent insulinotropic polypeptide
GFR	Glomerular filtration rate
GLP-1	Glucagon-like peptide-1

Abbreviation or special term	Explanation
GLP-1R	Glucagon-like peptide-1 receptor
GMP	Good Manufacturing Practices
GPV&E	Global Pharmacovigilance and Epidemiology (BMS)
HbA1c	Glycosylated haemoglobin A1c
HDL-C	High-density lipoprotein cholesterol
HOMA-β	Homeostasis model assessment beta cell function
HR	Hazard ratio
ICF	Informed Consent Form
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
IP	Investigational Product
IRB	Institutional Review Board
ITT	Intention-to-treat [population]
IVRS/IWRS	Interactive voice response system/Interactive web response system
LDL-C	Low-density lipoprotein cholesterol
MACE	Major adverse cardiovascular events
MDRD	Modification of Diet in Renal Disease
MedDRA	Medical Dictionary for Regulatory Activities
MI	Myocardial infarction
OAE	Other significant adverse event (see definition in Section 11.2.2)
od	Once daily
OPI	Operational Procedure Instruction
PI	Principal Investigator
POP	Project Operational Procedures
PRO	Patient reported outcome
RANTES	Regulated on Activation Normal T-Cell Expressed and Secreted; also known as chemokine (C-C motif) ligand 5 (CCL5)
SAE	Serious adverse event (see definition in Section 6.4.2)
SDF-1	Stromal cell-derived factor-1
SMS	Short Message Service
SU	Sulphonylurea

Abbreviation or special term	Explanation
T2DM	Type 2 diabetes mellitus
TB	Total bilirubin
TIMI	Thrombolysis in Myocardial Infarction
TZD	Thiazolidinedione
ULN	Upper Limit Normal
WBDC	Web-based data capture
WOCBP	Women of childbearing potential

1. INTRODUCTION

1.1 Background

1.1.1 Diabetes and cardiovascular risk – implications for drug development

Cardiovascular disease is the leading cause of death in patients with type 2 diabetes mellitus (T2DM). More than 60% of all patients with T2DM die of CV disease and an even greater percentage have serious cardiovascular (CV) related complications (Fox et al 2007, Duckworth et al 2009). Diabetes is associated with a 2- to 4-fold increase in the risk of coronary heart disease and death (Gregg et al 2007). Patients with T2DM who have not had a myocardial infarction (MI) have a risk of infarction similar to that among nondiabetic patients who have had a prior MI (Haffner et al 1998, Schramm et al 2008, Juutilainen et al 2005). Pooled data of patients with acute coronary syndrome (ACS) in 11 independent Thrombolysis in Myocardial Infarction (TIMI) Study Group clinical trials from 1997 to 2006 suggest that, despite modern therapies for ACS, diabetes confers a significant adverse prognosis with mortality rates of 7.2% to 8% during the first year after an event (Donahoe et al 2007). Thus, while microvascular complications can lead to significant morbidity and premature mortality, by far the greatest cause of death in people with diabetes is CV disease (Skyler et al 2009).

There are compelling data in patients with T2DM supporting a reduced risk of microvascular complications with improved long-term glycaemic control (Skyler et al 2009, CDER Guidance on Diabetes Mellitus 2008). The ability of glucose lowering to impact CV outcome is not as clear. The United Kingdom Prospective Diabetes Study (UKPDS) observed a nonsignificant 16% reduction in CV complications (combined fatal or non-fatal MI and sudden death) with intensive glycaemic treatment. In an analysis of the study cohort, a continuous association was observed such that for every percentage point of lower median on-study glycosylated haemoglobin (HbA1c) there was a statistically significant 18% reduction in CV disease events, with no glycaemic threshold (Skyler et al 2009). Long-term follow-up of UKPDS demonstrated a significant 15% reduction in CV disease in the intensive glycaemic treatment group UK Prospective Diabetes Study (UKPDS80) Group 2008. The Diabetes Control Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT-EDIC) study, which included 1441 patients with type 1 diabetes, demonstrated a significant reduction in CV events (57%) in the intensively treated group after more than 12 years of follow-up (Nathan et al 2005).

1.1.2 Intervention studies with a focus on T2DM

1.1.2.1 Glucose intensity lowering and CV disease risk reduction

The University Group Diabetes Program (UGDP), launched in 1960, was an early, placebo-controlled, multicentre, clinical trial devised to determine which, if any, of the treatments for T2DM was efficacious in reducing CV risk (University Group Diabetes Program (UGDP) 1970). Patients treated with tolbutamide, a first-generation sulphonylurea drug, had a significantly higher rate of CV death than those given placebo or insulin. The

resulting concerns over potential sulphonylurea-related cardiotoxicity led to additional studies that both supported and conflicted with this finding.

One study to examine this question was the UKPDS (UK Prospective Diabetes Study 16 1995, UK Prospective Diabetes Study (UKPDS) Group 1998, Turner et al 1999). Though glucose lowering, with sulphonylureas or insulin, was associated with improvements in retinopathy, nephropathy and possibly, neuropathy, the improvements in CV complications were not statistically significant (as discussed in the previous section). In overweight patients treatment with metformin was associated with risk reductions of 32% for any diabetes-related endpoint, 42% for diabetes-related death, and 36% for all-cause mortality. However, early addition of metformin, in patients not achieving glycaemic goal on a sulphonylurea, was associated with an increased risk of diabetes-related death compared with continued sulphonylurea alone (UK Prospective Diabetes Study (UKPDS) Group 1998a).

More recently several large outcome studies demonstrated no reduction in CV outcomes with intensive glycaemic control (Duckworth et al 2009, Skyler et al 2009, ADVANCE Collaborative Group 2008). In addition, the Action to Control Cardiovascular Risk in Diabetes (ACCORD) study terminated its glycaemic control arm early due to the finding of increased mortality in participants randomised to a strategy of intensive glycaemic control with a target HbA1c of <6% (Skyler et al 2009, ACCORD Study Group 2008).

1.1.2.2 Glucose-lowering agents and CV disease risk reduction

While the primary endpoint (reduction in a composite of all-cause mortality, non-fatal MI [including silent MI]), stroke, acute coronary syndrome, endovascular or surgical intervention in the coronary or leg arteries and amputation above the ankle) was not met in the PROspective pioglitAzone Clinical Trial In macroVascular Events (PROactive) study, pioglitazone treatment did result in significant risk reduction in major adverse CV event composite secondary endpoints (Wilcox et al 2008).

In 2009 the Rosiglitazone Evaluated for Cardiovascular Outcomes in oral agent combination therapy for type 2 Diabetes (RECORD) study found that there was no increase in CV hospitalisation or death with rosiglitazone added to metformin or a sulphonylurea, compared to the combination of metformin and a sulphonylurea, but the rate of heart failure causing admission to hospital or death was significantly increased (Home et al 2009).

The Bypass Angioplasty Revascularisation Investigation 2 Diabetes (BARI 2D) trial was designed to test treatment strategies for patients with coronary artery disease and diabetes (BARI 2D Study Group 2009). Overall, there was no significant difference in the rates of death and major CV events between patients undergoing prompt revascularisation (either coronary artery bypass grafting or percutaneous coronary intervention) and those undergoing medical therapy or between strategies of insulin sensitisation and insulin provision.

The aim of the Hyperglycaemia and its Effect After Acute Myocardial Infarction on Cardiovascular Outcomes in Patients With Type 2 Diabetes Mellitus (HEART2D) study was to demonstrate a difference between two insulin strategies, one targeting postprandial

hyperglycaemia and the other targeting fasting and pre-meal hyperglycaemia, on time to first CV event in survivors of acute MI (Raz et al 2009). There was no observed difference in CV event rates between the two strategies.

1.1.2.3 Lipid-lowering agents

The impact of lipid-lowering treatment in patients with diabetes mellitus has been examined in studies such as the Pravastatin or Atorvastatin Evaluation and Infection Therapy (PROVE IT) Thrombolysis In Myocardial Infarction (TIMI) 22 [PROVE IT-TIMI 22] trial (Ahmed et al 2006). In this study intensive statin therapy, administered to ACS patients with DM, was associated with a reduction in cardiac events.

Lipid modification with fenofibrate and its effects on CV events in patients with T2DM was the focus of the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study (FIELD study 2005). Fenofibrate did not significantly reduce the risk of the primary outcome of coronary events. It did reduce total CV events, mainly due to fewer non-fatal MIs and revascularisations.

Lipid-lowering treatment with statins was also utilised in the Atorvastatin Study for Prevention of Coronary Heart Disease Endpoints in non-insulin-dependent diabetes mellitus (ASPEN), Heart Protection Study funded by the Medical Research Council / British Heart Foundation (MRC/BHF), and Long-Term Intervention with Pravastatin in Ischaemic Disease (LIPID) trials (Knopp et al 2006, Heart Protection Study 2003, Keech et al 2003). These investigated CV outcomes in the setting of patients with DIABETES MELLITUS(latter two included a sub-analysis of patients with DM) treated with atorvastatin, simvastatin or pravastatin, respectively. Though the results of the ASPEN study weren't statistically significant, these 3 studies confirmed the beneficial effect of statin treatment on CV outcomes in patients with diabetes.

These data are additionally supported by results of the Cholesterol Treatment Trialists' (CTT) Collaborators study (Cholesterol Treatment Trialists' (CTT) Collaborators 2008). The authors completed a meta-analysis of nearly 19000 individuals with diabetes in the context of an additional ~72000 nondiabetic individuals in 14 randomised trials of statin therapy. Their findings demonstrated a significant benefit of statin therapy on major CV events in individuals with diabetes.

1.1.2.4 Blood pressure lowering agents

The utility of tight blood pressure (BP) control was investigated in the UKPDS 38 trial (UK Prospective Diabetes Study Group 1998b). In patients with both hypertension and T2DM tight control of BP was associated with improvements in several outcomes including a clinically important reduction in the risk of death related to diabetes.

The impact of BP lowering/control on macro- and microvascular complications in patients with T2DM was studied in the Action in Diabetes and Vascular disease: preterAx and diamicroN-MR Controlled Evaluation (ADVANCE) trial (ADVANCE Collaborative Group

2008). The results showed that BP reduction resulted in reduced risk of major CV events, including death.

Similar results were observed in the Microalbuminuria, Cardiovascular and Renal Outcomes (MICRO) HOPE substudy (Heart Outcomes Prevention Evaluation (HOPE) Study Investigators 2000) where ramipril was beneficial for CV events in people with diabetes.

1.1.2.5 Multifactorial intervention

The STENO-2 study (including 160 patients) studied the effect of multifactorial intervention on mortality in T2DM patients. After 13.3 years of follow-up, it demonstrated significant lowering of risk of death from CV causes in addition to a significant reduction of CV events (Gaede et al 2008).

1.1.2.6 CV safety with other antidiabetic compounds

CV safety concerns have been raised with several antidiabetic compounds (mostly agents with a peroxisome proliferator-activated receptor agonistic mechanism of action) approved or under development for the treatment of T2DM (Nissen et al 2005, Nissen et al 2007).

On 1 and 2 July 2008, the Endocrinologic and Metabolic Drugs Advisory Committee of the Food and Drug Administration (FDA) met to discuss CV risk with oral antidiabetic agents and the role of risk assessment in the premarketing and postmarketing setting. After considering the discussion at this meeting, as well as other available data and information, the FDA determined that effects on CV risk should be more thoroughly addressed during development of antidiabetic agents (CDER Guidance on Diabetes Mellitus 2008). The FDA Guidance document identifies an upper bound of the 95% confidence interval (CI) for the risk ratio of important cardiovascular events of less than 1.3 as a key criterion for excluding an unacceptable increase in CV risk for new treatments of T2DM.

1.1.3 DPP4 inhibitors

1.1.3.1 Incretin mechanism of action

Incretin hormones are gastrointestinal hormones which increase insulin secretion in response to enteric stimulation. The 2 primary incretin hormones are glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP). These hormones contribute to the control of postprandial glucose excursions through a mechanism that is dependent on plasma glucose levels. The significance of meal ingestion on incretin-induced insulin release is illustrated in studies comparing insulin secretion after oral glucose versus that seen with intravenously administered glucose. Orally administered glucose produces the larger insulin response compared to intravenously administered glucose.

In addition to enhancing postprandial insulin release, GLP-1 reduces glucagon release from the pancreatic α-cells, thereby decreasing hepatic glucose production. This effect is also glucose-dependent, such that when plasma glucose is normal or low, the counter-regulatory response of glucagon release is not impaired.

1.1.3.2 Saxagliptin

Saxagliptin (BMS-477118) is a highly potent, selective, reversible, and competitive dipeptidyl peptidase 4 (DPP4) inhibitor. DPP4 is the enzyme responsible for the inactivation of GLP-1 and GIP. By inhibiting the enzyme DPP4, saxagliptin potentiates active endogenous GLP-1 concentrations, augmenting the physiological mechanism of insulin secretion and decreasing glucagon release, thereby reducing postprandial and fasting glucose levels in patients with T2DM.

The results from the 8 clinical studies in the saxagliptin Phase IIb and III programmes in over 4600 patients combined with the results from clinical pharmacology studies support the oral dose of saxagliptin 5 mg once daily in a wide range of patients with T2DM, as either monotherapy, add-on combination therapy with metformin, a thiazolidinedione (TZD), or a sulphonylurea (SU), or initial combination therapy with metformin.

1.1.3.3 CV data from saxagliptin

The overall CV profile of saxagliptin was analysed in Phase IIb/III studies that were submitted for review by health authorities. Hazard ratios (HRs) and corresponding 95% CI for saxagliptin and comparator were calculated using the Cox proportional hazards model, as well as incidence rate ratios, and incidence ratios with corresponding 95% CI using the Mantel-Haenszel approach. In retrospective analyses of the Phase IIb/III Pooled Population capturing CV adverse events (AEs) according to a selective major adverse CV event (MACE)–like composite (referred to as primary MACE), the point-estimates of the HRs for all saxagliptin:control were less than 1 (range: 0.44 to 0.49), and the upper-bounds of the 95% CIs were less than 1 (range: 0.82 to 0.90).

A total of 41 patients in the Phase IIb/III Pooled Population were identified as having a primary MACE, 23 (0.7%) in the all saxagliptin group and 18 (1.4%) in the comparator group (Table 1). There was no evidence for an increased risk of primary MACE in the saxagliptin groups compared with the control groups. There was also no evidence for a dose-response relationship with primary MACE for saxagliptin doses of 2.5 through 10 mg.

Table 1 Summary of primary MACE (120-day database) phase IIb/III pooled population and phase IIb and III studies

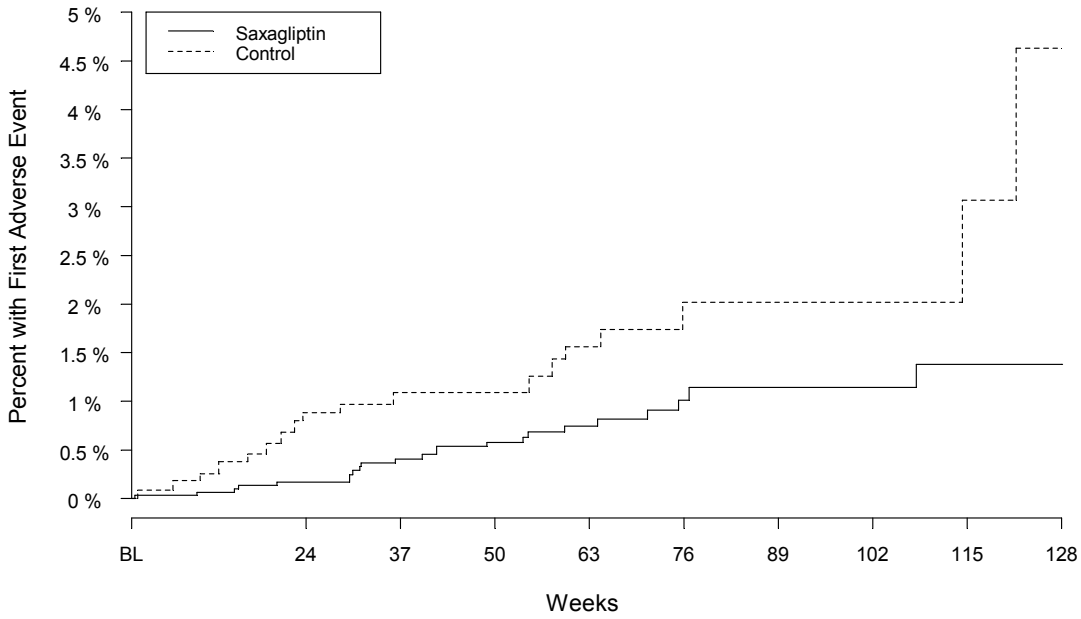
Population	Saxa 2.5 mg n/N (%)	Saxa 5 mg n/N (%)	Saxa 10 mg n/N (%)	All Saxa[1] n/N (%)	Comparator[2] n/N (%)
Pooled PIIb/III	6/937 (0.6)	6/1269 (0.5)	11/1000 (1.1)	23/3356 (0.7)	18/1251 (1.4)
Monotherapy					
CV181008[3]	0	0	0	0	0
CV181011[3]	0	2/106 (1.9)	0	2/306 (0.7)	1/95 (1.1)
CV181038[3]	0	0	NA	0	1/74 (1.4)
CV181041[3]	NA	0	NA	0	0

Population	Saxa 2.5 mg n/N (%)	Saxa 5 mg n/N (%)	Saxa 10 mg n/N (%)	All Saxa[1] n/N (%)	Comparator[2] n/N (%)
Add-on combination					
+Met CV181014[3]	1/192 (0.5)	1/191 (0.5)	4/181 (2.2)	6/564 (1.1)	4/179 (2.2)
+SU CV181040[3]	2/248 (0.8)	1/253 (0.4)	NA	3/501 (0.6)	6/267 (2.2)
+TZD CV181013[3]	3/195 (1.5)	1/186 (0.5)	NA	4/381 (1.0)	1/184 (0.5)
Initial comb. CV181039[3]	NA	1/320 (0.3)	7/658 (1.1)	8/978 (0.8)	5/328 (1.5)

[1]Includes 20 to 40 mg and 100 mg experience from CV181008[3]
[2]Includes metformin monotherapy from CV181039[3]
[3]FDA Meeting 2009

The time to onset of first primary MACE in the Phase IIb/III pooled population is shown in Figure 1. The data in Figure 1 indicate no increased risk of primary MACE for saxagliptin-treated patients during both the short-term and long-term periods of the clinical studies. Based on this comprehensive set of analyses designed for signal detection of CV events in the saxagliptin programme, there was no indication of an increase in CV risk with saxagliptin use or any indication of a CV safety-related signal. There was no evidence for imbalance in event frequency when looking at overall cardiac events. Although numbers of events were small, results were generally consistent across specific study settings (ie, monotherapy, add-on combination treatment, and initial combination treatment), and there was no evidence for a dose-response relationship for saxagliptin doses of 2.5 through 10 mg.

Figure 1 **Time to onset of first major adverse cardiac event - weighted Kaplan-Meier estimate for cumulative proportion during short-term + long-term treatment period (120-day safety update) - pooled**



Subjects at Risk:

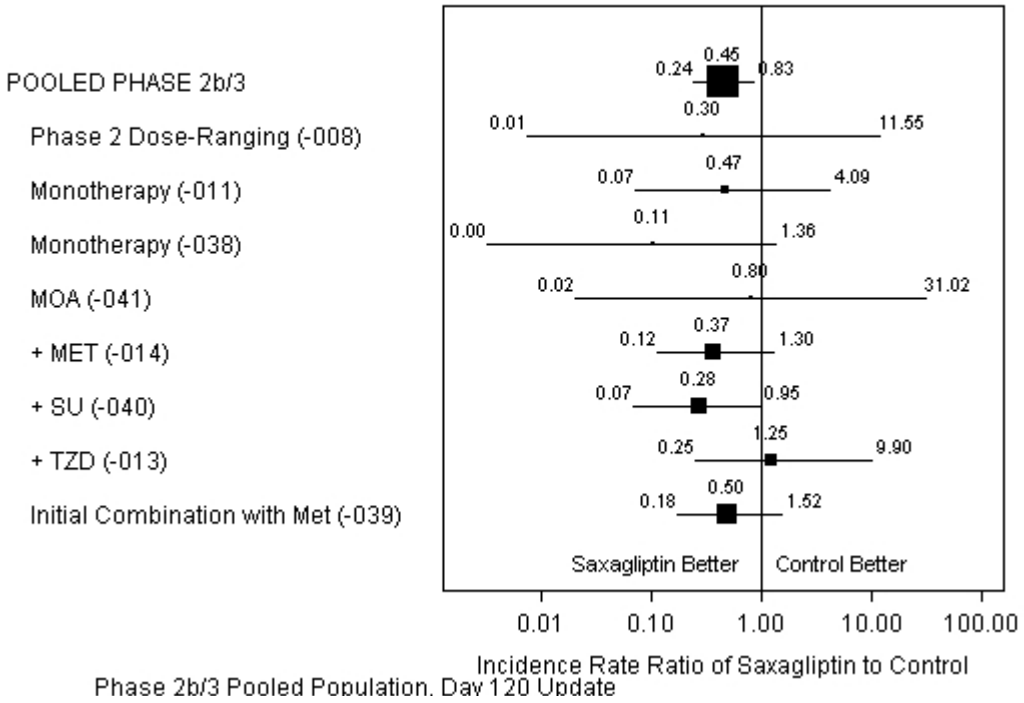
Saxagliptin:	3356	2615	2419	2209	1638	994	498	436	373	197
Control:	1251	935	860	774	545	288	144	123	102	57

Data set: Treated Subjects - Phase 2b/3 Pooled Population (CV181011 open label cohort excluded) - Day 120 Update
Source: Table 2.17.1
Program Path: P:/shared/Saxagliptin External Data/CV181ADCOM/val/graphs/final/km_mace.ssc
Run Date: 18Feb2009 15:20:48 EST

Fatal outcomes were assessed in the Phase IIb/III pooled population (120-day database). The frequency of CV deaths was 0.2% (7/3356) in patients treated with saxagliptin and 0.8% (10/1251) in patients in the control group. For all-cause mortality, the frequency was 0.3% (10/3356) in patients treated with saxagliptin and 1.0% (12/1251) in patients in the control group.

For the Phase IIb/III pooled population, the overall incidence rate ratio based on a stratified Mantel-Haenszel approach (95% CI) for primary MACE was 0.45 (0.24, 0.83). The results were consistent across the studies (Figure 2).

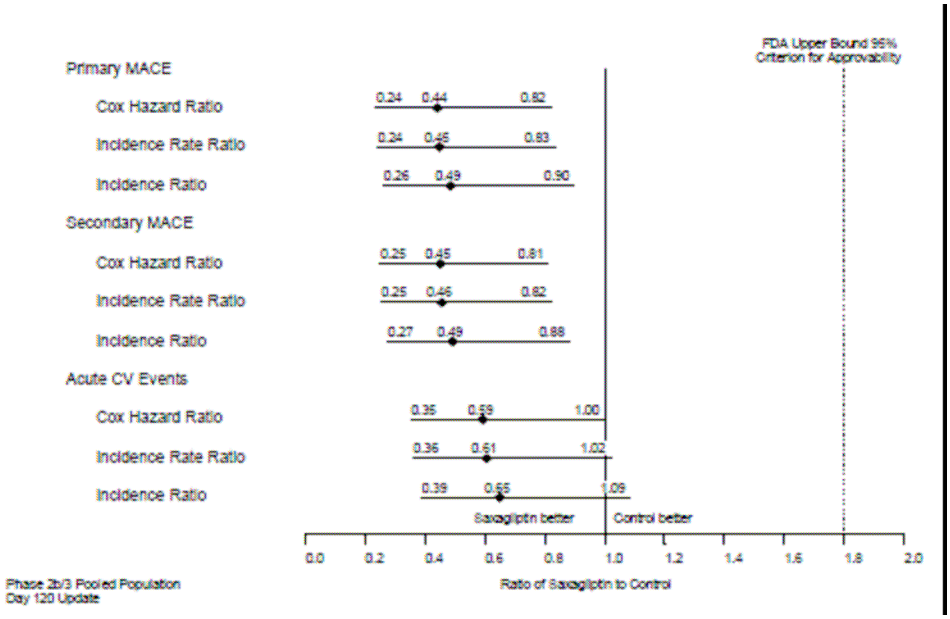
Figure 2 **Stratified analyses of incidence rate ratio of sponsor-defined primary MACE (120-day database) phase IIb/III pooled population and phase IIb and III studies**



Hazard ratios and corresponding 95% CI for saxagliptin and comparator using the Cox Proportional hazards model, as well as incidence rate ratios, and incidence ratios with corresponding 95% CI using the Mantel-Haenszel approach are summarised in Figure 3 for the endpoints primary MACE, secondary MACE (defined as MI, stroke and all-cause mortality), and acute CV events (defined as a broad set of adverse events with underlying cardiac etiology, including reversible and irreversible ischaemic events and revascularisation procedures). In all analyses of the Phase IIb/III pooled population, the point-estimates of the ratios were less than 1 (range: 0.44 to 0.65). In addition, in all analyses, the upper bound of the 95% CI was <1.1 (range: 0.81 to 1.09).

Based on this comprehensive set of analyses designed for signal detection of CV events in the saxagliptin programme, there was no indication for an increase in CV risk with saxagliptin use or any indication of a CV safety-related signal. There was no evidence for imbalance in event frequency when looking at overall cardiac events. Results were consistent across specific study settings (ie, monotherapy, add-on combination treatment, and initial combination treatment), and there was no evidence of a dose-response relationship for saxagliptin doses of 2.5 through 10 mg.

Figure 3 **Stratified analyses of sponsor-defined CV endpoints (120-day database) phase IIb/III pooled population**



CV risk factors in the Phase IIb/III pooled population

The baseline CV risk profile of the Phase IIb/III pooled population. A total of 569 patients had clinically evident CV disease upon entry to the Phase IIb/III studies, defined as a history of MI, congestive heart failure, hospitalisation for unstable angina pectoris, stable angina pectoris, prior percutaneous coronary intervention, prior coronary artery bypass surgery, coronary artery disease, cerebrovascular disease, or peripheral vascular disease (Table 2). While T2DM is a well-recognised risk factor for CV events, the majority (≥80%) of patients enrolled in the Phase IIb/III studies had at least one additional risk factor for CV events (including prior history of hypertension, hypercholesterolaemia, smoking, or first-degree relative with premature coronary heart disease). Approximately 15% of patients were elderly (≥65 years of age). The data in Table 2 indicate that the Phase IIb/III programme included a substantial number of patients at increased risk for CV events.

Table 2 **CV risk factors at baseline in the phase IIb/III pooled population**

	Saxa 2.5 mg N = 937	**Saxa 5 mg N = 1269**	**Saxa 10 mg N = 1000**	**All Saxa[1] N = 3356**	**Control[2] N = 1251**
History of CV disease[3], n (%)	118 (12.6)	150 (11.8)	118 (11.8)	404 (12.0)	165 (13.2)
At least one other CV risk factor (in addition to T2DM), n (%)	777 (82.9)	1015 (80.0)	803 (80.3)	2724 (81.2)	1035 (82.7)
Hypertension, n (%)	519 (55.4)	655 (51.6)	510 (51.0)	1750 (52.1)	688 (55.0)

	Saxa 2.5 mg N = 937	Saxa 5 mg N = 1269	Saxa 10 mg N = 1000	All Saxa[1] N = 3356	Control[2] N = 1251
Hypercholesterolaemia[4], n (%)	471 (50.3)	565 (44.5)	353 (35.3)	1475 (44.0)	566 (45.2)
Smoking history, n (%)	383 (40.9)	449 (35.4)	393 (39.3)	1301 (38.8)	471 (37.6)
First-degree relative with premature coronary heart disease, n (%)	190 (20.3)	248 (19.5)	186 (18.6)	677 (20.2)	265 (21.2)
Gender					
Male, n (%)	444 (47.4)	625 (49.3)	495 (49.5)	1659 (49.4)	620 (49.6)
Female, n (%)	493 (52.6)	644 (50.7)	505 (50.5)	1697 (50.6)	631 (50.4)
Age Categories					
<65 years, n (%)	783 (83.6)	1084 (85.4)	854 (85.4)	2850 (84.9)	1058 (84.6)
≥65 years, n (%)	154 (16.4)	185 (14.6)	146 (14.6)	506 (15.1)	193 (15.4)

[1] Includes 20-, 40- and 100-mg experience from CV181008 FDA Meeting 2009
[2] Includes metformin monotherapy from CV181039 FDA Meeting 2009
[3] CV history includes: previous MI, congestive heart failure and hospitalised for unstable angina, stable angina, percutaneous coronary intervention, coronary artery bypass graft, coronary artery disease, cerebrovascular disease, or peripheral vascular disease
[4] Includes mixed dyslipidemia

As a class, the long-term impact of DPP4 inhibitors on the major cause of morbidity and mortality in T2DM, namely CV complications, remains unknown as there are no long-term data regarding the CV safety and efficacy of these agents. However, the consistent findings of a HR <1.0 in the saxagliptin Phase IIb/III programme support the hypothesis that treatment with saxagliptin may confer a reduction in CV events.

1.1.3.4 Potential mechanisms for DPP4 inhibition to modify CV risk

Experimental data

Receptors for GLP-1 have been found in a variety of extrapancreatic tissues including the heart (Bullock et al 1996). Endothelium, cardiac and vascular myocytes express a functional glucagon-like peptide-1 receptor (GLP-1R). GLP-1 administration resulted in increased glucose uptake, cAMP and cGMP release, left ventricular developed pressure, and coronary flow in isolated mouse hearts (Ban et al 2008). GLP-1 also increased functional recovery and cardiomyocyte viability after ischaemia-reperfusion injury of isolated hearts and dilated preconstricted arteries from wild-type mice (Bose et al 2005, Bose et al 2007). GLP-1 increased myocardial glucose uptake and enhanced recovery of cardiac function after low-flow ischaemia in rats (Zhao et al 2006). GLP-1 attenuated postischaemic regional contractile dysfunction after brief coronary artery occlusion in conscious dogs and this effect was accompanied by improvement in left ventricular diastolic relaxation (Nikolaidis et al 2005).

Treatment with liraglutide for 7 days of male C57BL/6 mice demonstrated that GLP-1R activation engages prosurvival pathways in the normal and diabetic mouse heart, leading to improved outcomes and enhanced survival after MI in vivo (Noyan-Ashraf et al 2009).

Several additional DPP4 substrates such as stromal cell–derived factor-1 (SDF-1) and regulated on activation normal T-cell expressed and secreted (RANTES) chemokine may be associated with cardio-protective effects. SDF-1, which activates the cell-survival factor protein kinase B (PKB/Akt) via the G protein–coupled receptor CXCR4, protected tissue after an acute ischaemic event in mice (Saxena et al 2008). Exercise training simultaneously increased circulating SDF-1 and endothelial progenitor cells in patients with chronic heart failure (Sarto et al 2007). Low plasma levels of RANTES chemokine were shown to be an independent predictor of cardiac mortality in men referred for coronary angiography (including men with T2DM) (Cavusoglu et al 2007). Genetic polymorphisms that cause decreased expression of RANTES have been associated with increased mortality (mainly due to cardiac events) in patients with T2DM and end-stage renal disease undergoing haemodialysis (Boger et al 2005).

CV data with other DPP4 inhibitors

Inhibitors of DPP4, such as saxagliptin, have been shown to be safe and well-tolerated. Pooled analysis of data from the vildagliptin and sitagliptin development programmes suggest that the overall CV events were similar or somewhat lower between patients treated with a DPP4 inhibitor and comparator groups. In the vildagliptin programme, overall incidences of cardio- and cerebrovascular events for vildagliptin 50 mg once daily (od) (0.7%) and 50 mg bd (0.6%) were less than placebo (1.3%); the corresponding unadjusted odds ratios were less than 1 (0.55 and 0.45 respectively, $p<0.05$ vildagliptin 50 mg bd vs placebo) (Kothny et al 2008). In the sitagliptin programme, the overall incidence rates of CV serious adverse events (SAEs) were reported as 1.2% in the sitagliptin group and 1.5% in the non-exposed group (between-group difference 95% CI = -0.3% [-1.0, 0.3]) (Williams-Herman et al 2008).

Clinical data with GLP-1 agonists

Nikolaidis et al assessed the safety and efficacy of a 72-hour infusion of GLP-1 (1.5 pmol/kg per minute) added to background therapy in 10 patients with acute MI and left ventricular ejection fraction <40% after successful primary angioplasty compared with 11 control patients (Nikolaidis et al 2004). GLP-1 infusion improved regional and global left ventricular function in patients with acute MI and severe systolic dysfunction after successful primary angioplasty. Chronic (5-week) infusion of GLP-1 significantly improved left ventricular function, functional status, and quality of life in patients with severe heart failure (Sokos et al 2006). Perioperative use of GLP-1 prior to CV surgery achieves better glycaemic control and comparable haemodynamic recovery (Sokos et al 2007). However, the control group required greater use of inotropic and vasoactive infusions during the 48 hours after the procedure to achieved the same haemodynamic result. In addition, more frequent arrhythmias requiring anti-arrhythmic agents in the control group were noted. DPP4 inhibitors were not tested in similar conditions.

Summary

As discussed in Section 1.1.3.3, hypothesis-generating data derived from retrospective analyses of primary MACE in the Phase IIb/III programme, suggests a reduced HR for saxagliptin vs control. In addition, there is a growing base of data suggesting a direct effect of GLP-1 on the cardiac muscle and vasculature as well as a possible CV protective effect of other DPP4 substrates such as SDF-1 and RANTES.

1.1.4 Long-term glycaemic efficacy of antidiabetic drugs

Although it is well recognised that glycaemic control results in the reduction of microvascular complications (Nathan et al 2005, Nathan et al 2009), achieving long-term control is difficult. Glucose levels increase over time, probably as a consequence of declining β-cell function (UK Prospective Diabetes Study 16 1995). The UKPDS reported that, by 3 years after diagnosis of diabetes, approximately 50% of patients required more than 1 pharmacological agent (ie, multiple therapies) to achieve or maintain the target values of HbA1c, and by 9 years approximately 75% of patients required multiple therapies to achieve fasting plasma glucose (FPG) concentrations of less than 7.8 mmol/L (140 mg/dL) or HbA1c levels below 7% (Turner et al 1999). The progressive nature of T2DM was also demonstrated in the A Diabetes Outcome Progression Trial (ADOPT) study. Using the longitudinal linear model, a mean HbA1c level of <7% was maintained until the visit at 57 months in the rosiglitazone group, at 45 months in the metformin group, and at 33 months in the glyburide group. At 4 years, only 36% of the 1454 patients randomised to metformin treatment and 26% of the 1441 patients randomised to glyburide treatment had an HbA1c of <7% (Kahn et al 2006).

Short-term studies (12 months) with DPP4 inhibitors provided evidence of comparable glycaemic control vs sulphonylurea drugs (Nauck et al 2007, Ferrannini et al 2009). A growing database supports an enhanced β-cell function associated with the use of DPP4 inhibitors (D'Alessio et al 2009, Mari et al 2005). However, long-term studies (3 to 5 years) assessing the long-term implications of DPP4 inhibition and augmentation in incretin levels are not available. Sustained increase of GLP-1 was shown to preserve β in diabetic animal models and in human β cells in vitro, suggesting that treatment with DPP4 might preserve β cell mass and function.

1.2 Research hypothesis

The aims of this study are to definitively exclude unacceptable CV toxicity due to saxagliptin treatment and to test the hypothesis that treatment with saxagliptin will reduce CV events in patients with T2DM compared to placebo. As discussed in Section 1.1, hypothesis-generating data derived from retrospective analysis of MACE suggests a possible favourable effect on CV risk for saxagliptin.

1.3 Rationale for conducting this study

CV disease is a major cause of morbidity and mortality in patients with T2DM. While epidemiological data links glycaemic control to CV disease risk, so far, clinical trials have failed to definitively demonstrate that glucose-lowering reduces CV events. Data from several

recently reported large outcome studies demonstrated no reduction in CV outcomes with intensive glycaemic control (Duckworth et al 2009, Skyler et al 2009, ACCORD Study Group 2008). Furthermore, the Action to Control Cardiovascular Risk in Diabetes (ACCORD) study terminated its glycaemic control study early due to the finding of increased mortality in participants randomised to a strategy of intensive glycaemic control with a target HbA1c of <6% (Skyler et al 2009, ACCORD Study Group 2008). Thus, an antidiabetic therapy that provides reduced CV risk in addition to glucose lowering properties will be of great importance to clinical care of patients with T2DM. Animal and clinical data suggest that some of the DPP4 substrates may have a CV protective effect. In addition, hypothesis-generating data from the saxagliptin Phase IIb/III programme suggests not only lack of CV harm but also a positive trend in terms of CV risk reduction. Thus, the purpose of this Phase IV clinical study is to evaluate the effect of saxagliptin on the incidence of the composite assessment of CV death, non-fatal MI, or non-fatal ischaemic stroke in patients with T2DM with a primary superiority assessment.

1.4 Benefit/risk and ethical assessment

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

The results from the 8 studies in the saxagliptin Phase IIb/III programmes in over 4600 patients combined with the results from clinical pharmacology studies support the oral dose of saxagliptin 5 mg once daily in a wide range of patients with T2DM, as either monotherapy, add-on combination therapy with metformin, a thiazolidinedione, or a sulphonylurea, or initial combination therapy with metformin.

Currently none of the available antidiabetic agents are indicated for CV risk reduction in patients with T2DM. The Phase IIb/III programme has not only established the efficacy and safety of saxagliptin in lowering glucose levels (as assessed by HbA1c) but also created hypothesis-generating data suggesting fewer occurrences of MACE. This clinical study will test this hypothesis in a rigorous fashion. The potential results of such a study will be of great benefit to all patients with T2DM.

2. STUDY OBJECTIVES

2.1 Primary objectives

2.1.1 Primary efficacy objective

The primary efficacy objective is to determine, as a superiority assessment, whether treatment with saxagliptin compared with placebo when added to current background therapy will result in a reduction in the composite endpoint of CV death, non-fatal MI or non-fatal ischaemic stroke in patients with T2DM.

2.1.2 Primary safety objective

The primary safety objective of this trial is to establish that the upper bound of the 2-sided 95% CI for the estimated risk ratio comparing the incidence of the composite endpoint of CV death, non-fatal MI or non-fatal ischaemic stroke observed with saxagliptin to that observed in the placebo group is less than 1.3.

2.2 Efficacy objectives

2.2.1 Secondary efficacy objective

The **first** secondary efficacy objective is to determine whether treatment with saxagliptin compared with placebo when added to current background therapy in patients with T2DM will result in a reduction of the composite endpoint of CV death, non-fatal MI, non-fatal ischaemic stroke, hospitalisation for heart failure, hospitalisation for unstable angina pectoris or hospitalisation for coronary revascularisation.

The next secondary efficacy objective is to determine whether treatment with saxagliptin compared with placebo when added to current background therapy in patients with type 2 diabetes mellitus will result in a reduction of all-cause mortality.

2.2.2 Other efficacy objectives

Other efficacy objectives are to determine whether treatment with saxagliptin compared with placebo when added to current background therapy in patients with type 2 diabetes mellitus will result in a reduction of:

- Need for increase in dose or addition of new antidiabetic medication
- Initiation of insulin therapy in patients not receiving insulin therapy at baseline
- Hospitalisation for hypoglycaemia
- The individual components of the primary endpoint (CV death, non-fatal MI or non-fatal ischaemic stroke)
- The individual additional components of the secondary efficacy endpoint (hospitalisation for any of the following: heart failure, unstable angina pectoris and coronary revascularisation)
- **The primary composite endpoint (CV death, non-fatal MI or non-fatal ischaemic stroke) during the first year of follow-up and after the first year**
- Retinal laser treatment due to development of and/or deterioration in diabetic retinopathy
- New and/or progression of diabetic nephropathy

- **The composite event of death, doubling of serum creatinine, initiation of chronic dialysis, renal transplant, or a serum creatinine > 6.0 mg/dL (> 530 µmol/L)**

2.3 Safety objectives

2.3.1 Secondary safety objectives

Safety and tolerability will be evaluated by assessment of overall AEs and AEs of special interest. These will include assessment of the long-term effects of saxagliptin on decrease in lymphocyte counts, decrease in thrombocyte counts, severe infections, hypersensitivity reactions, liver abnormalities, bone fractures, pancreatitis, skin reactions and renal abnormalities. See Appendix I for information on identification of these events.

2.3.2 Other safety objectives

Other safety objectives will include assessment of hypoglycaemic events, cancers, peripheral oedema, laboratory tests, pulse, BP, waist circumference and body weight.

2.4 Exploratory objectives

Exploratory objectives include:

- Future biological research (optional), see Appendix H (does not apply to the People's Republic of China)
- Future genetic research (optional), see Appendix F (does not apply to the People's Republic of China)
- Collection of standard parameters used to assess glycaemic control. These include the change from baseline in HbA1c, FPG, homeostasis model assessment beta cell function (HOMA-β) and achievement of HbA1c ≤6.5% and <7% (every year and end of the study visit).

2.5 Health economic and patient reported outcomes

Health economic data (hospitalisation information) and the patient reported outcome (PRO) of health-related quality of life data (gathered by using the EuroQol-5D questionnaire [EQ-5D]) will be compared between the 2 study arms (see Sections 6.5 and 6.9).

3. STUDY PLAN AND PROCEDURES

This Clinical Study Protocol has been subjected to a peer review according to AstraZeneca and Bristol-Myers Squibb (BMS) standard procedures.

3.1 Overall study design and flow chart

This is a multicentre, randomised, double-blind, placebo-controlled Phase IV study to evaluate whether treatment with saxagliptin can reduce the composite endpoint of CV death, non-fatal MI or non-fatal ischaemic stroke in patients with T2DM and to definitively exclude unacceptable CV toxicity. The anticipated duration of the study is approximately **4-5** years, including an anticipated enrolment period of 1-2 years and follow-up period of 3 years. However, the duration of the trial will be based on accrual of the predetermined number of events, and therefore the study may be shorter or longer.

Patients with documented T2DM and with either a history of previous CV events or multiple risk factors for vascular disease (see Section 4.1) will be enrolled from sites throughout the world. To reflect a scenario as close to real life as possible, both patients who are treated with glucose-lowering medication including oral antidiabetics and/or insulin (with the exception of incretin-based therapy) and treatment-naïve patients will be enrolled.

All patients will be treated to regional standards of care for cardiovascular risk factors (eg, blood pressure, lipids) and HbA1c. Investigators will be duly informed of this requirement via study aids and via information provided at Investigator's Meetings.

The study will focus on recruiting T2DM patients at elevated risk for CV events according to the two categories below:

- Patients with established CV disease (secondary prevention)
- Patients with multiple risk factors for CV events, but without established CV disease (primary prevention)

Further grouping of the patients will be based on their renal function (estimated GFR) according to the Modification of Diet in Renal Disease (MDRD) formula, (Levy et al 2006), see (Section 11.2.1):

- Normal renal function and mild renal impairment (estimated GFR >50mL/min)
- Moderate renal impairment (estimated GFR 30 to 50 mL/min)
- Severe renal impairment (estimated GFR <30 mL/min), excluding patients on chronic dialysis

Approximately **16500** patients meeting all eligibility criteria at approximately **900** study sites will be randomised (1:1) to receive either saxagliptin or placebo. Patients will be distributed as follows: at least 30% in North America, approximately 30% in Europe, and the remainder in South America, Asia, Australia, and South Africa.

Patients considered as primary prevention patients (ie, presenting with multiple risk factors for vascular disease but having no confirmed history of previous CV disease) will be capped at **approximately 3500 patients, or approximately 21%** of the total cohort. All potentially

eligible patients will undergo a combined screening/enrolment/randomisation visit. Each patient will sign an Informed Consent Form (ICF) and have screening evaluations performed.

At least 800 patients with moderate to severe renal impairment will be randomised into the study, approximately 300 of them with severe renal impairment. No more than approximately **15700** patients with normal renal function or mild renal impairment will be randomised to ensure that at least 800 patients with moderate to severe renal impairment are included. Once 300 patients with severe renal impairment are randomised, randomisation into this group will be stopped. The dose of saxagliptin is 5 mg in patients with normal renal function and mild renal impairment and 2.5 mg in patients with moderate and severe renal impairment (see Figure 4).

As all randomised patients will belong to the Intention To Treat (ITT) population and be part of the efficacy and safety analyses, it is important to avoid randomisation of non-eligible patients into the study (see Section 5.3).

During the randomised treatment period, diet and life-style modification will be reinforced.

An independent Data Monitoring Committee (DMC), a blinded independent Clinical Event adjudication Committee (CEC) (see Section 12.4) and Executive and Steering Committees (see Section 12.5) will be selected by the Sponsor and the academic leadership (TIMI Study Group and Professor Raz, Hadassah Medical Center).

The study plan, including enrolment/randomisation and follow-up visits, is outlined in Table 3. If the study would need to be prolonged to accrue the predetermined number of the primary endpoint events, visits and assessments will be added according to the same schedule as described in the study plan (Table 3).

Patients will return every 6 months for assessment of events related to the objectives of the study, tolerability and safety. Assessment of treatment compliance and provision of study drug will be done at these 6-month visits. In addition, phone contacts will be performed at a 3-month interval in between regular visits. Following the decision of the Executive Committee to close the trial, all Investigators will receive communication to complete an End-of-Treatment (EoT)/Closing Visit for patients still being treated with investigational product (IP), or a Closing Visit to capture any AEs and clinical events for patients who have prematurely discontinued IP. The latter patients should have completed the EoT visit in connection with the discontinuation of IP and subsequently attended the scheduled visits to capture any clinical events. Refer to Section 5.8.1 for details on procedures for discontinuing patients from IP.

Unless there is a scheduled visit within approximately 4 weeks after the date estimated by the Executive Committee as the end of the study, the Investigator/qualified designee will arrange for an EoT/Closing visit as soon after the estimated end-of-study date as possible.

All randomised patients, whether taking randomised IP or not, should be followed up at the end of the study at a minimum for CV events and survival. Survival based on publicly

available sources in cases where patients have withdrawn consent will also be investigated at the study end.

Visit 1 (0 month)

All potentially eligible patients will undergo a combined screening/enrolment/randomisation visit (may be performed during a period of 14 days) following their signed informed consent. If the patient has been clinically stable, HbA1c and serum creatinine values performed within the prior 6 months may be used to determine eligibility and treatment dose. If they have not been measured within 6 months, they should be performed as part of the screening assessments before randomisation to determine eligibility.

Following an 8-hour fast, the patients will have screening evaluations performed. Demography, medical history, and concomitant medication will be recorded. Women of childbearing potential will be tested for pregnancy. A physical examination and vital signs (pulse and BP), height and weight, waist circumference, as well as blood sampling for laboratory assessments of HbA1c, FPG, insulin, complete blood count (CBC) with differential, serum creatinine, total bilirubin (TB), alanine aminotransferase (ALT) and aspartate aminotransferase (AST), and limited urinalysis (for assessment of albumin and creatinine) will be done. Standard 12-lead electrocardiogram (ECG) readings will be recorded. Optional addenda to the informed consent for biological research and genetic research, respectively, will be obtained. The PRO questionnaire (EQ-5D) is to be completed. See Section 6.2 for further details on data collection. Patients who cannot complete the procedures required in the screening/enrolment/randomisation visit may split the visit and complete it within 14 days. Patients meeting all inclusion criteria and with no exclusion criteria will be randomised in a 1:1 ratio to receive either saxagliptin or placebo. Diet and life-style advice will be given.

Telephone contacts every 3 months

The patients will be contacted every 3rd month between regular site visits by the Investigator/study site personnel to record any AEs, suspected clinical events, IP status and use of concomitant medication. An unscheduled visit may be conducted as a result of the phone contact (eg, to follow-up on suspected clinical events).

Short Message Service contacts

In addition to standard telephone contact, patients will be asked to participate in use of a Short Message Service (SMS) technology to enhance the communication between the study site and the individual. The main purpose of this tool is patient retention because of the better "partnering" of the patient with the study site personnel. Permission from the patient to use this tool will be obtained by the study site. All patients will receive the same type messages within the major local language of their country of residence. This tool is not intended as a data collection tool.

The patient will receive messages such as 1) a reminder of their next visit; 2) reminder as to what to bring to their next visit (such as IP); 3) and messages of encouragement such as "Congratulations, you have just completed your first visit!" or "Happy Birthday".

Visits 2, 4, 6, 8 and 10 (6, 18, 30, 42 and 54 months)

Suspected clinical events and AEs will be recorded. Women of childbearing potential will be tested for pregnancy. IP will be returned and compliance assessed and new bottles of IP via the Interactive voice response system/Interactive web response system (IVRS/IWRS) will be dispensed. Concomitant medication will be recorded and diet and life-style advice will be given. If any event included in the composite endpoint of CV death, non-fatal MI or non-fatal ischaemic stroke has occurred since the previous visit, the EQ-5D will be completed.

Visits 3 and 7 (12 and 36 months)

Suspected clinical events and AEs will be recorded. If required, a targeted physical examination will be done. Vital signs (pulse and BP) as well as blood sampling (fasting not required) for laboratory assessments of HbA1c, CBC with differential, serum creatinine, TB, ALT and AST will be done. Women of childbearing potential will be tested for pregnancy. IP will be returned and compliance assessed and new bottles of IP via the IVRS/IWRS will be dispensed. The EQ-5D will be completed. Concomitant medication and weight will be recorded. Added assessments of urinalysis (microalbumin and creatinine) will be done. Diet and life-style advice will be given.

Visit 5 (24 months)

Suspected clinical events and AEs will be recorded. If required, a targeted physical examination will be done. Vital signs (pulse and BP) as well as fasting blood sampling for laboratory assessments of HbA1c, FPG, insulin, **lipids (Total-Cholesterol, LDL-Cholesterol, HDL-Cholesterol, and TG),** CBC with differential, serum creatinine, TB, ALT, AST as well as exploratory biomarkers will be done. Women of childbearing potential will be tested for pregnancy. IP will be returned and compliance assessed and new bottle of IP via the IVRS/IWRS will be dispensed. The EQ-5D will be completed. Concomitant medication will be recorded and diet and life-style advice will be given. Added assessments of urinalysis (microalbumin and creatinine), waist circumference and weight will be done.

Visit 9 (48 months)

Procedures according to Visit 3, with addition of limited urinalysis (for assessment of albumin and creatinine) will be done.

End of Study - End of Treatment (EoT)/Closing Visit (anticipated at approximately 60 months or within 4 weeks after the closing date)

This visit should occur within approximately 4 weeks following the closing date as declared by the Executive Committee. **The actual time window will be determined by the global SAVOR operational team.** The anticipated time is at approximately 60 months. The time may be sooner or later as the study is event driven; hence, there cannot be a specified number assigned to this visit.

For patients on randomised treatment the procedures to be completed at the Closing Visit are the complete EoT procedures as described in Table 3. They comprise the following: recording of suspected clinical events and AEs, a targeted physical examination, vital signs (pulse and BP), weight, waist circumference as well as fasting blood sampling for laboratory assessments of HbA1c, FPG, insulin, **lipids (Total-Cholesterol, LDL-Cholesterol, HDL-Cholesterol, and TG),** CBC with differential, serum creatinine, TB, ALT and AST, and limited urinalysis (for assessment of albumin and creatinine), pregnancy testing of women of childbearing potential, completion of the EQ-5D questionnaire, recording of concomitant medication, and return of IP, including compliance assessment.

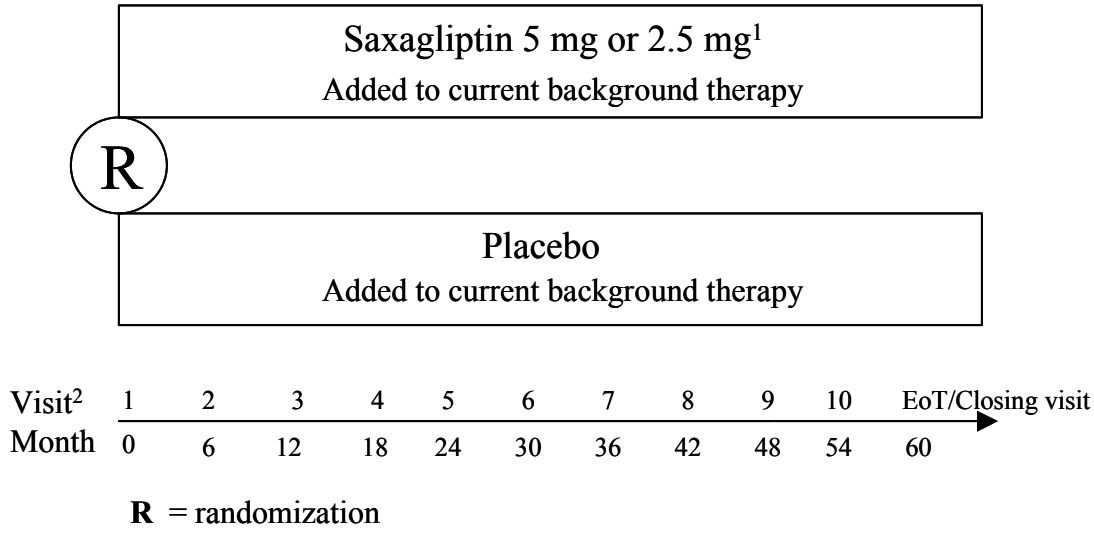
For patients who prematurely discontinued the randomised treatment, only AEs and suspected clinical events will be recorded at the Closing Visit. No further assessments are needed. The same is applicable for the other visits following the premature EoT, where the EoT assessments should be done at the time for discontinuation of treatment, if possible.

Clinical events are defined as all fatal events and all events comprised by the primary objectives (efficacy and safety) and the secondary efficacy objective (see Sections 2.1 and 2.2).

Unscheduled visits

Unscheduled visits or phone contacts may be performed for safety laboratory follow-up, (see Section 6.4.5), event follow-up or EoT assessments in case of early discontinuation of IP. Phone contacts or unscheduled visits can also be done any time during the study at the discretion of the Investigator.

Figure 4 Study design



The study is CV-event driven with an anticipated total duration of **4-5** years, including an enrolment period of **1-2** years and follow-up period of 3 years.

1 For patients with moderate to severe renal insufficiency, ie estimated GFR $\leq$50 ml/min
2 If study duration is reduced or extended, visits will be withdrawn or added as required every 6 months until the study is closed.

Table 3 Study plan

Activity	**Enrolment/ Randomisation**	**Double-blind treatment period (anticipated to 60 months)**									
Visit number[1,2,3,4]	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**EoT/ Closing visit[4]**
Study month	**0**	**6**	**12**	**18**	**24**	**30**	**36**	**42**	**48**	**54**	
Informed consent	X										
Demography and medical history	X										
Inclusion/exclusion criteria	X										
Randomisation	X										
Physical examination	X		X[5]		X[5]		X[5]		X[5]		X[5]
Vital signs	X		X		X		X		X		X
Weight	X		X		X		X		X		X
Height	X										
Waist circumference	X				X						X
12-lead ECG[6]	X										
Concomitant medication[7]	X	X	X	X	X	X	X	X	X	X	X
Pregnancy testing	X	X	X	X	X	X	X	X	X	X	X
Efficacy and Safety Laboratory assessments[8]											
HbA1c	X		X		X		X		X		X
FPG	X				X						X
Insulin	X				X						X
Albumin and creatinine excretion (urine)	X		X		X		X		X		X
CBC with differential	X		X		X		X		X		X

Table 3 Study plan

Activity	**Enrolment/ Randomisation**	**Double-blind treatment period (anticipated to 60 months)**									
Visit number[1,2,3,4]	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**EoT/ Closing visit**[4]
Study month	**0**	**6**	**12**	**18**	**24**	**30**	**36**	**42**	**48**	**54**	
Serum creatinine[9]	X		X		X		X		X		X
Total bilirubin	X		X		X		X		X		X
Aspartate aminotransferase (**AST** [SGOT])	X		X		X		X		X		X
Alanine aminotransferase (**ALT** [SGPT])	X		X		X		X		X		X
Lipids[14]					**X**						**X**
Patient reported outcomes EQ-5D questionnaire[10]	X		X		X		X		X		X
Informed consent and blood samples for biological research[11]	X				X						
Informed consent and blood sample for genetic research[12]	X										
Adverse events and Clinical events [13]		X	X	X	X	X	X	X	X	X	X
Dispense investigational product through IVRS/IWRS	X	X	X	X	X	X	X	X	X	X	
IP compliance		X	X	X	X	X	X	X	X	X	X
Diet and lifestyle advice	X	X	X	X	X	X	X	X	X	X	X

[1] Every 3 months sites will perform a documented phone call with each patient to follow up on events, concomitant medication and adherence to treatment.
[2] At the close of the study all patients will return for the EoT/Closing Visit. Patients who prematurely discontinued IP need only to be assessed for AEs and clinical events. These patients should, if possible, have the EoT assessments at the time of their discontinuation from IP.
[3] Unscheduled visits may be done for safety lab follow-up, event follow-up or EoT in case of early discontinuation of IP.

[4] Visits will be repeated every 6 months and also phone calls every 3 months, according to the previous pattern until the Closing Visit as required. If the study needs to be prolonged to accrue the number of required primary endpoints, visits would be added, ie assessments according to Visits 9 and 10 may be repeated.

[5] Targeted physical exam based on patient interview, AEs and laboratory results.

[6] May be obtained within prior 21 days if patient is clinically stable.

[7] Concomitant medication will be recorded according to Section 5.6.3.

[8] Fasting blood samples will be taken at Visits 1, 5 and EoT. Other blood samples may be taken under non-fasting conditions. Analyses will be done at a central laboratory.

[9] Estimated GFR will be estimated according to the Modification of Diet in Renal Disease (MDRD) formula.

[10] EQ-5D: In addition to annual assessment, the EQ-5D will be completed at the visit after any event included in the composite endpoint of CV death, non-fatal MI, or non-fatal ischaemic stroke has occurred.

[11] Blood samples to be drawn at Visits 1 and 5 **or at the End of Treatment visit in case of premature discontinuation of IP or if patient has not had a Visit 5 sample drawn at time of study closure,** following the specific informed consent; refer to Appendix H (Biological Research).

[12] Blood sample may be drawn after Visit 1 following the specific informed consent; refer to Appendix F (Pharmacogenetic Research).

[13] To be recorded also for patients who prematurely discontinued IP, includes all AEs and all events comprised by the primary objectives (efficacy and safety) and the secondary efficacy objective.

[14] Total-Cholesterol, LDL-Cholesterol, HDL-Cholesterol, and TG.

A description of the visit structure including the window for completion of the planned visits is depicted in Table 4.

Table 4 Visit design and visit windows

Visit ID	Visit description	Visit window
Visit 1	Enrolment/Randomisation	Can be performed over 14 days. Visit 1 date is the day the patient is randomised and receives IP, Day 0
Visit 2	Treatment	6 months (±14 days) after Visit 1
Visit 3	Treatment	12 months (±14 days) after Visit 1
Visit 4	Treatment	18 months (±14 days) after Visit 1
Visit 5	Treatment	24 months (±14 days) after Visit 1
Visit 6	Treatment	30 months (±14 days) after Visit 1
Visit 7	Treatment	36 months (±14 days) after Visit 1
Visit 8	Treatment	42 months (±14 days) after Visit 1
Visit 9	Treatment	48 months (±14 days) after Visit 1
Visit 10	Treatment	54 months (±14 days) after Visit 1
Visit X[1]	Treatment	XX months (±14 days) after Visit 1
	End of Treatment[2]/Closing Visit	60 months (±14 days) after Visit 1 or within 4 weeks of the study closing date

[1] Repeated visits as needed.
[2] EoT assessments will be done at a planned or unscheduled visit when a patient is prematurely discontinuing randomised treatment.
Telephone contacts every third month will also have a ±14 days visit window

3.2 Rationale for study design, doses and control groups

The aims of the study are to definitively exclude unacceptable cardiovascular toxicity with saxagliptin treatment and to test the hypothesis that treatment with saxagliptin will reduce CV events in patients with T2DM. As described in the introduction, Phase IIb/III clinical data support testing this hypothesis for saxagliptin in patients with T2DM. Currently, there is no clearly established risk benchmark for approved antidiabetic agents in terms of CV events and none is indicated for CV risk reduction. Thus, the appropriate comparator is placebo. The patient population proposed (ie, patients with T2DM at higher risk for CV events) is appropriate as this population may benefit the most from treatment that, in addition to glucose lowering, can also reduce CV risk.

The study will be double-blind, single-dummy, to minimise the risk of bias.

A composite assessment that includes CV death, non-fatal MI or non-fatal ischaemic stroke, is the accepted most rigorous way to assess CV effects of any given treatment.

3.2.1 Dose consideration

Data from the Phase IIb/III programme suggest that in patients with T2DM, treatment with saxagliptin resulted in consistent, clinically meaningful and statistically significant reductions in HbA1c, FPG and postprandial plasma glucose, as well as achievement of treatment targets for HbA1c. The 5 mg dose was consistently found to be safe and efficacious. Beneficial effects were demonstrated across subgroups of demographic and baseline diabetic characteristics, confirming the applicability of the data to the broader T2DM population.

Assessment of primary events included in the composite endpoint of CV death, non-fatal MI, or non-fatal ischaemic stroke in the Phase IIb/III population did not reveal any dose response across the 2.5- to 10-mg dose range. Since the mode of action for a potential effect to reduce CV risk is unknown at this stage, the dose selection for the planned study is based on the glycaemic efficacy and safety data in the Phase IIb/III programme. Furthermore, the 5 mg dose provides greater inhibition of DPP4 activity at trough (24 hours) compared with the 2.5 mg dose with only marginal increased inhibition with the 10 mg dose, supporting the use of the 5 mg dose also for a nonglycaemic–related endpoint, assuming the effect is related to DPP4 inhibition. Thus, the dose of saxagliptin used in this study will be 5 mg once daily in patients with normal renal function or mild impaired renal function.

A single dosage adjustment to 2.5 mg daily is recommended for patients with moderate or severe renal impairment (estimated GFR ≤50 mL/min), approximately corresponding to serum creatinine levels of ≥1.7 mg/dL (≥150 µmol/L) in men and ≥1.5 mg/dL (≥132 µmol/L) in women. Thus, patients with moderate to severe renal impairment (estimated GFR ≤50 mL/min) will be randomised to either saxagliptin 2.5 mg or matching placebo. Patients who develop renal impairment during the course of the study will have their dose of randomised treatment adjusted.

4. PATIENT SELECTION CRITERIA

Investigator(s) should keep a record, the patient screening log, of patients who entered pre-study screening using the Clinical Trial Screening Tool.

The study will focus on recruiting T2DM patients at elevated risk for CV events according to the 2 categories below (for further information on stratification and capping, see Section 5.2.1):

- Patients with established CV disease (secondary prevention)
- Patients with multiple risk factors for CV events, but without established CV disease (primary prevention)

Further grouping of the patients will be based on their renal function:

- Normal renal function and mild renal impairment (estimated GFR >50 mL/min)
- Moderate renal impairment (estimated GFR 30 to 50 mL/min)
- Severe renal impairment (estimated GFR <30 mL/min), excluding patients on chronic dialysis

Cardiologists, diabetologists, endocrinologists, nephrologists, primary care physicians and general practitioners are the primary Investigators of interest.

Each patient 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, patients should fulfil the following criteria:

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

2. Age ≥40 years

3. Diagnosed with T2DM based on the current American Diabetes Association guidelines

4. HbA1c ≥6.5% (based on the last measured and documented laboratory measurement in the previous 6 months)

5. High risk for a CV event defined as having either established CV disease and/or multiple risk factors:

   Established CV disease (see Appendix E):

   – Ischaemic heart disease, and/or

   – Peripheral vascular disease (eg, intermittent claudication), and/or

   – Ischaemic stroke

   Multiple Risk Factors

   Patient must be at least 55 years old (men) and 60 years old (females) and have at least one additional risk factor (treated or non-treated) from the following:

   – Dyslipidemia (based on the last measured and documented laboratory measurement in the previous 6 months and defined as at least 1 of the following):

- High level of low-density lipoprotein cholesterol (LDL-C), defined as >130 mg/dL (> 3.36 mmol/L)
- Low level of high-density lipoprotein cholesterol (HDL-C), defined as <40 mg/dL (<1.04 mmol/L) for men or <50 mg/dL (<1.30 mmol/L) for women

– Hypertension, as confirmed at the enrolment visit

- BP >140/90 mm/Hg or on a BP-lowering agent with BP >130/80 mm/Hg

– Currently smoking, as confirmed at the enrolment visit

6. Women of childbearing potential (WOCBP) must take precautions to avoid pregnancy throughout the study and for 4 weeks after intake of the last dose.

   WOCBP must have a negative urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of human chorionic gonadotropin) within 72 hours prior to the start of study medication.

   WOCBP include any female who has experienced menarche and who has not undergone successful surgical sterilisation (hysterectomy, bilateral tubal ligation or bilateral oophorectomy) or is not postmenopausal (defined as amenorrhea ≥2 consecutive years).

Inclusion criteria for the optional biological research

The inclusion criteria for the optional biological research are provided in Appendix H.

If a patient declines to participate in the biological research, there will be no penalty or loss of benefit to the patient. The patient will not be excluded from other aspects of the study as described in this protocol, as long as consent to the main study has been obtained.

Inclusion criteria for the optional genetic research

The inclusion criteria for the optional genetic research are provided in Appendix F.

If a patient declines to participate in the genetic research, there will be no penalty or loss of benefit to the patient. The patient will not be excluded from other aspects of the study as described in this protocol, as long as consent to the main study has been obtained.

It is possible that a patient may be randomised into the main study before the genetic component has been approved by the institution's Institutional Review Board (IRB). If that patient elects to participate in the genetic portion of this study, after IRB approval is granted, he/she may do so. The genetic sample is not limited to collection at Visit 1 but may be collected at any visit, provided that written informed consent for collecting the sample has been obtained.

4.2 Exclusion criteria

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

1. Any conditions that, in the opinion of the Investigator, may render the patient unable to complete the study including non-CV disease (eg, active malignancy, cardiomyopathy, cirrhosis, or chronic lung disease) with a likely fatal outcome within 5 years
2. Current or previous (within 6 months) treatment with an incretin-based therapy such as DPP4 inhibitors and or GLP-1 mimetics
3. Acute vascular (cardiac or stroke) event <2 months prior to randomisation
4. Initiation of chronic dialysis and/or renal transplant and/or a serum creatinine >6.0 mg/dL
5. Pregnant or breast-feeding patients
6. History of human immunodeficiency virus
7. Patients being treated for severe auto immune diseases such as lupus
8. Any patient currently receiving chronic (>30 consecutive days) treatment with an oral steroid
9. Patients with:
   - Body mass index >50 kg/m^2
   - Last measured HbA1c ≥12%
   - Sustained BP >180/100 mm Hg
   - LDL-C >250 mg/dL (> 6.48 mmol/L) (based on the last measured and documented laboratory measurement in the previous 6 months)
   - Triglycerides >1000 mg/dL (>11.3 mmol/L) (based on the last measured and documented laboratory measurement in the previous 6 months)
   - HDL-C <25 mg/dL (<0.64 mmol/L) (based on the last measured and documented laboratory measurement in the previous 6 months)
   - Known liver function tests >3 times upper limit of normal (ULN), (based on the last measured and documented laboratory measurement in the previous 6 months)
10. Involvement in the planning and/or conduct of the study (applies to both AstraZeneca and BMS or representative staff and/or staff at the study site)
11. Previous randomisation in the present study
12. Participation in another clinical study with IP and/or intervention within 30 days prior to Visit 1
13. Individuals at risk for poor protocol or medication compliance

For procedures for withdrawal of incorrectly randomised patients, see Section 5.3.

Exclusion criteria for the optional genetic research

The exclusion criteria for the optional genetic research are provided in Appendix F.

5. STUDY CONDUCT

5.1 Restrictions during the study

For Visits 1, 5 and EoT, to accommodate the fasting laboratory assessments, all patients will visit the clinic on a fasting stomach in the morning. The patients will be instructed not to have ingested any food or beverages 8 hours before visiting the clinic (however, intake of medication and drinking water is allowed).

Restricted concomitant medications are listed in Section 5.6.

5.2 Patient enrolment and randomisation and initiation of investigational product

The Principal Investigator (PI) **or delegate** will:

- Obtain signed informed consent from the potential patient before any study-specific procedures are performed
- Assign potential patient a unique enrolment number consisting of country, study centre, and a patient specific number, beginning with "E"
- Determine patient eligibility (see Sections 4.1 and 4.2)
- Assign eligible patient a unique randomisation number (patient number)

Patients can only be randomised into the study once.

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

5.2.1 Procedures for randomisation

Randomisation to IPs will be done via an IVRS/IWRS at Visit 1 in balanced blocks in order to ensure approximate balance between the two treatment arms (1:1). Randomisation will be stratified by baseline renal impairment category (normal-mild; moderate; severe) and by CV risk category (established CV disease; multiple risk factors without established CV disease). Approximately **16500** patients will be enrolled in this study. No more than **approximately 15700** patients with normal renal function or mild renal impairment (estimated GFR >50 mL/min) will be randomised, to ensure that at least 800 patients with moderate to severe renal impairment (estimated GFR ≤50 mL/min) are included. The study will ensure the inclusion of

300 patients with severely impaired renal function; once 300 patients with severe renal function (Estimated GFR <30 mL/min) are randomised, no additional patients with severe renal impairment will be enrolled. To meet the goal of including a sufficient number of high-risk CV patients in the study, the study will stop enrolment **approximately 21% (or a total of 3500 patients)** for patients with multiple risk factors but without established CV disease.

The enrolment code (E-code) will be used to identify the patient throughout study participation. Randomisation numbers (patient numbers) will be assigned strictly sequentially as patients become eligible for randomisation.

The IVRS/IWRS will sequentially allocate the IPs through the AstraZeneca prepared randomisation scheme and provide the randomisation number and the appropriate bottle numbers from Investigational Products Services available at the study centre. Randomisation numbers will be prepared by the global randomisation administrator at AstraZeneca and made available for IVRS/IWRS use.

Randomisation is carried out at the study level and the assigned randomisation number and the associated bottle numbers will not be sequential within a centre. Forced randomisation is not allowed.

The patient should always be provided medication with the bottle number allocated by the IVRS/IWRS. If a patient receives the incorrect randomised treatment at any time during the study, this must be corrected as soon as discovered.

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

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

When patients who do not meet the eligibility criteria are randomised in error or incorrectly started on treatment, or when patients subsequently fail to meet the study criteria post-initiation, a discussion should occur between the TIMI Study Group representative and the Investigator regarding whether to continue or discontinue the patient from treatment.

The TIMI Study Group representative is to ensure all such decisions are appropriately documented. In situations where an agreement cannot be reached, the patient´s study therapy should be stopped.

5.4 Blinding and procedures for unblinding the study

5.4.1 Methods for ensuring blinding

The blinding is ensured by using double-blind, single-dummy technique. The active tablets and the respective placebo tablets will be identical in size, colour, smell, and taste. The bottles with investigational products will be labelled with unique identification numbers allocated from the IVRS/IWRS.

No member of the study delivery team at AstraZeneca or BMS or representative, personnel at study centres or any clinical research organisation (CRO) handling data will have access to the randomisation scheme during the conduct of the study, with the exception of the AstraZeneca personnel generating the randomisation scheme as well as AstraZeneca Investigational Products, BMS Global Pharmacovigilance & Epidemiology (BMS GPV&E) and the CRO companies providing the IVRS/IWRS and carrying out the packaging and labelling of investigational products. The DMC will have access to unblinded data.

5.4.2 Methods for unblinding the study

Unblinding can be carried out in emergencies by the Investigator(s) or pharmacists at the study centre and the personnel who are independent of the study evaluation at BMS GPV&E. The DMC will have access to the individual treatment codes and will be able to merge these with the collected study data while the study is ongoing (see Section 12.4.2).

Individual treatment codes, indicating the treatment randomisation for each randomised patient, will be available to the Investigator(s) or pharmacists and to BMS GPV&E 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. In such an emergency, the Investigator will, if time and circumstances permit, contact the TIMI Study Group representative prior to breaking the treatment code. The Investigator documents and reports the action to the TIMI representative without revealing the treatment given to the patient to TIMI staff (see Section 13.1).

BMS GPV&E retains the right to unblind treatment assignment for SAEs that are unexpected and are suspected to be causally related to an IP and that potentially require expedited reporting to regulatory authorities. Treatment will not be unblinded 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 following IP and additional drug will be supplied by BMS Pharmaceutical Research Institute. The IP contain lactose, which may cause discomfort in lactose-intolerant individuals.

Investigational product	Dosage form and strength	Manufacturer
Saxagliptin	Plain, yellow, biconvex, round, film-coated tablet, 5 mg	BMS
Saxagliptin	Plain, yellow, biconvex, round, film-coated tablet, 2.5 mg	BMS

Investigational product	Dosage form and strength	Manufacturer
Placebo for saxagliptin	Plain, yellow, biconvex, round, film-coated tablet to match saxagliptin, 5 mg and 2.5 mg	BMS

5.5.2 Doses and treatment regimens

Active treatment will comprise the doses of 5 mg and 2.5 mg, respectively. Patients with a estimated GFR >50 mL/min will be randomised to 5 mg saxagliptin or placebo and patients with an estimated GFR ≤50 mL/min to 2.5 mg saxagliptin or placebo.

The IP will be packed in bottles covering the period from one visit to the next including the visit window (ie, 6 months ±14 days). Each patient will receive the IP at the regular site visits.

The blinding of the IPs is ensured by using single-dummy technique. The IPs saxagliptin or placebo will be taken orally once daily, immediately before or together with a meal. The IPs should be taken at approximately the same time of the day during the study period.

Patients should be instructed to abstain from all food for 8 hours prior to Visits 1, 5 and EoT visit; however, drinking water is allowed. In the morning prior to these visits, randomised treatment and concomitant medications can be taken with water only.

Dose adjustment during the study

Patients who, during the course of the study, develop renal impairment (Estimated GFR ≤50 mL/min on 2 consecutive tests at least 1 week apart) will have their dose adjusted to 2.5 mg saxagliptin or matching placebo. Once reduced to 2.5 mg saxagliptin or placebo, there will be no further dose-adjustment even if the estimated GFR subsequently increased sufficiently to meet initial requirements for the 5 mg saxagliptin or placebo dosing regimen. The IVRS/IWRS will be used to allocate the adjusted IP.

5.5.3 Labelling

Packing and labelling of the IP will be carried out by AstraZeneca or the CRO in accordance with current Good Manufacturing Practices (GMPs). The labels will be prepared in accordance with GMP and local regulatory guidelines. The labels will fulfil GMP Annex 13 requirements for labelling and will be translated into the local language. Booklet labels or single panel labels will be used.

5.5.4 Storage

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

5.6 Concomitant and post-study treatment(s)

Background medication and post-study treatment will not be provided by the Sponsor.

5.6.1 Prohibited medication

Treatment with DPP4 inhibitors or GLP-1 mimetics is not allowed for the duration of the study and within 6 months of the start of the study.

5.6.2 Use with medications known to cause hypoglycaemia

Insulin secretagogues, such as sulphonylureas, cause hypoglycaemia. Therefore, a lower dose of the insulin secretagogue or injectible insulin may be required to reduce the risk of hypoglycaemia when used in combination with saxagliptin.

5.6.3 Other medication

Patients are eligible, at the Investigator's discretion and based on local treatment guidelines, for adjustments in their antidiabetic treatment. This includes discontinuing or changing the dose of their concomitant antidiabetic medication as well as adding other antidiabetic treatments. All patients will be treated to regional standards of care for cardiovascular risk factors (eg, blood pressure, lipids) and HbA1c. Investigators will be duly informed of this requirement via study aids and via information provided at Investigator's Meetings. However, the medications for other medical conditions are allowed based on the current local saxagliptin label. Regardless of the need for a change in concomitant medication, patients will remain on the randomised study medications unless specifically meeting criteria for discontinuation of IP.

Other medication, which is considered necessary for the patient's safety and well-being, may be given at the discretion of the Investigator.

Recording of concomitant medication with a duration of ≥3 months in the appropriate sections of the Case Report Form (CRF) will be according to type of medication:

- Glucose-lowering drugs including injectables (insulin) by drug category or generic drug. Dose and dose step increase of ≥1 step for oral antidiabetics and ≥25% for insulin to be recorded if the dose regimen lasts at least 3 months
- CV medications including angiotensin-converting enzyme inhibitors and angiotensin-receptor blockers by drug category
- All other medication by drug category only, with no collection of start/stop dates

5.7 Treatment compliance

The administration of all medication (including IPs and other medication) should be recorded in the appropriate sections of the CRF.

Patients will be instructed to return all unused IP and any empty packages at each study visit. Compliance will be discussed at each study visit and assessed based on returned IP as follows, the Investigator will make a subjective judgement of the compliance based on 2 categories ("good": ≤20% deviation from expected number of tablets; and "questionable": >20% deviation). If compliance is "questionable", the Investigator should counsel or instruct the patient on the importance of taking his/her IP as prescribed.

5.7.1 Accountability

The study drug provided for this study will be used only as directed in the study protocol.

The study personnel will account for all IP drugs dispensed to and returned from the patient.

AstraZeneca or its representative will oversee that study personnel account for IPs received at the study centre, unused IP and IP for appropriate destruction. At the termination of the study or at the request of AstraZeneca or its designee, the Investigator must return any unused supplies to AstraZeneca or its representative. Certificates of delivery, destruction and return should be signed.

5.8 Discontinuation of investigational product

Patients may be discontinued from IP in the following situations:

- Voluntary discontinuation by the patient who is at any time free to discontinue treatment, without prejudice to further treatment
- Safety reasons as judged by the Investigator, by AstraZeneca, BMS and/or a representative.

Study-specific discontinuation criteria are listed below:

- Increase of ALT and/or AST >3 times the upper limit of normal (ULN) **and** increase of TB >1.5 times ULN confirmed at a repeated measurement within 4 days
- Increase of ALT or AST >10 times ULN confirmed at a repeated measurement within 4 days
- Pregnancy (discontinue IP and notify AstraZeneca or its representative), see Section 13.3

Cases where patients are incorrectly randomised (ie, the patient does not meet the required inclusion/exclusion criteria for the study), should be discussed with TIMI Study Group representative prior to any actions being taken (see Section 5.3).

5.8.1 Procedures for discontinuation of a patient from investigational product

Patients who are discontinued from IP should always be asked to continue in the study until the closing of the study.

A patient who decides, and/or is recommended by treating physician to discontinue IP, will always be asked about the reason(s) and the presence of any AEs. If possible (all efforts taken), the patient will be seen and assessed by an Investigator(s) and as scheduled for other patients preferably complete all assessments of the EoT/ Closing Visit. AEs will be followed up (See Section 6.4.3) and IP should be returned by the patient. Following EoT assessments the patient should be followed for **AEs and** clinical events at the scheduled visits until the study end. The Closing Visit should preferably be a visit to the site.

Alternatively, if the patient does not agree to this option, a modified follow up through regular telephone contacts or a contact at study closure should be arranged, if agreed to by the patient and in compliance with local data privacy laws/practices.

Restart of IP

Whenever possible restart of IP should be encouraged. Even if a premature EoT visit was completed due to the discontinuation of IP, this should not prevent complete study follow-up procedures including the final EoT/Closing Visit, following restart of randomised treatment.

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

5.9 Withdrawal from study

Patients are at any time free to withdraw from the study (IP and assessments), without prejudice to further treatment (withdrawal of consent). Such patients 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. AEs will be followed up (see Section 6.4.3). IP should be returned by the patient.

Survival, based on publicly available sources, will be investigated at the scheduled study end and in cases where patients have withdrawn consent.

To prevent patients being lost to follow-up, their contact details, including next of kin contacts should be collected initially and updated regularly by the site staff or representative.

6. COLLECTION OF STUDY VARIABLES

6.1 Recording of data

A 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 CRF as specified in the study protocol and in accordance with the instructions provided.

The Investigator will sign the completed CRF. A copy of the completed CRF will be archived at the study site.

All suspected events included in the composite endpoint of CV death, non-fatal MI, or non-fatal ischaemic stroke and secondary CV endpoints will be recorded in the respective

appropriate modules of the CRF. Investigators are also required to provide the CEC copies of source documents, eg, medical records (discharge summary, death certificate, autopsy report, etc). Refer to the *Investigator Manual for Events to be Adjudicated* which will be available at study start.

6.2 Data collection and enrolment

The following data will be collected at enrolment and recorded in the appropriate sections of the CRF (see Table 3).

- Date of signed informed consent
- Inclusion and exclusion criteria
- Demography: Date of birth, gender, race, and geographic region
- Pregnancy test at entry (excluding females postmenopausal ≥2 years)
- Fasting blood sampling for laboratory assessments of HbA1c, FPG, insulin, CBC with differential, serum creatinine, TB, ALT and AST, and limited urinalysis for assessment of albumin and creatinine (central laboratory)
- Medical history information including number of years of T2DM, previous history of CV disease and CV risk factors
- Physical examination including vital signs (BP and pulse), height, weight, waist circumference, and 12-lead ECG
- Prior and concomitant medication:
  - Glucose-lowering drugs including injectables (insulin) by drug category or generic drug. Dose and dose step increase of ≥1 step for oral antidiabetics and ≥25% for insulin to be recorded if the dose regimen lasts at least 3 months
  - CV medications including angiotensin-converting enzyme inhibitors and angiotensin-receptor blockers by drug category, where the treatment lasts at least 3 months
  - All other medication by drug category only, with no collection of start/stop dates, where the treatment lasts at least 3 months
- PRO questionnaire: the EQ-5D (in countries with validated translation available)
- Diet and lifestyle advice

- Optional: Date of signed addendum of the ICF for blood sampling for biological research.

- Optional: Date of signed addendum of the ICF for blood sampling for genetic researching.

6.2.1 Follow-up procedures

Randomised patients who discontinue randomised treatment prematurely should complete the procedures described for EoT/Closing Visit at the time of the discontinuation of IP. Following discontinuation of treatment, these patients should attend the remaining study visits or will be contacted by phone to have AEs and suspected clinical events recorded until the end of the study. The Closing Visit should preferably be a visit at the site.

Patients on randomised treatment, also where IP was interrupted and restarted, should attend all remaining visits for assessments, procedures, and provision of IP (according to Table 3) until the end of the study.

The blood sample for pharmacogenetic research may be drawn after Visit 1 if needed, provided written informed consent is given, see Appendix F.

Diet and lifestyle advice will be provided at each visit. The following assessments will be done at the follow-up visits:

- Telephone contact every 3rd month (ie, between clinic visits):
  - Recording of AEs
  - Recording of clinical events (applicable also to patients who prematurely stopped randomised treatment)
  - Recording of use of IP
  - Recording of concomitant medication.
- Visits 2, 4, 6, 8 and 10 (6, 18, 30, 42 and 54 months):
  - Recording of AEs (applicable also to patients who prematurely stopped randomised treatment)
  - Recording of clinical events (applicable also to patients who prematurely stopped randomised treatment)
  - Pregnancy test (excluding females postmenopausal ≥2 years)
  - Return of IP and assessment of compliance

  - Dispensing of new IP
  - Recording of concomitant medication
  - If any event included in the composite endpoint of CV death, non-fatal MI or non-fatal ischaemic stroke has occurred, the EQ 5D will be completed

- Visits 3 and 7 (12 and 36 months):
  - Recording of AEs (applicable also to patients who prematurely stopped randomised treatment)
  - Recording of clinical events (applicable also to patients who prematurely stopped randomised treatment)
  - Pregnancy test (excluding females postmenopausal ≥2 years)
  - Return of IP and assessment of compliance
  - Dispensing of new IP
  - Recording of concomitant medication
  - Non-fasting blood sampling for assessments of HbA1c, CBC with differential, serum creatinine, TB, ALT and AST (central laboratory)
  - Limited urinalysis for assessment of albumin and creatinine (central laboratory)
  - Targeted physical examination as well as vital signs: weight, BP and pulse
  - PRO questionnaire: the EQ-5D (in countries with validated translation available)

- Visit 5 (24 months):
  - Recording of AEs (applicable also to patients who prematurely stopped randomised treatment)
  - Recording of clinical events (applicable also to patients who prematurely stopped randomised treatment)
  - Pregnancy test (excluding females postmenopausal ≥2 years)
  - Return of IP and assessment of compliance
  - Dispensing of new IP

- Recording of concomitant medication
- Fasting blood sampling for laboratory assessments of HbA1c, FPG, insulin, **lipids (Total-Cholesterol, LDL-Cholesterol, HDL-Cholesterol and TG)**, CBC with differential, serum creatinine, TB, ALT and AST, and limited urinalysis for assessment of albumin and creatinine (central laboratory)
- Targeted physical examination as well as vital signs: weight, waist circumference, BP and pulse
- PRO questionnaire: the EQ-5D (in countries with validated translation available)
- Optional blood sample for biological research.

- Visit 9 (48 months):
  - Recording of AEs (applicable also to patients who prematurely stopped randomised treatment)
  - Recording of clinical events (applicable also to patients who prematurely stopped randomised treatment)
  - Pregnancy test (excluding females postmenopausal ≥2 years)
  - Return of IP and assessment of compliance
  - Dispensing of new IP
  - Recording of concomitant medication
  - Non-fasting blood sampling for assessment of HbA1c, haematology and CBC with differential, serum creatinine, TB, ALT and AST, and limited urinalysis for assessment of albumin and creatinine (central laboratory)
  - Targeted physical examination as well as vital signs: weight, BP and pulse
  - PRO questionnaire: the EQ-5D (in countries with validated translation available)
- End of Treatment/ Closing Visit:
  - Recording of AEs (applicable also to patients who prematurely stopped randomised treatment)

- Recording of clinical events (applicable also to patients who prematurely stopped randomised treatment)
- Pregnancy test (excluding females postmenopausal ≥2 years)
- Return of IP and assessment of compliance
- Recording of concomitant medication
- Fasting blood sampling for laboratory assessments of HbA1c, FPG, insulin, lipids (Total-Cholesterol, LDL-Cholesterol, HDL-Cholesterol and TG), CBC with differential, serum creatinine, TB, ALT and AST, and limited urinalysis for assessment of albumin and creatinine (central laboratory)
- Targeted physical examination as well as vital signs: weight, waist circumference, BP and pulse
- PRO questionnaire: the EQ-5D (in countries with validated translation available).

6.3 Efficacy

The following primary and secondary CV efficacy variables will be adjudicated by the independent, blinded CEC. For documents to be sent to the CEC, refer to *Investigator Manual for Events to be Adjudicated*.

6.3.1 Primary efficacy variable

The primary outcome efficacy variable of the study is the composite endpoint of CV death, non-fatal MI or non-fatal ischaemic stroke (time to first event).

This is also the primary safety outcome variable of the study.

6.3.2 Secondary efficacy variable

The **first** secondary efficacy variable is the composite endpoint of CV death, non-fatal MI, non-fatal ischaemic stroke, hospitalisation for heart failure, hospitalisation for unstable angina pectoris or hospitalisation for coronary revascularisation.

The next secondary efficacy variable is time to any documented death

6.3.3 Other efficacy variables

The other efficacy variables comprise the following:

- Addition of new antidiabetic medication or ≥1 step increase in dose for an oral antidiabetic drug or ≥25% increase in insulin dose which lasts for ≥3 months
- Start of insulin regimen which lasts for ≥3 months

- Hospitalisation for hypoglycaemia
- Cardiovascular death
- Non-fatal MI
- Non-fatal ischaemic stroke
- Hospitalisation for heart failure
- Hospitalisation for unstable angina pectoris
- Hospitalisation for coronary revascularisation
- **Primary endpoint composite (CV death, non-fatal MI or non-fatal ischaemic stroke) occurring during the first year of follow-up and after the first year**
- Documented laser treatment due to development of and/or deterioration in diabetic retinopathy
- Diabetic renal disease progression (diabetic nephropathy) as assessed by the following:
  - Reduction from baseline of the microalbumin/creatinine ratio
  - Categorical change from baseline in albuminuria (normoalbuminuria, microalbuminuria and/or macroalbuminuria)
  - Doubling of serum creatinine levels
  - Initiation of chronic dialysis and/or renal transplant and/or a serum creatinine >6.0 mg/dL (> 530 µmol/L)
- **The composite event of death, doubling of serum creatinine, initiation of chronic dialysis, renal transplant, or a serum creatinine > 6.0 mg/dL (> 530 µmol/L)**

6.3.4 Exploratory variables

Exploratory variables include the following:

- Future biological research, see Appendix H
- Future genetic research, see Appendix F
- Change from baseline in HbA1c, FPG and HOMA-β and achievement of HbA1c ≤6.5% and <7%.

6.3.5 Laboratory variables

The laboratory variables that will be measured to assess efficacy and visits at which they will be measured are shown in Table 3. These variables will be assessed at a central laboratory (Quintiles Central Laboratory Services). For information on methods of collection, assessment, labelling, storage and shipment of samples, see the Laboratory Manual. Urinary albumin excretion will be measured as the albumin/creatinine ratio (mg/g) for assessment of diabetic nephropathy.

Regarding procedures for blood collection, labelling and shipment, see Section 7.

Patients should be instructed to abstain from all food for 8 hours prior to Visits 1, 5 and the End of Treatment/Closing Visit, when fasting samples are to be collected; however, drinking water is allowed.

6.4 Safety

The methods for collecting safety data by AstraZeneca and BMS, per the Safety Data Exchange Agreement between these 2 companies, are described below.

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

6.4.1 Definition of adverse events

An adverse event (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 product. An undesirable medical condition can be symptoms (eg, nausea, chest pain), signs (eg, tachycardia, enlarged liver) or the abnormal results of an investigation (eg, laboratory findings, ECG). In clinical studies, an AE can include an undesirable medical condition occurring at any time, even if no study treatment has been administered.

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

6.4.1.1 AEs of special interest

Secondary objectives will include an assessment of the long-term effects of saxagliptin on the following AEs of special interest: decrease in lymphocyte counts, decrease in thrombocyte counts, the risk of severe infections, hypersensitivity reactions, liver abnormalities, bone fractures, pancreatitis, skin reactions and renal abnormalities. For hypersensitivity reactions, especially angioedema, reports will include detailed information on concomitant use of an angiotensin-converting enzyme inhibitor or an angiotensin-receptor blocker. For cases of pancreatitis, serum lipase and/or amylase concentrations with accompanying normal ranges and any imaging study reports will be included in the narratives.

Specific clinical details for decrease in lymphocyte counts or thrombocyte counts, severe infections, hypersensitivity reactions, liver abnormalities, skin reactions and renal

abnormalities, bone fractures, pancreatitis, opportunistic infections and liver abnormalities with serum AST or ALT greater than or equal to 3 times ULN and serum TB greater than 2 times ULN or evidence of jaundice will be captured in supplemental CRF pages regardless of seriousness.

See Appendix I for information on identification of AEs of special interest.

6.4.1.2 Hypoglycaemic events

In this study a hypoglycaemic event will be defined as either minor or major. Regardless of symptoms any recorded blood glucose <54 mg/dL (<3.0 mmol/L) will be considered an hypoglycaemic event and will trigger an hypoglycaemia adverse event report. The patient will be provided a patient diary to record symptoms of hypoglycaemic episodes **and** any blood glucose values measured in connection with the episode as well as any value <54 mg/dL (<3.0 mmol/L).

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

Minor hypoglycaemic events are considered when there is an awareness of the event, the event is tolerated and the patient recovers by her/himself. In addition the events resolves within 30 minutes of ingestion of carbohydrates (if possible confirmed with a fingerstick value). A measurement of blood glucose <54 mg/dL (<3.0 mmol/L) without symptoms, is also considered an AE.

A major hypoglycaemic event is an event requiring assistance of another person to actively administer carbohydrate, glucagons, or other resuscitative actions. These episodes may be associated with sufficient neuroglycopenia to induce seizure or coma. Plasma glucose measurements may not be available during such an event, but neurological recovery attributable to the restoration of plasma glucose to normal is considered sufficient evidence that the event was induced by a low blood glucose concentration.

Data to be collected for each hypoglycaemic event will include but are not limited to:

- Date of start and stop, and time of the day for start
- Maximal intensity (mild or severe)
- If fingerstick value obtained and the blood glucose value
- Action taken in regard to the investigational therapy or other anti-diabetic agents

The patient diary will be reviewed and data regarding hypoglycaemic events transcribed into the hypoglycaemia CRF at each clinical visit. A hypoglycaemic event that meets any criterion for seriousness should be reported as an SAE. A new diary for the next period will be provided the patient if needed. If a major hypoglycaemic event, or more than one minor event occur since the last visit, the patient should contact the investigator.

Hospitalisation for hypoglycaemia will be recorded with admission and discharge dates.

6.4.2 Definition of serious adverse event

An SAE is an AE occurring during any study period (ie, treatment, follow-up) and at any dose of the IPs (including placebo) that fulfils 1 or more of the following criteria:

- Results in death
- Is immediately life-threatening
- Requires in-patient hospitalisation or prolongation of existing hospitalisation
- Results in persistent or significant disability or incapacity
- Is a congenital abnormality or birth defect
- Is an important medical event that may jeopardise the 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

For the purposes of regulatory reporting, the following events/medical concepts should be transmitted as described in Section 6.4.4 in the same timelines as SAEs.

- Pancreatitis
- Opportunistic infections (eg, tuberculosis, Herpes zoster, cytomegalovirus, *Pneumocystis jirovecii*, etc)
- Serum AST or ALT greater than or equal to 3 times ULN, and serum TB greater than 2 times ULN or evidence of jaundice.
- **Angioedema**
- **Anaphylaxis**

- **Steven Johnson syndrome**

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

6.4.3 Recording of adverse events

Time period for collection of AEs

AEs will be collected from time of first administration of IPs throughout the study until and including the last visit/contact (ie, Closing Visit).

SAEs will be collected from the signing of informed consent throughout the study until and including the last visit/contact (ie, Closing Visit).

Follow-up of unresolved AEs

Any AEs that are unresolved at the last visit/contact (ie, Closing Visit) in the study are followed up by the Investigator for as long as medically indicated, but without further recording in the CRF. AstraZeneca Patient Safety, BMS GPV&E and TIMI retain the right to request additional information for any patient with ongoing AE(s)/SAE(s) 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 clinical report. 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 the TIMI study group representative, who will notify the appropriate BMS GPV&E contact.

AEs reported after the end of study

Only unsolicited SAEs will be collected for a period of up to 30 days after the end of the study. All SAEs will be recorded and reported to BMS GPV&E (see Section 6.4.4).

Variables

The following variables will be collected for each AE:

- AE (verbatim)
- Date when the AE started and stopped
- Maximum intensity
- Whether or not the AE is serious
- Investigator causality rating against the investigational product (yes or no)
- Action taken with regard to IP
- Whether or not AE caused patient's withdrawal from IP

- Outcome

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

- Date AE met criteria for serious AE
- Date Investigator became aware of serious AE
- Reason for classification as serious
- Date of hospitalisation
- Date of discharge
- Reason for hospitalisation
- Probable cause of death
- Date of death
- Autopsy performed
- Causality assessment in relation to study procedure(s)
- Causality assessment in relation to other medication
- Causality assessment in relation to additional study drug
- Description of AE.

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria in Section 6.4.2. 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 an 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 an SAE. If the intensity of an AE changes, only the maximum intensity of the event will be recorded.

Intensity is defined as 1 of the following:

- Mild (awareness of event but easily tolerated)
- Moderate (discomfort enough to cause some interference with usual activity)
- Severe (inability to carry out usual activity)

- Very severe (debilitating, significantly incapacitates patient despite symptomatic therapy).

Causality collection

The Investigator will assess causal relationship between IP and each AE, and answer “yes” or “no” to the question “Do you consider that there is a reasonable possibility that the event may have been caused by the investigational product?” If there is any valid reason, even if undetermined or untested, for suspecting a possible cause-and-effect relationship between the IP and the occurrence of the AE, then this should be answered "yes." Otherwise, if no valid reason exists for suggesting a possible relationship, then this should be answered "no." If more than 1 AE is identified, a causality assessment must be made for each AE.

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

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

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

AEs based on examinations and tests

The results from 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 IP.

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

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

AE dictionary

The latest version of the AE 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 in the BMS GPV&E database and coded using MedDRA.

6.4.4 Reporting of serious adverse events

All SAEs must be reported, whether or not considered causally related to the investigational product or to the study procedure(s).

Events reported in the CRF by the Investigator and confirmed by the TIMI medical representative as suspected endpoint events, will not be reported **by TIMI** to the Sponsor as SAEs. See Section 6.4.4.2 for further details.

If any SAE **or potential primary or secondary endpoint** occurs in the course of the study, then Investigators or other site personnel inform appropriate TIMI representatives within 1 day ie, immediately but **no later than the end of the next business day** of when he or she becomes aware of it.

The designated TIMI representative works with the Investigator to ensure that all the necessary information is provided to BMS GPV&E **within 3 calendar days** of initial receipt **of all non fatal and non life-threatening AEs**.

For fatal or life-threatening AEs where important or relevant information is missing, active follow-up is undertaken immediately. Investigators or other site personnel inform TIMI representatives of any follow-up information on a previously reported SAE within 1 calendar day ie, immediately but **no later than the end of the next business day** of when he or she becomes aware of it.

All SAEs will be recorded and reported to TIMI in the CRF as described in Section 6.4.3. AstraZeneca or the Investigator is responsible for informing the Ethics Committees of the SAE as per local requirements. Reporting of SAEs to Regulatory Authorities is the responsibility of BMS. In territories where AstraZeneca is the Marketing Authorisation Holder, AstraZeneca will report SAEs to Regulatory Authorities.

Follow-up information on SAEs should also be reported to TIMI by the Investigator(s) within the same time frames. If a non-serious AE becomes serious, this and other relevant follow-up information should also be provided to TIMI within 1 day as described above.

The TIMI representative will work with the Investigator to compile all the necessary information and ensure that TIMI receives a report within 1 day **for all SAEs**. The TIMI representative will notify the appropriate BMS GPV&E member to ensure regulatory compliance.

The following information is required in the initial SAE report to TIMI from the Investigator(s): study code, site number, E-code, AE, seriousness, start date. The following detailed information should be sent to TIMI as soon as it becomes available: severity, outcome (including stop date, if available), causality (IP and, if applicable, any other concomitant drug), date when a non-serious AE became serious, withdrawal of study treatment, treatment of AE, concurrent therapy (except for treatment of AE), concurrent medication (including pre-study medication if the causality of the AE cannot be assessed), date of birth, sex, other current illnesses, relevant medical history and if applicable, date and course of death.

6.4.4.1 Reporting procedure for SAEs using WBDC system

The Investigator(s) and other site personnel will access the WBDC system and report SAE information by entering it into the relevant CRF module. An automated e-mail alert will be sent to the designated TIMI representative who will work with the Investigator to ensure that all of the necessary information is available in the system within the required time frames. If the system is unavailable, the Investigator should fax a paper back-up SAE report to the TIMI representative immediately, recognising that the same reporting time frames still apply. The Investigator is responsible for completing the CRF as soon as the system becomes available again.

6.4.4.2 Protocol-specific exceptions to SAE reporting

Suspected CV outcome events in the study including the primary efficacy and safety objectives as well as the secondary **CV** efficacy objective **will not be reported to Regulatory Authorities as SAEs during the study**. They are considered part of the natural history of the condition under investigation and therefore are not subject to SAE reporting. All other events will be reported as AEs/SAEs as detailed in Section 6.4.4. Once a **potential primary or secondary endpoint** has been identified, the Investigator will record this in the respective appropriate modules of the eCRF and following confirmation by TIMI report it to the CEC for central adjudication (see Section 12.4.1). For these events, all necessary information, including whether or not the event meets the definition of "serious," will be collected on the CRF. **If the primary or secondary endpoint event meets the criteria of "serious" it must be reported by the investigator within the regular SAE reporting timelines. (see Section 6.4.4).** Specifically, the events covered in this exception are as follows:

- CV death
- Non-fatal MI
- Non-fatal ischaemic stroke
- Hospitalisation for any of the following: heart failure, unstable angina pectoris or coronary revascularisation

The detailed definitions of these events are provided in Appendix G.

Serious suspected CV events failing to meet the study criteria for an endpoint should be handled as SAEs and reported by TIMI to the Sponsors as detailed in Section 6.4.4. In addition to the normal monitoring by AstraZeneca and BMS, the independent DMC will monitor these suspected efficacy and safety endpoints and other safety data to ensure the safety of patients in the trial (see Section 12.4.2).

6.4.5 Laboratory safety assessment

The laboratory variables that will be measured to assess safety and the visits at which they will be measured are shown in Table 3. Blood and urine specimens will be collected for laboratory analyses. The date and time of sampling will be recorded on the laboratory requisition form. The samples will be processed by a central laboratory and results will be reported back to the clinic within 72 hours.

For Visits 1, 5 and EoT, to accommodate the fasting laboratory assessments, all patients will visit the clinic on a fasting stomach in the morning. The patients will be instructed not to have ingested any food or beverages 8 hours before visiting the clinic (however, intake of medication and drinking water is allowed).

All samples should be taken by adequately trained study personnel and handled in accordance with 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 each centre as source data for laboratory variables.

Regarding procedures for blood collection, labelling and shipment, see Section 7

For blood volume, see Section 7.1.

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

Unscheduled laboratory assessments

- If ALT and/or AST >3 times ULN **and** increase of TB >1.5 times ULN, a repeated measurement should be done within 4 days. If the increase is confirmed, the patient should be discontinued from IP. Similarly, an increase of ALT or AST >10 times ULN – confirmed at a repeated measurement within 3 to 4 days – should lead to discontinuation of IP (see Section 5.8).

- If an estimated GFR ≤50 mL/min, a repeated measurement should be done after 1 week. If the repeat value is still ≤50 mL/min, then the patient should be assigned 2.5 mg or matching placebo via the IVRS/IWRS. The estimated GFR will be calculated from serum creatinine according to MDRD, (see Section 11.2.1).

- For cases of suspected pancreatitis, serum lipase analysis should be performed at the central laboratory, if possible; otherwise, the local laboratory values of serum lipase and/or amylase should be recorded.

- When clinically indicated, such as in settings of unusual or prolonged infections, lymphocyte counts should be measured.

6.4.6 Physical examination

A complete physical examination will be performed at Visit 1 and include an assessment of the following: general appearance, skin inspection, lymph nodes, thyroid, abdomen, musculoskeletal/extremities, CV system, lungs and reflexes. Baseline data is recorded at Visit 1.

New findings at the subsequent visits, as assessed by a targeted physical examination based on patient complaints, AEs, or laboratory results, are recorded as a change from baseline.

6.4.7 ECG

A 12-lead ECG will be taken (supine position, standard ECG with a paper speed of 25 mm/second covering at least 6 sequential beats) after the patient has been lying down resting for at least 5 minutes, at baseline only (Visit 1). The ECG will be evaluated by the Investigator and entered as 'Normal' or 'Abnormal' in the CRF.

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 following the study plan (see Table 3).. Weight and height will be measured as part of vital signs.

6.4.8.1 Pulse and BP

Pulse and BP will be measured twice (5 minutes apart) before any blood sampling is done using a standardised cuff adapted to the size of the patient's arm after the patient has been sitting and resting for least 5 minutes. For timings of assessments see Table 3).

6.4.8.2 Weight and height

The patient's weight will be recorded in kilograms, to 1 decimal place, **recorded at Visits 1,3, 5, 7, 9 and EoT/Closing visit**. The patient's height will be recorded at Visit 1 in centimetres, with no shoes.

6.4.8.3 Waist circumference

The waist should be measured in the morning before breakfast in the 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.

6.5 Patient reported outcomes (PROs)

The PRO questionnaire used in this study is the EuroQol-5D (EQ-5D). Methods for collecting the PRO data are presented below.

6.5.1 EuroQol-5D (EQ-5D)

The EQ-5D is a generic, preference-based utility questionnaire and consists of two parts, the EuroQol-visual analog scale (EQ-VAS) and the EQ-5D index (Kind 1996). 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 5-dimension questionnaire. The dimensions consist of mobility, self-care, usual activity, pain/discomfort and anxiety/depression. Each item has 3 levels: no problems, some problems and severe problems.

6.5.2 Method of assessment

The EQ-5D will be self-administered using a paper version of the questionnaire. The questionnaire will be assessed at baseline and then annually. In addition, the EQ-5D will be assessed at a visit after non-fatal MI, or non-fatal ischaemic stroke has occurred. The questions (VAS and 5 dimensions) will take approximately 5 minutes to answer. The patient should be able to read and be fluent in the local language to be able to answer the questions.

The EQ-5D will only be administered in countries where the official language version of the questionnaire is available.

6.5.3 Coding and calculation

The respondent rates his/her current health state on the EQ-VAS by drawing a line from the box marked "your health state today" to the appropriate point on the EQ-VAS. A 3-digit number between 000 and 100 is read off the thermometer, from the exact point where the line crosses the scale, (eg, 046 or 098). This is the EQ-VAS score. To achieve comparable results, it is necessary to adhere to the standard text, instructions and layout of EQ-VAS.

The EQ-5D index includes 5 dimensions and each dimension has 3 levels: no problem, some problems and severe problems. Altogether there are 243 health states defined. A utility weight is assigned to each health state. Utility weights are elicited from general population surveys that use one of the available direct utility assessment methods.

6.5.4 Administration of PRO questionnaires

It is important to administer the questionnaire according to the recommendation for standardised administration. The patient should be informed about how important his/her participation is. The questionnaire should be completed in a quiet place without influence from study personnel or accompanied family or friend. The staff at the clinic should never help the patient to choose an answer and must be neutral in their responses to the patient's questions. The staff at the clinic is not allowed to interpret or rephrase the questions for the patient. After the patient has completed the questionnaire, the study personnel will review the questionnaire for completeness only. The study staff will transfer the responses into the CRF.

6.6 Pharmacokinetics (Not applicable)

6.7 Pharmacodynamics (Not applicable)

6.8 Pharmacogenetics

See Appendix F.

6.9 Health economics

6.9.1 Method of assessment

Hospitalisation information for patients in both study arms will be collected. Specifically dates of admission and discharge and reason for hospitalisation will be collected.

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 shown in Table 5.

Table 5 Volume of blood to be drawn from each patient

Assessment		Sample volume (mL)	No. of samples	Total volume (mL)
Efficacy and Safety	Clinical chemistry	5	8	40
	Haematology	6	8	48
Biological samples[1]		10	2	20
Genetic sample[1]		10	1	10
Total				200[2]

[1]Optional; the People's Republic of China will not participate.

[2]Includes a margin for additional visits in case study lasts >60 months as well as for unscheduled sampling.

7.1.1 Blood and urine samples

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

7.2 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.

7.3 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 will be 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.

7.4 Sample shipment

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

7.5 Handling, storage and destruction of biological samples

After the analyses are complete the samples will be either completely consumed during the analytical process, disposed of after analysis, or retained for further use as described here.

Biological samples for future research can be retained at AstraZeneca, or a representative on behalf of AstraZeneca, for a maximum of 15 years following the finalisation of the CSR. The results from future analysis will not be reported in the CSR but separately in a CSR Amendment/Errata/Scientific Report or Scientific Publication.

7.6 Labelling and shipment of biohazard samples

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

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.

7.7 Chain of custody of biological samples

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

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

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

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

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

7.8 Withdrawal of informed consent for donated biological samples

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

As collection of the biological samples is an optional part of the study, the patient should continue in the study.

The PI at each centre will ensure:

- that patients' withdrawal of informed consent to the use of donated samples is notified immediately to AstraZeneca;

- that biological samples from that patient, if stored at the study site, are immediately identified, disposed/destroyed, and the action documented;

- that the laboratory(ies) holding the samples is/are informed about the withdrawn consent immediately and that samples are disposed/destroyed, the action documented and the signed document returned to the study site; and

- that the patient and AstraZeneca are informed about the sample disposal.

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

8. ETHICAL AND REGULATORY REQUIREMENTS

8.1 Ethical conduct of the study

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with International Conference on Harmonisation (ICH)/Good Clinical Practice, applicable regulatory requirements and the AstraZeneca policy on Bioethics and Human Biological Samples.

8.2 Patient data protection

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

8.3 Ethics and regulatory review

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

The opinion of the Ethics Committee should be given in writing. The Investigator should submit the written approval to AstraZeneca or representative before enrolment of any patient into the study. The Ethics Committee should approve all advertising used to recruit patients for the study.

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

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

Before enrolment of any patient into the study, the final study protocol, including the final version of the ICF, is approved by the national regulatory authority or a notification to the national regulatory authority is done, according to local regulations.

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

AstraZeneca will provide regulatory authorities, Ethics Committees and PIs with safety updates/reports according to local requirements, including SUSARs (suspected unexpected serious adverse reactions), where relevant.

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

8.4 Informed consent

The PI(s) at each 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 he/she is 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 ICF(s) is/are stored in the Investigator's Study File
- Ensure that ICF for the SMS use is signed and stored, if applicable
- Ensure that ICFs for the optional pharmacogenetic and/or biological sampling portions of the study are signed and stored, if applicable
- Ensure a copy of the signed ICF(s) is/are 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 Ethics Committee

8.5 Changes to the protocol and informed consent form

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

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

The amendment should be approved by each Ethics Committee 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 protocol to each PI(s). For distribution to Ethics Committee, see Section 8.3.

If a protocol amendment requires a change to a centre's ICF, AstraZeneca and the centre's Ethics Committee should approve the revised ICF before the revised form is used.

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

8.6 Audits and inspections

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

9. STUDY MANAGEMENT BY ASTRAZENECA OR REPRESENTATIVE

9.1 Pre-study activities

Sites that the TIMI study organisation, the Hadassah Medical Center, BMS and/or AstraZeneca have had previous experience with will participate in the study. A determination of the suitability of the Investigator site will be made mainly based on historical performance and confirmatory telephone contact with site personnel. In rare cases, such as where the site personnel are markedly changed, further examination may be needed. The information on the site suitability will be documented.

9.2 Training of study site personnel

A representative of the TIMI study organisation, of the Hadassah Medical Center or an AstraZeneca or other representative will review and discuss the requirements of the Clinical Study Protocol and related documents with the investigational staff and also train them in any study-specific procedures and the electronic systems utilised.

9.3 Monitoring of the study

Monitoring of the site, site documents and data will be limited.

Site visits will comprise about 1 or 2 visits per year unless “for cause”.

The monitor will confirm the following:

- There is a complete patient file for each patient enrolled in the study.
- There is an informed consent for the patient and this consent process has been administered correctly.

The monitor will review the patient file to ensure that all study endpoints (ie, the composite endpoint of CV death, non-fatal MI or non-fatal ischaemic stroke and other secondary endpoints) have been recorded onto the CRF and that the adjudication packets are complete. Likewise, the monitor will review all AEs or SAEs that have been recorded on the CRF. Also key is the need to ensure all events and data pertaining to “adverse events of special interest” are adequately captured.

At the time of the monitor visit, it is appropriate to discuss the study progress with site personnel to confirm all processes and procedures in the protocol are being adhered to correctly, data in the CRF´s are being recorded in a timely manner, biological and/or genetic samples are being handled correctly, and IP accountability checks are being performed.

9.3.1 Source data

For location of source data, see the Clinical Study Agreement.

9.4 Study agreements

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

Agreements between AstraZeneca or its representative and the PI should be in place before any study-related procedures can take place or patients are enrolled.

9.4.1 Archiving of study documents

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

9.5 Study timetable and end of study

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

The study is expected to start in Q2 to Q3 2010 and to end by **Q3 2014 to Q2 2015**.

However, as the study is event driven, the accrual of the predetermined number of events included in the composite endpoint of CV death, non-fatal MI or non-fatal ischaemic stroke will finally determine the duration of the study.

The study may be terminated at individual 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.

The study can also be stopped at the interim analysis for efficacy (see Section 12.2.4).

10. DATA MANAGEMENT BY ASTRAZENECA OR DELEGATE

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

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

AEs will be classified according to the terminology of the latest version of the MedDRA. Medications will be classified according to the AstraZeneca Drug Dictionary. All coding will be performed by AstraZeneca Data Management Centre staff, with the exception of SAE coding, which will be completed by BMS.

Data queries will be raised for inconsistent, impossible or missing data. The data will be validated as defined in the Data Management Plan. Quality control procedures will be applied to each stage of data handling to ensure that all data are reliable and have been processed correctly.

When all data have been coded, validated, signed and locked, a clean file will be declared. Any treatment revealing data may thereafter be added and the final database will be locked.

Each individual electronically signing electronic CRFs must meet AstraZeneca training requirements and must only access the AstraZeneca electronic data capture tool using the unique user account provided by AstraZeneca or their designee. User accounts are not to be shared or reassigned to other individuals.

Laboratory and IVRS/IWRS data will be electronically transferred to AstraZeneca. The processes will be documented in the Data Management Plan, and the validation performed under the direction of the responsible Data Manager, according to the data validation plan.

In the case of genotype data, only the date the patient gave consent to participation in the genetic research and the date the blood sample was taken from the patient will be recorded in the CRF and database. In the case of biological sample data, only the date the patient gave consent to participation in the biological sample research and the date the blood sample was taken from the patient will be recorded in the CRF and database.

The genotype data generated from the study will be stored in an appropriate secure system separate from the database used for the main study. Some or all of the dataset from the main study may be duplicated in this database for exploratory genetic analysis. The same is applicable for the biological sample research data.

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

11. EVALUATION AND CALCULATION OF VARIABLES BY ASTRAZENECA

11.1 Calculation or derivation of efficacy variable(s)

The primary efficacy endpoint is the time to the first event included in the composite endpoint of CV death, non-fatal MI or non-fatal ischaemic stroke. For this endpoint and for the secondary time-to-event endpoints, the time from randomisation to event or time to last documented contact for patients with no event will be calculated.

A patient may have 1 or more events. However, only a patient's first occurring event will contribute to the analysis of the specified variable.

Only events adjudicated and confirmed by the CEC will be included in the primary and secondary time to CV event analyses.

Total days of hospitalisation will be calculated as the date of discharge from the hospital minus the date admitted to hospital + 1. For each patient, the baseline for glycaemic measures (eg, HbA1c) are defined as the last assessment before the first dose of double-blind study drug. Change from baseline to any randomised treatment period Month t is defined as follows:

CMonth t = MMonth t - Mbaseline, where:

- CMonth t is the change from baseline at Month t
- MMonth t is the measurement at Month t
- Mbaseline is the baseline measurement

11.2 Calculation or derivation of safety variable(s)

The baseline value of each safety laboratory test or physical exam endpoint is defined as the last assessment before the date and (where available) time of the first dose of double-blind study drug.

Change from baseline will be calculated using the same method as for glycaemic efficacy variables.

11.2.1 Derivation or calculation of outcome variables

The mean BP measurements (diastolic and systolic BP) will be computed by AstraZeneca for each patient at each visit.

Estimated GFR will be using the MDRD formula (Levy et al 2006),

Estimated GFR = 175 x standardized $S_{cr}^{-1.154}$ x $age^{-0.203}$ x 1.212 [if black] x 0.742 [if female]

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 or as AEs leading to discontinuation of IP. 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 adverse events (OAEs) and reported as such in the CSR.

Examples of OAEs 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

This will be presented in a separate statistical analysis plan (SAP).

11.4 Calculation or derivation of pharmacokinetic variables (Not applicable)

11.5 Calculation or derivation of pharmacodynamic variables (Not applicable)

11.6 Calculation or derivation of pharmacogenetic variables

Please see Appendix F.

11.7 Calculation or derivation of health economic variables

The number of hospitalisations and percent of patients hospitalised will be calculated and summarised for both study arms. In addition, the length of the stay (using the admission and discharge dates) between the two arms will be computed.

12. STATISTICAL METHODS AND SAMPLE SIZE

12.1 Description of analysis sets

12.1.1 Efficacy analysis set

All patients used in the analyses of the primary and secondary objectives will belong to the ITT population. This population is defined as all randomised patients. The patients will be analysed according to the treatment group to which they were randomised (not to which treatment they actually received).

12.1.2 Safety analysis set

The safety population will be identical to the ITT population.

12.1.3 Endpoint definitions

All primary and secondary efficacy endpoint events are defined in Appendix G.

12.1.3.1 Primary efficacy and safety endpoint

The primary endpoint is the time to first event included in the composite endpoint of CV death, non-fatal MI or non-fatal ischaemic stroke, using events adjudicated and confirmed by the independent adjudication committee. This endpoint will be used to assess both the primary efficacy objective and the primary safety objective.

12.1.3.2 Secondary efficacy endpoint

The **first** secondary efficacy endpoint is the time to the first event included in the composite endpoint of CV death, non-fatal MI, non-fatal ischaemic stroke, hospitalisation for heart failure, hospitalisation for unstable angina pectoris or hospitalisation for coronary revascularisation.

The next secondary efficacy endpoint is time to any documented death.

12.1.3.3 Other efficacy endpoints

Other efficacy endpoints include the time to the first event for the first 11 bullet points:

- Addition of new antidiabetic medication or ≥1 step increase in dose for an oral antidiabetic drug or ≥25% increase in insulin dose which lasts for ≥3 months
- Start of insulin regimen which lasts for ≥3 months
- Hospitalisation for hypoglycaemia
- CV death
- Non-fatal MI

- Non-fatal ischaemic stroke
- Hospitalisation for heart failure
- Hospitalisation for unstable angina pectoris
- Hospitalisation for coronary revascularisation
- **Primary endpoint composite (CV death, non-fatal MI or non-fatal ischaemic stroke) occurring during the first year of follow-up and after the first year**
- Documented laser treatment due to development of and/or deterioration in diabetic retinopathy
- Diabetic renal disease progression (diabetic nephropathy) as assessed by the following parameters:
  - Reduction from baseline of the microalbumin/creatinine ratio
  - Categorical change from baseline in albuminuria (normoalbuminuria, microalbuminuria, and/or macroalbuminuria)
  - Doubling of serum creatinine levels
  - Initiation of chronic dialysis and/or renal transplant and/or a serum creatinine >6.0 mg/dL (> 530 µmol/L)
- **The composite event of death, doubling of serum creatinine, initiation of chronic dialysis, renal transplant, or a serum creatinine > 6.0 mg/dL (> 530 µmol/L)**

12.1.3.4 Exploratory endpoints

Exploratory endpoints include the following:

- Future biological research, (see Appendix H)
- Future genetic research, (see Appendix F)
- Change from baseline in HbA1c, FPG, HOMA-β and achievement of HbA1c ≤6.5% and <7% (every year and end of the study visit)

12.1.3.5 Safety endpoints

Safety is evaluated by the following endpoints:

- Secondary safety endpoints:

- Incidence of overall AEs and AEs of special interest

- Other safety endpoints:
  - Changes from baseline in laboratory tests, pulse, BP, waist circumference and body weight
  - Incidence of hypoglycaemic events, cancers and peripheral oedemas

12.2 Methods of statistical analyses

12.2.1 Demographics and baseline characteristics

Demographic and baseline characteristics will be summarised, using frequency distributions and summary statistics based on the ITT data set, for each treatment group as well as for all patients combined. Key baseline characteristics will be summarised. No statistical test will be performed for comparison of any baseline measurement among treatment groups.

Demographic and baseline characteristics will be summarised for the total study population. An additional summary of demographic and baseline characteristics will be done for patients with moderate and severe renal function (patients with baseline estimated GFR <50 mL/min).

12.2.2 Safety analyses

The primary safety endpoint is the time to first event included in the composite endpoint of CV death, non-fatal MI or non-fatal ischaemic stroke. The primary safety analysis will be based on the ITT population, using events adjudicated and confirmed by the independent CEC.

The baseline value of each laboratory parameter or physical examination endpoint is defined as the last assessment before the date and when available, time of the first dose of double-blind study drug.

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, BP and pulse will be summarised by treatment group. In addition, the number and percent of patients with a predefined marked abnormality in clinical laboratory tests will be summarised by treatment group.

12.2.3 Efficacy analyses

The primary efficacy endpoint is the time to first event included in the composite endpoint of CV death, non-fatal MI, or non-fatal ischaemic stroke. The primary efficacy analysis will be based on the ITT population, using events adjudicated and confirmed by the CEC. Secondary time to event variables will be treated similarly.

For the primary and secondary time to event variables, HRs and CIs will be derived from a Cox proportional hazards model stratified by baseline renal impairment category and by CV risk category (established CV disease, multiple risk factors without established CV disease).

The primary and secondary analyses will not be adjusted for covariates. Exploratory proportional hazards models of the primary and selected secondary endpoints will determine whether control for baseline CV risk factors has any effect on the relative risk associated with randomised treatment. A forest plot will show HRs and CIs of treatment effects within subgroups.

The primary and secondary analyses will be repeated to assess robustness of results when patients with severe renal impairment (based on baseline estimated GFR) are excluded.

The primary and secondary analyses will also be repeated for the subgroup of patients who consented to use SMS, to assess consistency of results with the overall population.

Control of Type I error

The Type I error rate for the analysis of the primary endpoint will be adjusted for the interim analyses performed by the DMC.

For the primary endpoint the following hypothesis will first be tested at the 2.45% 1-sided level:

H_{01}: HR [saxagliptin:placebo] $\geq$1.30

vs

H_{11}: HR [saxagliptin:placebo] <1.30.

If the null hypothesis is rejected, then an increased CV risk of 1.30 for saxagliptin-treated patients is ruled out and superiority will then be tested in terms of:

H_{02}: HR [saxagliptin:placebo] $\geq$1

vs

H_{12}: HR [saxagliptin:placebo] <1

in a closed test procedure. The closed test procedure will apply the same nominal alpha level to the secondary endpoint (composite endpoint of major adverse cardiovascular events, hospitalisation for heart failure, hospitalisation for unstable angina pectoris or hospitalisation for coronary revascularisation **and then all-cause mortality**) in a fixed stepwise fashion provided the primary endpoint is significant at the same level.

12.2.4 Interim analyses

When 50% of the total number of events has been accrued (ie, at 520 events), an interim analysis for superiority only will be performed. The analysis will test for superiority at the 1-sided 0.15% level ($p<0.0015$) (Lan-deMets [O'Brien-Fleming] spending function, East 5.2, Copyright © 2008 Cytel Inc.), the sequential testing methodology specified for the final analysis will be used, although the study will not be stopped for non-inferiority at the interim

unless superiority is also shown. The 1-sided alpha level used for the final analyses will be 0.0245.

12.3 Determination of sample size

Assuming a 2.1% annual event rate on placebo, an approximately 15 months - accrual period, with an approximate 3-year additional follow-up period, a 17% reduction of risk in the saxagliptin group and a 2.8% rate of annual study discontinuation, randomising 16500 patients is expected to yield 1040 primary endpoint events, which would provide 85% power to test for superiority of saxagliptin versus placebo at the 2.45% 1-sided level. This number of events will also provide at least 98% power to test the following hypothesis at the 2.45% 1-sided level:

H01: HR [saxagliptin:placebo] ≥1.30

vs

H11: HR [saxagliptin:placebo] <1.30.

The original event rate was based on the following assumptions:A 2.5% annual event rate for patients without moderate to severe renal impairment is assumed based upon CV event rates observed in previous studies conducted in patients with T2DM. With an assumed 5% annual event rate in the patients with moderate renal impairment, and an assumed 10% annual event rate in patients with severe renal impairment, the overall annual event rate in the study population is estimated to be 2.8%. **Based on the current observed event rate, the assumed overall event rate will be 1.8%.**

12.4 Data monitoring committees

12.4.1 Clinical Event Adjudication Committee

An independent, blinded CEC will be appointed jointly by the Sponsors and the academic leadership of the study.

The CEC will adjudicate all primary and secondary CV endpoints. A manual will be prepared to detail precise responsibilities and procedures applicable for the CEC.

12.4.2 Data Monitoring Committee

An independent DMC will be appointed jointly by the Sponsors and the academic leadership of the study.

The DMC will be responsible for safeguarding the interests of the patients in the outcome study by assessing the safety of the intervention during the trial, and for reviewing the overall conduct of the clinical trial. In addition, the DMC will have the responsibility to assess the efficacy data of the interim analysis and decide if stopping rules are met (see interim analysis section below). The DMC will have access to the individual treatment codes and will be able to merge these with the collected study data while the study is ongoing.

The DMC charter will be prepared to detail precise roles and responsibilities and procedures to ensure maintenance of the blinding and integrity of the study in the review of accumulating data and interactions with the Executive Committee.

12.4.2.1 Study termination guidelines due to interim analysis results

When 50% of the total number of events has been accrued (ie, at 520 events) an interim analysis for superiority only will be performed. Formal stopping regulations will be detailed in the DMC charter.

12.5 Study organisation

12.5.1 Committee organisations

In consideration of the large nature of this trial, several key groups will act as alliances to provide direction and guidance throughout this study. The Executive and Steering Committees focus mainly on the scientific aspects of the trial whereas the Operations Committee and Joint Working Group are study tactics and operational in nature.

All committee meetings, unless otherwise noted, are considered open in that others may join in a listening-only mode.

A joint governance process will be issued by members of the academic institutions and the Sponsors.

12.5.1.1 Executive Committee

The Executive Committee will be responsible for the overall design, conduct, and supervision of the study, including the development of the committee and any protocol amendments. The EC will take the decision to stop the study based on the information from the DMC. The Executive Committee membership will comprise designated academic leaders and members of the Sponsor.

12.5.1.2 Steering Committee

The Steering Committee will be responsible for providing clinical guidance on study implementation and conduct of the study, and interpretation of results. The Steering Committee will comprise designated members from among the PIs and recognised leaders in the field of diabetes and CV disease, and all members of the Executive Committee.

12.5.1.3 Operations Committee

The Operations Committee will include key members from the academic leadership institutions for the study in addition to representatives from the Sponsors. This group is charged with developing strategies and tactics of key aspects of this study providing guidance in aspects of study operations.

12.5.1.4 Joint Working Group

The Joint Working Group will include key leaders of the study aspects from the academic institutions and the study Sponsors. The group, meeting frequently, will direct, on a daily level, all aspects of study operations.

12.5.2 Study Project Operational Procedures

For this study, a Project Operational Procedures (POP) manual will be developed. The POP will be developed jointly between AstraZeneca, BMS, the TIMI study group and Hadassah Medical Center.

All procedures (aligned with Standard Operating Procedures), Operational Procedural Information and guidances will be described in detail in the POP. As such, the POP will supersede internal AstraZeneca documents where there is a case of overlapping procedures. Any compliance monitoring will be performed using the procedures, processes, or guidances listed in the POP.

The POP will be reviewed, discussed and signed by members of senior management of both the Sponsors and academic institutions.

13. IMPORTANT MEDICAL PROCEDURES TO BE FOLLOWED BY THE INVESTIGATOR

13.1 Medical emergencies and TIMI contacts

The PI 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 TIMI Study Hotline.

The treatment code may not be broken unless in an emergency situation when the appropriate management of the patient necessitates knowledge of the treatment allocation. In such an emergency, the Investigator will, if time and circumstances permit, contact the TIMI Study Group representative prior to breaking the treatment code. If the treatment code is broken, the date, time, and reason should be recorded and the Investigator should sign the record (see also Section 5.4.2).

For reporting of unsolicited SAE 30 days after end of study treatment, see Section 6.4.4.

13.2 Overdose

All overdoses should be reported as follows:

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

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

For the purpose of this study, an overdose is defined as >8 tablets per day if 5 mg tablets (>16 tablets per day if 2.5 mg tablets) prior to unblinding, and >40 mg per day after code break. If an overdose on an AstraZeneca study drug occurs in the course of the study, then Investigators or other site personnel inform appropriate TIMI representatives **within 1 day** (ie, immediately but no later than **the end of the next business day**) of when he or she becomes aware of it.

The designated TIMI representative works with the Investigator to ensure that all relevant information is provided to BMS GPV&E.

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

13.3 Pregnancy

All outcomes of pregnancy should be reported to BMS GPV&E.

13.3.1 Maternal exposure

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

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

If any pregnancy occurs in the course of the study, then Investigators or other site personnel inform the appropriate TIMI representative **within 1 day** ie, immediately but no later than the **end of the next business day** of when he or she becomes aware of it.

The designated TIMI representative works with the Investigator to ensure that all relevant information is provided to BMS GPV&E 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.

13.3.2 Paternal exposure

Male patients should refrain from fathering a child or donating sperm during the study and 4 weeks following the last dose.

Pregnancy of the patient's partners is not considered to be an AE. However, the outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth or congenital abnormality) should, if possible, be followed up and documented.

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Clinical Study Protocol Appendix B

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Appendix B
Additional Safety Information

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

Life threatening

'Life-threatening' means that the patient was at immediate risk of death from the adverse event (AE) as it occurred or it is suspected that use or continued use of the product would result in the patient´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 patient 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 jeopardise the patient 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.

2. 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 patient 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.

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

1. 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 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 and life-threatening or fatal disease in otherwise healthy humans or animals (eg, Ebola, Lassa fever virus). These substances 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 (eg, hepatitis A, B, C, D, and E viruses, human immunodeficiency virus types 1 and 2). They are assigned the following UN number and proper shipping name and packed as noted:

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

Exempt substances are 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.

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Appendix D
Cardiovascular Event Rate in Clinical Studies Involving T2DM Patients

1. CARDIOVASCULAR EVENT RATE IN CLINICAL STUDIES INVOLVING T2DM PATIENTS

Clinical Study Name	Details (including patient population)	Length of study (follow-up)	Primary endpoint	Annual event rate
PROVE-IT (Cannon et al 2004) (Ahmed et al 2006)	Atorvastatin vs simvastatin in acute coronary syndom patients within 10 days of event	18 –36 months	Composite of death from any cause, myocardial infarction, documented unstable angina requiring re-hospitalisation, revascularization (performed at least 30 days after randomisation), and stroke	28.8% over 2 years (excluding first 3 months– 6-7%)
FIELD (FIELD study 2005)	Fenofibrate (sub-analysis of patients with diabetes and previous cardiovascular disease)	5 years	Composite of cardiovascular death, myocardial infarction, stroke, and coronary and carotid revascularisation	~6%
ASPEN (Knopp et al 2006)	Prevention with atorvastatin, sub-analysis of previous cardiovascular disease patients	4 years	Cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, recanalisation, coronary artery bypass surgery, resuscitated cardiac arrest, and worsening or unstable angina requiring hospitalization	6.55%
MRC / BHF (Heart Protection Study 2003)	Simvastatis, sub-analysis of previous cardiovascular disease patients	4.8 years	Major coronary event, stroke or revascularisation	6%
LIPID (Keech et al 2003)	Pravastatin arm	6 years	Coronary Heart Disease death or non-fatal myocardial infarction and other cardiovascular outcomes	7.53%

Clinical Study Name	Details (including patient population)	Length of study (follow-up)	Primary endpoint	Annual event rate
PROactive 10 (Wilcox et al 2008)	Sub-analysis of high risk patients	2.85 years	Major adverse cardiovascular events: Cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke	3.44%
Cholesterol Treatment Trialists metaanalysis (Cholesterol Treatment Trialists' (CTT) Collaborators 2008)	Analyzed data from 18 686 individuals with diabetes (1466 with type 1 and 17 220 with type 2). 36% with history of heart disease	4.3 years	Major vascular events	3.27%
ADVANCE (ADVANCE Collaborative Group 2008)	At least 1 risk factor	5-year study	Composite of non-fatal stroke, non-fatal myocardial infarction or cardiovascular death	2 – 2.2%
ACCORD (ACCORD Study Group 2008)	2 risk factors	3.5 years	Composite of non-fatal stroke, non-fatal myocardial infarction or cardiovascular death	2.2 – 2.29%
Veterans outcome study (Duckworth et al 2009)	40% with previous cardiovascular event	5.6 years	Composite of myocardial infarction, stroke, death from cardiovascular causes, congestive heart failure, surgery for vascular disease, inoperable coronary disease, and amputation for ischaemic gangrene	5.4%

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Appendix E
Definitions of Prior History of Vascular Disease

1. DEFINITIONS OF PRIOR HISTORY OF VASCULAR DISEASE

- Myocardial infarction (MI)
    - Includes presumed spontaneous MI (Universal Definition, type 1 [Thygesen et al 2007]) that led to hospitalisation with a final diagnosis of MI.
    - Excludes periprocedural MI (Universal Definition, type 4 or 5) and secondary MI (Universal Definition, type 2) as a result of sepsis, anaemia, or supraventricular tachycardia, for example.
- Ischaemic stroke
    - Acute focal neurological deficit lasting more than 24 hours, which was diagnosed as being due to a cerebral lesion of vascular origin, excluding known subarachnoid haemorrhage. Wherever possible, diagnosis should be based on diagnostic neuro-imaging but in instances where this was not performed, a clinical diagnosis may be accepted.
    - Does not include strokes felt to be of cardio-embolic origin such as atrial fibrillation or valvular disease, or from other causes such as dissection.
- Percutaneous coronary intervention or coronary artery bypass graft with revascularisation of >1 artery
- Objective evidence of coronary artery disease (equal or greater than 50% stenosis) in at least 2 arteries
- Peripheral arterial obstructive disease:
    - Current symptoms of intermittent claudication

  AND

    - Ankle brachial pressure index or toe brachial pressure index <0.90 obtained at any time in the previous 12 months, or
    - Prior peripheral revascularisation, or
    - An amputation of the legs at any level due to arterial obstructive disease.

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Appendix F
Pharmacogenetics Research

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1. BACKGROUND AND RATIONALE

AstraZeneca and Bristol-Myers Squibb plan to include investigations into genetic variations and their effect on drug response as part of the drug development programme for all projects where it is considered to be appropriate. By using this information, the aim is to better understand the impact of genetic variation and how it can be utilised to bring better drugs to the market.

To achieve this goal, a systematic collection of deoxyribonucleic acid (DNA) for genetic analysis (derived from blood samples taken from consenting study patients) will be implemented across a broad range of relevant clinical studies. The ability to acquire appropriate consent to collect blood samples to establish a DNA archive to allow future meta-analysis of data derived from a number of studies for saxagliptin is of the utmost importance. This genetic research forms part of this strategy.

Bristol-Myers Squibb and AstraZeneca intend to perform genetic research in the saxagliptin clinical development programme to explore how genetic variations may affect the clinical parameters associated with saxagliptin where appropriate.

The benefits of being able to explore associations between genes and clinical outcomes within the saxagliptin programme are potentially many and may include:

- Examination of drug response
- Efficacy
- Safety
- Toxicity
- Overall survival

2. GENETIC RESEARCH OBJECTIVES

The objective of this research is to collect and store DNA for future exploratory research into genes.

Investigations may include genes that encode:

- Genes encoding drug targets (of study drug[s])
- Genes encoding proteins which function in drug transport and metabolism
- Genes encoding products that may play a role in response to therapy

In addition to the above, it is likely that additional information on other genes important for this investigational product and for type 2 diabetes and other metabolic diseases for which the investigational product is being developed will become available in the future. It is, therefore, important to retain the possibility of investigating additional genes in the context of the saxagliptin clinical study.

3. GENETIC RESEARCH PLAN AND PROCEDURES

3.1 Selection of genetic research population

This appendix to the Clinical Study Protocol has been subjected to peer review according to AstraZeneca and Bristol-Myers Squibb standard procedures.

The patient will be asked to participate in this genetic research at Visit 1. If the patient agrees to participate, a single blood sample will be taken for genetic research at Visit 1. If the sample is not drawn at visit 1, it may be drawn at any other scheduled visit after Visit 1 until Visit 11.

3.1.1 Study selection record

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

3.1.2 Inclusion criteria

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

3.1.3 Exclusion criteria

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

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

3.1.4 Discontinuation of patients from this genetic research

A specific reason for discontinuing a patient from this genetic research is withdrawal of consent for genetic research.

Patients may withdraw from this genetic research at any time, independent of any decision concerning participation in other aspects of the main study. Voluntary discontinuation will not prejudice further treatment. Procedures for discontinuation are outlined in Section 7.8 of the main Clinical Study Protocol.

3.2 Collection of samples for genetic research

The blood sample for genetic research will be obtained from the patients at Visit 1. If the patient agrees to participate, a single blood sample will be taken for genetic research at Visit 1. If the sample is not drawn at Visit 1, it may be drawn at any other scheduled visit until the last study visit.

Although genotype is a stable parameter, early sample collection is preferred to avoid introducing bias through excluding patients who may withdraw due to an adverse event, such patients would be important to include in any genetic analysis. If for any reason the sample is not drawn at Visit 1, it may be taken at any visit until the last study visit. Only one sample should be collected per patient for genetics during the study. Samples will be collected, labelled, stored and shipped as detailed in the Laboratory Manual.

3.3 Coding and storage of DNA samples

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

For all samples, irrespective of the type of coding used, the DNA will be extracted from the blood sample. The DNA sample will be assigned a unique number replacing the information on the sample tube. Thereafter, the DNA sample will be identifiable by the unique DNA number only. The DNA number will be used to identify the sample and corresponding data at the Bristol-Myers Squibb and/or at AstraZeneca genetics laboratories, or at the designated contract laboratory. No personal details identifying the individual will be available to any person (AstraZeneca employee or contract laboratory staff working with the DNA).

The samples and data for genetic analysis in this study will be de-identified.

The link between the patient enrolment/randomisation code and the DNA number will be maintained and stored in a secure environment OUTSIDE of the Clinical Genotyping Group Laboratory Information Management System database at AstraZeneca. The link file will be used to identify the relevant DNA samples for analysis, facilitate correlation of genotypic results with clinical data, allow regulatory audit and trace samples for destruction in the case of withdrawal of consent.

This will require each blood sample to be double coded and labelled with a second unique identifier. The sample and data will not be labelled with a personal identifier. The study number and patient number will be linked to this second unique identifier. The Investigator will not be able to link the blood sample to the patient. The link between the clinical study/patient number and the unique second number will be maintained by the Bristol-Myers Squibb Sample Bank, but unknown to the Investigator.

Once DNA is extracted from the de-identified blood sample it is given another unique identifier. The DNA number will be used to identify the sample and corresponding data at the designated contract laboratory. No personal details identifying the individual donor will be available to any AstraZeneca or Bristol-Myers Squibb employee or external provider working with the DNA. A link between the blood sample and the DNA extracted from the sample will be maintained in a confidential link file.

All genetic samples will be stored under secure conditions with restricted access at Bristol-Myers Squibb and/or AstraZeneca. The blood or data derived from the samples may be made available to groups or organisations working with Bristol-Myers Squibb and AstraZeneca on this study or as part of the development drug project. However, the samples and any results will remain the property of Bristol-Myers Squibb and AstraZeneca at all times. Bristol-Myers Squibb or AstraZeneca will not give blood, DNA samples or data derived from the samples to any other parties, except as required by law. All samples and DNA will be destroyed within 15 years following the finalisation of the Clinical Study Report or according to local legislation. Samples may be destroyed prior to this timeframe if the patient has withdrawn consent.

4. ETHICAL AND REGULATORY REQUIREMENTS

The principles for ethical and regulatory requirements for the study, including this genetics research component, are outlined in Section 8 of the main Clinical Study Protocol.

4.1 Informed consent

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

4.2 Patient data protection

Bristol-Myers Squibb or AstraZeneca will not provide individual genotype results to patients, any insurance company, any employer, their family members, general physician or any other third party, unless required to do so by law.

Extra precautions will be taken to preserve confidentiality and prevent genetic data from being linked to the identity of the patient. In exceptional circumstances, however, certain individuals might see both the genetic data and the personal identifiers of a patient. For example, in the case of a medical emergency, an Bristol-Myers Squibb and/or an AstraZeneca Physician or an Investigator might know a patient's identity and also have access to his or her

genetic data. Also regulatory authorities may require access to the relevant files, though the patient's medical information and the genetic files would remain physically separate.

5. DATA MANAGEMENT

Any genotype data generated in this study will be stored in the Bristol-Myers Squibb or other appropriate secure system within Bristol-Myers Squibb and/or AstraZeneca and/or third party contracted to work with Bristol-Myers Squibb and/or AstraZeneca to analyse the samples.

The results from this genetic research may be reported in the Clinical Study Report for the main study, or in a separate report as appropriate.

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

6. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

The number of patients who will agree to participate in the genetic research is unknown. It is therefore not possible to establish whether sufficient data will be collected to allow a formal statistical evaluation or whether only descriptive statistics will be generated. A statistical analysis plan will be prepared where appropriate.

AstraZeneca

Clinical Study Protocol Appendix G	
Drug Substance	Saxagliptin
Study Code	D1680C00003
Edition Number	2.0
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Appendix G
Definitions of Cardiovascular Events

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1. DEFINITIONS OF CARDIOVASCULAR EVENTS

The D1680C00003 study (SAVOR-TIMI 53) definitions for cardiovascular endpoints are based on definitions developed at the TIMI Study Group. These definitions have evolved with experience in order to 1) incorporate improved diagnostic techniques, 2) emphasize specificity in identifying true cardiovascular events, and 3) permit implementation in large multinational, multicenter clinical trials.

1.1 Myocardial Infarctions

All myocardial infarctions (MIs) will be counted as events whether they represent the reason for the hospitalisation or occurred during a hospitalisation. In addition, they will be counted as events whether they occurred spontaneously or as the direct consequences of an investigation/procedure or operation. In order to meet the criteria as an endpoint, an MI must be distinct from the qualifying event (ie, re-infarction for a patient who qualified for the study based on recent MI). The definition of MI as an endpoint will take into account whether a patient had a recent MI or has undergone revascularisation with percutaneous coronary invention (PCI) or coronary artery bypass graft (CABG) surgery. In cases where both cardiac troponin and CK-MB are available (drawn at similar time points) and are discordant, biomarker criteria will be applied using cardiac troponin. The definitions of MI are as follows for the 4 clinical settings in which it may occur:

A. **Spontaneous MI (normal biomarkers) -** For patients with no recent revascularisation in whom biomarkers were never elevated or have been documented to return to normal after a qualifying (or recent) MI, criteria 1 and 2 or criterion 3 or criterion 4 must be met:

1. Typical cardiac biomarker rise and/or fall with the following degrees of elevation accepted as biochemical evidence of myocardial necrosis (either one or both):
    - Troponin T or I: maximal concentration greater than the MI decision limit
    - CK-MB: maximal concentration greater than the ULN

AND

2. At least 1 of the following additional supportive criteria:
    (a) Ischaemic discomfort at rest lasting >10 minutes or
    (b) ECG changes indicative of ischaemia (ST elevation > 0.1 mV or ST depression > 0.05 mV, or new T-wave inversions)

OR

3. Development of new, abnormal Q waves (>30 msec in duration and >1 mm in depth) in >2 contiguous precordial leads or >2 adjacent limb leads; or increase R amplitude in V1-V3 consistent with posterior infarction

OR

4. Pathologic findings of an acute MI.

B. **Spontaneous MI (Elevated biomarkers) -** For patients with no recent revascularisation in whom biomarkers from a qualifying (or recent) MI remain elevated, criteria 1 and 2, or criterion 3, or criterion 4 must be met:

1. Cardiac biomarker re-elevation defined as:

   (a) Increase by at least 20% of the previous value; and

   (b) Documentation that the biomarker assayed was decreasing prior to the suspected new MI;

AND

2. At least 1 of the following additional supportive criteria:

   (a) Ischaemic discomfort at rest lasting >10 minutes; or

   (b) ECG changes indicative of ischaemia (ST elevation > 0.1 mV or ST depression > 0.05 mV, or new T-wave inversions);

OR

3. Development of new, abnormal Q waves (>30 msec in duration and >1 mm in depth) in >2 contiguous precordial leads or >2 adjacent limb leads; or increase R amplitude in V1-V3 consistent with posterior infarction;

OR

4. New elevation of ST-segments > 0.1 mV in > 2 contiguous precordial or adjacent limb leads

AND

   (a) Ischaemic discomfort at rest lasting > 20 minutes; or

   (b) Ischaemia-mediated new hemodynamic decompensation requiring pharmacologic or mechanical support; or

   (c) Angiographic evidence of acute coronary occlusion

C. Within 24 hours after **PCI** a patient must have EITHER:

1. CK-MB >3× ULN and, if the pre-PCI CK-MB was >ULN, both an increase by at least 50% over the previous value and documentation that CK-MB was decreasing prior to the suspected recurrent MI;

OR

2. Pathologic findings of an acute MI.

Note: symptoms are not required.

D. Within 24 hours after **CABG** a patient must have EITHER:

1. CK-MB >5× ULN and, if the pre-CABG CK-MB was >ULN, both an increase by at least 50% over the previous value and documentation that CK-MB was decreasing prior to the suspected recurrent MI;

AND

2. At least one of the following supportive criteria:

   (a) Development of new, abnormal Q waves (>30 msec in duration and >1 mm in depth) in >2 contiguous precordial leads or >2 adjacent limb leads; or increase R amplitude in V1-V3 consistent with posterior infarction, or

   (b) Angiographically documented new graft or native coronary occlusion, or

   (c) Imaging evidence of new loss of viable myocardium

OR

3. Pathologic findings of an acute MI.

Note: symptoms are not required.

Note: If cardiac troponin measurements are the only cardiac biomarker data available, they may be used by the Clinical Event Adjudication Committee (CEC), along with the ECG and clinical scenario, in the adjudication of suspected MI after revascularisation (PCI or CABG).

The reviewers should also consider the clinical features (eg, renal insufficiency), possible alternative diagnoses (eg, pericarditis), pattern of marker release (eg, absence of a rise and/or fall), and known sensitivity/specificity of the various cardiac markers in the adjudication of infarction, particularly when there is discordance in the results of multiple markers.

Universal Definitions of MI Criteria

Myocardial infarctions will be also be classified according to the following universal definition of MI criteria:

- Type 1: Spontaneous MI related to ischaemia due to a primary coronary event such as plaque erosion and/or rupture, fissuring, or dissection.
- Type 2: MI secondary to ischaemia due to either increased oxygen demand or decreased supply, eg, coronary artery spasm, coronary embolism, anemia, arrhythmias, hypertension, or hypotension.
- Type 3: Sudden unexpected cardiac death, including cardiac arrest, often with symptoms suggestive of myocardial ischaemia, accompanied by presumably new ST elevation, or new LBBB, or evidence of fresh thrombus in a coronary artery by angiography and/or at autopsy, but death occurring before blood samples could be obtained, or at a time before the appearance of cardiac biomarkers in the blood.
- Type 4a: MI associated with PCI .
- Type 4b: MI associated with stent thrombosis as documented by angiography or at autopsy.
- Type 5: MI associated with CABG.

1.2 Stroke

Stroke is defined as an acute focal neurological deficit of sudden onset,

(a) that is not reversible within 24 hours or results in death (in < 24 hrs) and is not due to an identifiable non-vascular cause (ie, brain tumour, trauma), or

(b) that resolves in < 24 hrs and is accompanied by clear evidence of a new stroke on cerebral imaging

Stroke will be sub-classified into one of the following 4 groups:

Non-hemorrhagic Cerebral Infarction - Stroke without focal collections of intracerebral blood on a brain imaging. This category will be sub-classified into suspected embolic vs other.

Non-hemorrhagic Infarction with Hemorrhagic Conversion - Cerebral infarction with blood felt to represent hemorrhagic conversion and not a primary hemorrhage. Hemorrhagic conversion usually occurs on the cortical surface. Hemorrhagic conversion in the deeper brain requires evidence of nonhemorrhagic infarction in the same vascular territory. Microhemorrhages evident on MRI, whether in the cortex or deep brain structures, are not considered to be consistent with a hemorrhagic conversion endpoint.

Primary Hemorrhagic

Intracerebral Hemorrhage - Stroke with focal collections of intracerebral blood seen on a brain image (CT or MRI) or a postmortem examination, not likely to represent hemorrhagic conversion. Primary hemorrhages cause hematomas which are usually easily discriminated by their subcortical location and rounded or elliptical shape. Microhemorrhages incidentally discovered on brain imaging in the absence of associated symptoms will not be considered to be a primary intracranial hemorrhage endpoint.

Subarachnoid hemorrhage - High density fluid collection in subarachnoid space on brain images or blood in the subarachnoid space on autopsy.

Uncertain - Any stroke without brain image (CT or MRI) or autopsy documentation of type, or if tests are inconclusive

Subdural hematoma will not be classified as a stroke but will be classified as a bleeding event (intracranial hemorrhage).

Intracerebral microhemorrhages will be classified in a separate category for analysis. Microhemorrhage is defined as rounded foci of <10 mm that appear hypointense and that are distinct from other causes of signal loss on gradient-echo MRI sequences (eg, vascular flow voids, leptomeningeal hemasidarosis, or non-hemorrhagic subcortical mineralisation).

Transient ischaemic attack is defined by:

(a) an acute focal neurological deficit ending lasting <24 hours, and not due to an identifiable non-vascular cause (ie, brain tumour, trauma), and

(b) absence of new infarct on brain imaging (if obtained)

1.3 Unstable Angina requiring Hospitalisation

Unstable angina requiring hospitalisation is defined as

(a) No elevation in cardiac biomarkers (cardiac biomarkers are negative for myocardial necrosis)

AND

(b) Clinical Presentation (one of the following) with cardiac symptoms lasting ≥ 10 minutes and considered to be myocardial ischaemia on final diagnosis

1. Rest angina *or*

2. New-onset (< 2 months) severe angina (Canadian Cardiovascular Society Grading Scale* (or CCS classification system) classification severity ≥ III)

AND

(c) Requiring an unscheduled visit to a healthcare facility and overnight admission (does not include chest pain observation units)

AND

(d) At least one of the following:

1. New or worsening ST or T wave changes on ECG. ECG changes should satisfy the following criteria for acute myocardial ischaemia in the absence of LVH and LBBB:

   (a) ST elevation
   New transient (known to be < 20 minutes) ST elevation at the J-point in two contiguous leads with the cut-off points:

   - ≥ 0.2 mV in men or ≥ 0.15 mV in women in leads V2-V3 and/or ≥ 0.1 mV in other leads

   (b) ST depression and T-wave changes
   New horizontal or down-sloping ST depression ≥ 0.05 mV in two contiguous leads; and/or T inversion ≥ 0.1 mV in two contiguous leads with prominent R-wave or R/S ratio > 1.

2. Evidence of ischaemia on stress testing with cardiac imaging

3. Evidence of ischaemia on stress testing without cardiac imaging but with angiographic evidence of ≥ 70% lesion and/or thrombus in an epicardial coronary artery *or* initiation/increased dosing of antianginal therapy.

4. Angiographic evidence of ≥ 70% lesion and/or thrombus in an epicardial coronary artery

1.4 Heart Failure requiring Hospitalisation:

Heart failure requiring hospitalisation is defined as an event that meets the following criteria:

(a) Requires hospitalisation defined as an admission to an inpatient unit or a visit to an emergency department that results in at least a 12 hour stay (or a date change if the time of admission/discharge is not available).

AND

(b) Clinical manifestations of heart failure including at least one of the following:

New or worsening

- dyspnea
- orthopnea
- paroxysmal nocturnal dyspnea
- oedema
- pulmonary basilar crackles
- jugular venous distension
- new or worsening third heart sound or gallop rhythm, or
- radiological evidence of worsening heart failure.

AND

(c) Additional/Increased therapy

1. Initiation of intravenous diuretic, inotrope, or vasodilator therapy
2. Uptitration of intravenous therapy, if already on therapy
3. Initiation of mechanical or surgical intervention (mechanical circulatory support, heart transplantation or ventricular pacing to improve cardiac function), or the use of ultrafiltration, hemofiltration, or dialysis that is specifically directed at treatment of heart failure.

Biomarker results (eg, brain natriuretic peptide) consistent with congestive heart failure will be supportive of this diagnosis.

1.5 Definition of Coronary Revascularisation Procedure

A coronary revascularisation procedure is defined as either CABG or a PCI (eg, angioplasty, coronary stenting). CABG is defined as the successful placement of at least one conduit with either a proximal and distal anastomosis or a distal anastomosis only. PCI is defined as successful balloon inflation with or without stenting and the achievement of a residual stenosis < 50%. The balloon inflation and/or stenting could have been preceded by device activation (eg, angiojet, directional coronary atherectomy, or rotational atherectomy).

1.6 Definition of Cardiovascular Death

Cardiovascular death includes sudden cardiac death, death due to acute myocardial infarction, death due to heart failure, death due to stroke, and death due to other cardiovascular causes, as follows:

1. **Sudden Cardiac Death**: refers to death that occurs unexpectedly in a previously stable patient and includes the following deaths:

   (a) Witnessed and instantaneous without new or worsening symptoms

   (b) Witnessed within 60 minutes of the onset of new or worsening cardiac symptoms

   (c) Witnessed and attributed to an identified arrhythmia (eg, captured on an electrocardiographic (ECG) recording or witnessed on a monitor by either a medic or paramedic)

   (d) Patients unsuccessfully resuscitated from cardiac arrest or successfully resuscitated from cardiac arrest but who die within 24 hours without identification of a non-cardiac etiology

   (e) Unwitnessed death or other causes of death (information regarding the patient's clinical status within the week preceding death should be provided)

2. **Death due to Acute Myocardial Infarction**: Death occurring up to 14 days after a documented acute myocardial infarction [verified either by the diagnostic criteria outlined for acute myocardial infarction or by autopsy findings showing recent myocardial infarction or recent coronary thrombus] and where there is no conclusive evidence of another cause of death.

   If death occurs before biochemical confirmation of myocardial necrosis can be obtained, adjudication should be based on clinical presentation and ECG evidence.

   Death due to a myocardial infarction that occurs as a direct consequence of a cardiovascular investigation/procedure/operation will be classified as death due to other cardiovascular cause.

3. **Death due to Heart Failure or Cardiogenic Shock**: refers to death occurring in the context of clinically worsening symptoms and/or signs of heart failure without evidence of another cause of death. New or worsening signs and/or symptoms of congestive heart failure (CHF) include any of the following:

   (a) New or increasing symptoms and/or signs of heart failure requiring the initiation of, or an increase in, treatment directed at heart failure or occurring in a patient already receiving maximal therapy for heart failure.

(b) Heart failure symptoms or signs requiring continuous intravenous therapy or oxygen administration

(c) Confinement to bed predominantly due to heart failure symptoms

(d) Pulmonary oedema sufficient to cause tachypnea and distress not occurring in the context of an acute myocardial infarction or as the consequence of an arrhythmia occurring in the absence of worsening heart failure

(e) Cardiogenic shock not occurring in the context of an acute myocardial infarction or as the consequence of an arrhythmia occurring in the absence of worsening heart failure.

Cardiogenic shock is defined as systolic blood pressure (SBP) < 90 mm Hg for greater than 1 hour, not responsive to fluid resuscitation and/or heart rate correction, and felt to be secondary to cardiac dysfunction and associated with at least one of the following signs of hypoperfusion:

- Cool, clammy skin *or*
- Oliguria (urine output < 30 mL/hour) *or*
- Altered sensorium *or*
- Cardiac index < 2.2 L/min/m^2

Cardiogenic shock can also be defined as SBP ≥ 90 mm Hg as a result of positive inotropic or vasopressor agents alone and/or with mechanical support in less than 1 hour.

The outcome of cardiogenic shock will be based on CEC assessment and must occur after randomisation. Episodes of cardiogenic shock occurring before and continuing after randomisation will not be part of the study endpoint.

This category will include sudden death occurring during an admission for worsening heart failure.

4. **Death due to Cerebrovascular Event** (intracranial hemorrhage or non-hemorrhagic stroke): refers to death occurring up to 30 days after a suspected stroke based on clinical signs and symptoms as well as neuroimaging and/or autopsy, and where there is no conclusive evidence of another cause of death.

   Definition of Death due to Stroke: refers to death occurring up to 30 days after a stroke that is either due to the stroke or caused by a complication of the stroke.

5. **Death due to Other Cardiovascular Causes**: death must be due to a fully documented cardiovascular cause not included in the above categories (eg, dysrhythmia, pulmonary embolism, or cardiovascular intervention).

1.7 Definition of Non-Cardiovascular Death

Non-cardiovascular death is defined as any death not covered by cardiac death or vascular death and is categorised as follows:

- Pulmonary causes
- Renal causes
- Gastrointestinal causes
- Infection (includes sepsis)
- Non-infectious (eg, systemic inflammatory response syndrome (SIRS))
- Malignancy (ie, new malignancy, worsening of prior malignancy)
- Hemorrhage, not intracranial
- Accidental/Trauma
- Suicide
- Non-cardiovascular system organ failure (eg, hepatic failure)
- Non-cardiovascular surgery

1.8 Definition of Presumed Cardiovascular Death

Presumed Cardiovascular Death: All deaths not attributed to the categories of cardiovascular death and not attributed to a non-cardiovascular cause, are presumed cardiovascular deaths and as such are part of the cardiovascular mortality endpoint.

AstraZeneca

Clinical Study Protocol Appendix H	
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Date	

Appendix H
Biological Research

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1. BACKGROUND AND RATIONALE

Circulating biomarkers have proven to play a pivotal role in the evaluation and treatment of patients who are at risk of developing or have established atherosclerotic vascular disease, and their full potential has likely yet to be realized. Like atherosclerosis, diabetes is also considered a chronic inflammatory disease with activation of multiple pathologic inflammatory, thrombotic, and metabolic pathways (Pradhan et al 2002). Patients with elevated levels of circulating pro-inflammatory and thrombotic biomarkers are at a particularly high risk of developing incident diabetes (Meigs et al 2004, Festa et al 2006), however, data regarding the risk associated with elevated levels of biomarkers, alone and in combinations, in patients with established diabetes is remarkably scarce.

Biomarkers may be used to facilitate diagnosis, enhance risk assessment, direct therapeutic decision-making, and monitor therapy (Morrow et al 2007). In particular, there is proof of principle that the combined use of multiple biomarkers that reflect distinct pathobiological contributors to atherothrombotic risk enhances assessment of prognosis. (Sabatine et al 2002). There is a need for prospective evaluation of established and novel biomarkers, both alone and in a multimarker strategy, in a broader population of patients with diabetes either with established atherosclerotic vascular disease or with multiple risk factors.

New insight into the pathobiology of the causes and consequences of atherothrombosis and diabetes has fostered a steady pace of emergence of candidate novel cardiovascular and metabolic biomarkers. Using novel markers that reflect the inflammatory, thrombotic, metabolic, and haemodynamic mediators of risk in patients with diabetes and atherosclerotic disease, it may be possible to characterise non-invasively the participation of these different pathobiological contributors in an individual patient and to monitor response to therapy (Morrow et al 2003).

For example, high-sensitivity testing for C-reactive protein (hs-CRP) has emerged as a convenient tool for detecting low-level systemic inflammation that portends a higher risk of a first myocardial infarction or stroke, as well as poor short-term and long-term prognosis (Ridker et al 1997). BNP and NT-proBNP have now been also shown to act as robust predictors of the short-term and long-term risk of cardiovascular death across the spectrum of acute coronary syndromes, as well as in patients with stable ischaemic heart disease or in the general population (Kragelund et al 2005, Morrow et al 2005, Zethelius et al 2008). Other novel biomarkers that are associated with prognosis in patients with atherothrombosis include soluble CD40 ligand (a marker of platelet activation), metalloproteinases (enzymes that disrupt the integrity of the atheroma's protective cap), myeloperoxidase (a potential participant in oxidative injury during atherogenesis) and vascular growth factors such as placental growth factor. In addition, improvements in technology have allowed for the measurement of earlier upstream precursors that may enable the identification of novel markers and the earlier detection of ischaemia, before myonecrosis. Proteomic and metabolomic techniques have been explored for this purpose (Sabatine et al 2005, Lewis et al 2008, Gerszten et al 2009).

It has become increasingly recognized that many of the pathobiological processes underlying acute and chronic atherosclerotic disease are present in patients with diabetes as well. These shared pathological mechanisms, including inflammation (Schillinger et al 2003) and procoagulant properties (Santilli et al 2006), provide insights into the increased cardiovascular risk associated with diabetes as well as the severity of diabetes itself (Pradhan et al 2002, Ndumele et al 2006, Katakami et al 2007).

Specific markers reflecting the vascular effects associated with glucose and lipid dysregulation have also been proposed with specific focus on patients with diabetes. For example, circulating advanced glycation products (AGEs), the soluble receptor for these AGEs (sRAGE), as well plasma phospholipid levels and ratios have been proposed as prognostic markers for vascular disease and heart failure (Katakami et al 2006, Guo et al 2008, Koyama et al 2008).

While a significant proportion of the existing research has explored biomarkers in the setting of diagnosis and risk stratification, it has been recognised that in some cases they may be active components or closely related to the pathobiological mechanisms underlying acute coronary syndrome and as such may be useful in assessing adequacy of therapy or even as therapeutic targets.

Several pharmacologic therapies have been shown to modify biomarkers and therefore offer insight into their potential mechanism of benefit. Statins as well as other lipid-lowering therapies, for example, have been shown to reduce markers of inflammation, such as CRP. Patients who achieved the greatest reduction in CRP with statin therapy were less likely to have recurrent atherothrombotic events (Ridker et al 2005, Morrow et al 2006).

In terms of antidiabetic agents, thiazolidinedione have the most compelling data regarding reduction in inflammatory makers. Multiple small studies lasting weeks or months have shown that rosiglitazone and pioglitazone reduce levels of CRP compared to placebo or sulphonylureas in patients with and without diabetes (Haffner et al 2002, Hetzel et al 2005, Forst et al 2007, Hanefeld et al 2007). There is little data regarding the effect of insulin or metformin on inflammatory markers in patients with diabetes. One small study of poorly controlled diabetic patients found a reduction in CRP in patients treated with insulin, but not sulphonylureas. (Yudkin et al 2000). Another study of 22 patients found treatment with metformin reduced levels of CRP by 33% at 4 months when it was added to sulphpfonylureas (Chu et al 2002).

There are few reports regarding the effect of incretin therapy on inflammatory models, however, animal studies have suggested that glucagon-like-peptide-1 (GLP-1) agonist may improve myocardial function (Fields et al 2009, Timmers et al 2009). The evaluation of cardiovascular biomarkers in patients treated with saxagliptin, which will increase levels of GLP-1, may provide important insight into the pathology of diabetic cardiovascular disease.

This study presents a unique opportunity to study the performance of a broad array of established and novel biomarkers in a diabetic population with established cardiovascular

disease or multiple risk factors in terms of response to therapy with saxagliptin and overall association with clinical outcomes.

2. BIOLOGICAL RESEARCH OBJECTIVES

AstraZeneca and Bristol-Myers Squibb desire the opportunity to study the effects of treatment with saxagliptin on changes in biomarkers in patients with type type 2 diabetes and either established atherosclerotic disease or multiple risk factors, with the following possible objectives:

- Evaluate the effect of treatment with saxagliptin compared to placebo on the change in baseline biomarkers of inflammation, thrombosis, atherogenesis, metabolism, hemodynamic stress and myocardial injury
- Evaluate the interaction between baseline biomarkers of inflammation, thrombosis, atherogenesis, metabolism, hemodynamic stress and myocardial injury with the clinical efficacy of saxagliptin
- Prospectively evaluate the prognostic efficacy of a multimarker approach to risk assessment utilising baseline levels of inflammation, ventricular stress, myocardial necrosis and metabolic dysregulation.
- Evaluate the prognostic performance of other established and novel plasma/serum markers of inflammation, endothelial function, oxidative stress, hemodynamic stress, ischaemia/necrosis, metabolic dysregulation and renal dysfunction alone and in combination for clinical outcomes
- Assess the change in these biomarkers over time in a population with a history of diabetes

As such, the following list of biomarkers is proposed at this time. The entire list may not be studied, or additional biomarkers may be added as knowledge in the field develops, as deemed appropriate by the Executive Committee.

Biomarkers of Inflammation and Atherogenesis

- hs-CRP
- metalloproteinases (PAPP-A, MMP-9, MMP-11, cathepsins, myeloperoxidase)
- cytokines (IL-1β, IL-1Ra, IL-6, IL-18)
- chemotactic molecules (MCP-1, CCR1, CCR2)
- placental growth factor and soluble Flt-1

Biomarkers of Endothelial Function

- vWF, E-selectin, VCAM-1, ICAM-1

Biomarkers of Thrombosis

- tissue factor, sCD40L, prothrombin fragment 1.2, thrombin precursor protein

Biomarkers of Oxidative Stress

- oxidized amino acids, oxidized apoA1,
- ADMA and other arginine metabolism products,
- secretory phospholipase,
- $LpPLA_2$

Biomarkers of Ischaemia/Necrosis

- high-sensitivity cardiac troponin, malondialdehyde-modified low-density lipoprotein

Glycation end products and associated receptors

- AGE, sRAGE, RAGE

Biomarkers of Hemodynamic Stress

- BNP/NT-proBNP, ST-2, Copeptin

Biomarker of Metabolic/Lipid Dysregulation

- Adiponectin, leptin, resistin, c-peptide, red blood cell phospholipid fatty acids (EPA and DHA

Biomarker of Renal Dysfunction

- cystatin-C

3. BIOLOGICAL RESEARCH PLAN AND PROCEDURES

3.1 Selection of biological research population

This appendix to the Clinical Study Protocol has been subjected to peer review according to AstraZeneca and Bristol-Myers Squibb standard procedures.

The patient will be asked to participate in this biological research at Visit 1. If the patient agrees to participate, a blood sample will be taken for biological research at Visit 1 (baseline) and at Visit 5 (24 months) or at the End of Treatment visit in case of premature discontinuation of IP **or if patient has not had a Visit 5 sample drawn at time of study closure**.

3.1.1 Study selection record

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

3.1.2 Inclusion criteria

For inclusion in this biological research, patients must fulfil all of the inclusion criteria described in the main body of the Clinical Study Protocol **and**:

- Provide informed consent for the biological sampling and analyses.

3.1.3 Exclusion criteria

Exclusion from this biological research may be for any of the exclusion criteria specified in the main study.

3.1.4 Discontinuation of patients from this biological research

Specific reasons for discontinuing a patient from this biological research are:

Withdrawal of consent for biological research: Patients may withdraw from this biological research at any time, independent of any decision concerning participation in other aspects of the main study. Voluntary discontinuation will not prejudice further treatment. Procedures for discontinuation are outlined in Section 7.8 of the main Clinical Study Protocol.

3.2 Collection of samples for biological research

A blood sample (6 mL EDTA-anticoagulated, 6 mL serum tubes) will be taken at baseline and month 24 in all randomised patients. Detailed procedures are described in the Laboratory Manual.

The biomarker samples will be labelled (or "coded") with a study specific code. Samples do not carry any patient identifying information.

Careful separation of plasma and serum will be performed on site and stored at -20°C or colder until shipped to the central laboratory on dry ice, where samples will be stored at -70°C or colder until thawed for analysis. Samples will be shipped to **Biobanken Mölndal, AstraZeneca R&D** (intermediate storage) for subsequent transfer to the (TIMI) Biomarker Core Lab (Boston, MA) for analysis.

In addition to analysis of biomarkers of necrosis/ischaemia, inflammation, and coagulation listed above, proteomics analysis may be performed to develop and test novel protein markers of inflammation and coagulation.

3.3 Coding and storage of samples

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

4. ETHICAL AND REGULATORY REQUIREMENTS

The principles for ethical and regulatory requirements for the study, including this biological research component, are outlined in Section 8 of the main Clinical Study Protocol.

4.1 Informed consent

The biological component of this study is optional and the patient may participate in other components of the main study without participating in the biological component. To participate in the biological component of the study, the patient must sign and date both the consent form for the main study and the biological component of the study. Copies of both signed and dated consent forms must be given to the patient and the original filed at the study centre. The principal investigator(s) is responsible for ensuring that consent is given freely and that the patient understands that he/she may freely discontinue from the biological aspect of the study at any time.

4.2 Patient data protection

Bristol-Myers Squibb or AstraZeneca will not provide individual results to patients, any insurance company, any employer, their family members, general physician or any other third party, unless required to do so by law.

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

5. DATA MANAGEMENT

Biomarker data from the TIMI Biomarker Core Lab will be merged with the clinical database for statistical analysis.

The results from this biological research will be reported in a CSR Amendment/Errata/Scientific Report or Scientific Publication.

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

6. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

The number of patients who will agree to participate in the biological research is unknown. It is therefore not possible to establish whether sufficient data will be collected to allow a formal statistical evaluation or whether only descriptive statistics will be generated.

Biomarker data from the TIMI Biomarker Core Lab will be merged with the clinical database for statistical analysis. Analyses will be for exploratory purposes. Correlation between serum/plasma markers and outcomes will be analysed with the marker data both as continuous and categorical variables. Clinical outcomes examined will include the primary efficacy endpoint, and major secondary endpoint, the composite of cardiovascular death or myocardial infarction, the composite of cardiovascular death and heart failure, progression and complications of diabetes, as well as each element individually. Additional analyses will be performed to assess the effect of saxagliptin on the change in biomarkers from baseline 24 months. In addition, analyses to test for interaction between the effect of saxagliptin and baseline biomarkers will be performed using stratified analyses as well as logistic regression with the main effects and an interaction term. A statistical analysis plan will be prepared where appropriate.

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AstraZeneca

Clinical Study Protocol Appendix I

Drug Substance	Saxagliptin
Study Code	D1680C00003
Edition Number	2.0
Date	

Appendix I
Identification of Events in the Secondary Safety Objectives

TABLE OF CONTENTS PAGE

1 EVENTS OF SPECIAL INTEREST

The Medical Dictionary for Regulatory Activities (MedDRA) Version 12.0 is used for the definitions of the events of special interest and is subject to updates.

2 DECREASE IN LYMPHOCYTE OR THROMBOCYTE COUNTS

Adverse events related to decrease in lymphocyte and thrombocyte counts will be identified using the following MedDRA preferred terms (PTs).

PTs for Lymphopenia:

Lymphopenia

Lymphocyte count decreased

Lymphocyte percentage decreased

B-lymphocyte count decreased

T-Lymphocyte count decreased

CD4 lymphocytes decreased

CD8 lymphocytes decreased

PTs for Thrombocytopenia:

Autoimmune Thrombocytopenia

Haemolytic uraemic syndrome

Idiopathic thrombocytopenic purpura

Platelet count decreased

Platelet destruction increased

Platelet production decreased

Plateletcrit decreased

Thrombocytopenia

Thrombocytopenic purpura

Thrombotic thrombocytopenic purpura

3 SEVERE INFECTIONS

Adverse events related to severe infections will be identified by meeting (a) and (b)

(a) All MedDRA PTs fall under the **system** organ class of infections and infestations

(b) The event meets the regulatory criteria for seriousness (eg, hospitalisation)

4 OPPORTUNISTIC INFECTIONS

The medical concept for this list of PTs of infections includes all those that appear on the 1993 CDC List of AIDS-Defining Diagnoses, and that are specific for immunosuppression.

The following is a breakdown of the Preferred Terms in the list, by organism category and organism.

Organism category	**Organism**
Bacteria	Listeria MAC Mycobacterial Salmonella sepsis Tuberculosis Tubo-ovarian abscess Bacillary angiomatosis/Bartonellosis
Fungus	Coccidioides Cryptococcus Histoplasmosis Pneumocystis Fungal (esophageal, neurological, systemic or visceral) Candida (esophageal, neurological, systemic or visceral)
Protoza	Cryptosporidia Isospora Toxoplasmosis
Virus	CMV HSV (esophageal, neurologic, systemic or visceral) Herpes Zoster (multidermatomal, neurological or disseminated) JC Virus, PML
Opportunistic infection (unspecified)	Opportunistic infection (unspecified)

Opportunistic infections will be identified using the following MedDRA PTs:

Acute pulmonary histoplasmosis

Adrenal gland tuberculosis

Arthritis fungal

Atypical mycobacterial infection

Atypical mycobacterial lymphadenitis

Atypical mycobacterium pericarditis

Bacillary angiomatosis

Bartonellosis

Biliary tract Infection cryptosporidial

Biliary tract infection fungal

Bone tuberculosis

Bovine tuberculosis

Bronchitis fungal

Candida osteomyelitis

Candida pneumonia

Candida sepsis

Cerebral fungal infection

Cerebral toxoplasmosis

Chronic pulmonary histoplasmosis

Coccidioides encephalitis

Coccidioidomycosis

Congenital tuberculosis

Conjunctivitis tuberculous

Cryptococcal cutaneous infection

Cryptococcal fungaemia

Cryptococcosis

Cryptosporidiosis infection

Cutaneous coccidioidomycosis

Cutaneous tuberculosis

Cytomegalovirus antigen positive

Cytomegalovirus chorioretinitis

Cytomegalovirus colitis

Cytomegalovirus duodenitis

Cytomegalovirus enteritis

Cytomegalovirus enterocolitis

Cytomegalovirus gastritis

Cytomegalovirus gastroenteritis

Cytomegalovirus gastrointestinal infection

Cytomegalovirus hepatitis

Cytomegalovirus infection

Cytomegalovirus mononucleosis

Cytomegalovirus mucocutaneous ulcer

Cytomegalovirus myelomeningoradiculitis

Cytomegalovirus myocarditis

Cytomegalovirus oesophagitis

Cytomegalovirus pancreatitis

Cytomegalovirus pericarditis

Cytomegalovirus proctocolitis

Cytomegalovirus syndrome

Cytomegalovirus test positive

Cytomegalovirus urinary tract infection

Cytomegalovirus viraemia

Disseminated cryptococcosis

Disseminated cytomegaloviral infection

Disseminated tuberculosis

Ear tuberculosis

Encephalitis cytomegalovirus

Encephalitis fungal

Endocarditis candida

Endocarditis histoplasma

Enterocolitis fungal

Epididymitis tuberculous

Extrapulmonary tuberculosis

Eye infection toxoplasmal

Female genital tract tuberculosis

Fungal abscess central nervous system

Fungal cystitis

Fungal endocarditis

Fungal oesophagitis

Fungal peritonitis

Fungal retinitis

Fungal rhinitis

Fungal sepsis

Gastritis fungal

Gastroenteritis cryptococcal

Gastroenteritis cryptosporidial

Gastrointestinal fungal infection

Hepatic candidiasis

Hepatic infection fungal

Hepatitis toxoplasmal

Herpes oesophagitis

Herpes sepsis

Herpes simplex hepatitis

Herpes simplex visceral

Herpes zoster disseminated

Herpes zoster infection neurological

Herpes zoster multi-dermatomal

Histoplasmosis

Histoplasmosis cutaneous

Histoplasmosis disseminated

Isosporiasis

JC virus infection

Joint tuberculosis

Listeria encephalitis

Listeria sepsis

Listeriosis

Lower respiratory tract infection fungal

Lymph node tuberculosis

Lymphadenitis fungal

Male genital tract tuberculosis

Meningitis candida

Meningitis coccidioides

Meningitis cryptococcal

Meningitis fungal

Meningitis herpes

Meningitis histoplasma

Meningitis listeria

Meningitis toxoplasmal

Meningitis tuberculous

Mycobacterial infection

Mycobacterium abscessus infection

Mycobacterium avium complex immune restoration disease

Mycobacterium avium complex infection

Mycobacterium chelonei infection

Mycobacterium fortuitum infection

Mycobacterium kansasii infection

Mycobacterium kansasii pneumonia

Mycobacterium marinum infection

Mycobacterium ulcerans infection

Myocarditis toxoplasmal

Necrotising fasciitis fungal

Neurocryptococcosis

Oesophageal candidiasis

Oesophageal tuberculosis

Opportunistic infection

Osteomyelitis fungal

Pancreatitis fungal

Pericarditis fungal

Pericarditis histoplasma

Pericarditis tuberculous

Peritoneal tuberculosis

Pneumocystis jiroveci infection

Pneumocystis jiroveci pneumonia

Pneumonia cryptococcal

Pneumonia cytomegaloviral

Pneumonia fungal

Pneumonia toxoplasmal

Presumed ocular histoplasmosis syndrome

Progressive multifocal leukoencephalopathy

Prostatitis tuberculous

Pulmonary tuberculoma

Pulmonary tuberculosis

Pyelonephritis fungal

Renal tuberculosis

Retinitis histoplasma

Salmonella bacteraemia

Salmonella sepsis

Salpingitis tuberculous

Silicotuberculosis

Sinusitis fungal

Spleen tuberculosis

Splenic infection fungal

Systemic candida

Thyroid tuberculosis

Toxoplasmosis

Tuberculoma of central nervous system

Tuberculosis

Tuberculosis bladder

Tuberculosis gastrointestinal

Tuberculosis liver

Tuberculosis of central nervous system

Tuberculosis of eye

Tuberculosis of genitourinary system

Tuberculosis of intrathoracic lymph nodes

Tuberculosis of peripheral lymph nodes

Tuberculosis serology test positive

Tuberculosis test positive

Tuberculosis ureter

Tuberculous abscess central nervous system

Tuberculous laryngitis

Tuberculous pleurisy

Tuberculous tenosynovitis

Tubo-ovarian abscess

Urine cytomegalovirus positive

5 HYPERSENSITIVITY REACTIONS

Hypersensitivity adverse events will be identified using the following MedDRA PTs:

Allergic oedema

Anaphylactic reaction

Anaphylactic shock

Anaphylactoid reaction

Anaphylactoid shock

Angioedema

Auricular swelling

Bronchial oedema

Circumoral oedema

Conjunctival oedema

Drug hypersensitivity

Endotracheal intubation

Epiglottic oedema

Eye oedema

Eye swelling

Eyelid oedema

Face oedema

Gastrointestinal oedema

Genital swelling

Gingival oedema

Gingival swelling

Gleich's syndrome

Hereditary angioedema

Hypersensitivity

Idiopathic urticaria

Intubation

Laryngeal dyspnoea

Laryngeal obstruction

Laryngeal oedema

Laryngospasm

Laryngotracheal oedema

Lip oedema

Lip swelling

Nasal oedema

Oedema genital

Oedema mouth

Oedema mucosal

Oral allergy syndrome

Orbital oedema

Oropharyngeal spasm

Oropharyngeal swelling

Palatal oedema

Penile oedema

Penile swelling

Periorbital oedema

Pharyngeal oedema

Scrotal oedema

Scrotal swelling

Small bowel angioedema

Stridor

Swelling face

Swollen tongue

Throat tightness

Tongue oedema

Tracheal obstruction

Tracheal oedema

Tracheostomy

Type I hypersensitivity

Urticaria

Urticaria cholinergic

Urticaria chronic

Urticaria papular

Vaginal oedema

Vaginal swelling

Visceral oedema

Vulval oedema

6 LIVER ABNORMALITIES

Detection of liver test abnormalities accompanied by jaundice or hyperbilirubinemia

(a) Laboratory criteria will include: all cases with the following two criteria in the same sample:

i) ALT or AST elevated ≥ 3 times ULN

AND

ii) Total bilirubin > 2 times ULN

(b) Criteria by adverse event submissions will include:

Liver test abnormalities accompanied by jaundice or hyperbilirubinemia- a combination of at least one PT from column A and at least one PT from column B below. The MedDRA version is 12.1.

A (transaminase elevation)	B (bilirubin elevation, or jaundice)
Alanine aminotransferase abnormal	Hyperbilirubinaemia
Alanine aminotransferase increased	Icterus index increased
Aspartate aminotransferase abnormal	Jaundice
Aspartate aminotransferase increased	Jaundice cholestatic
Gamma-glutamyltransferase abnormal	Jaundice hepatocellular
Gamma-glutamyltransferase increased	Ocular icterus
Hepatic enzyme abnormal	Yellow skin
Hepatic enzyme increased	Bilirubin conjugated abnormal
Hepatic function abnormal	Bilirubin conjugated increased
Hypertransaminasaemia	Blood bilirubin abnormal

Liver function test abnormal	Blood bilirubin increased
Mitochondrial aspartate aminotransferase increased	Blood bilirubin unconjugated increased
Transaminases abnormal	Urine bilirubin increased
Transaminases increased	Urobilin urine present

7 BONE FRACTURES

Adverse events related to bone fractures will be identified by searching for any PT including the text string ‘fracture’ excluding ‘tooth fracture’

8 PANCREATITIS

Adverse events related to pancreatitis will be identified using the following PTs:

Cullen's sign

Hereditary pancreatitis

Ischaemic pancreatitis

Oedematous pancreatitis

Pancreatic abscess

Pancreatic haemorrhage

Pancreatic necrosis

Pancreatic phlegmon

Pancreatic pseudocyst

Pancreatic pseudocyst drainage

Pancreatitis

Pancreatitis acute

Pancreatitis chronic

Pancreatitis haemorrhagic

Pancreatitis necrotising

Pancreatitis relapsing

Pancreatorenal syndrome

9 SKIN REACTIONS

Adverse events related to skin reactions will be identified using the following PTs:

Anal erosion

Anal ulcer

Anal ulcer haemorrhage

Anorectal ulcer

Auditory meatus external erosion

Diabetic neuropathic ulcer

Diabetic ulcer

Epidermal necrosis

Eyelid erosion

Fungating wound

Genital erosion

Genital ulceration

Infected skin ulcer

Lip erosion

Lip ulceration

Nasal necrosis

Nasal septum ulceration

Nasal ulcer

Neuropathic ulcer

Nipple ulceration

Penile necrosis

Penile ulceration

Scab

Scrotal ulcer

Skin erosion

Skin necrosis

Skin ulcer

Skin ulcer excision

Skin ulcer haemorrhage

Testicular necrosis

Vulval ulceration

Vulvar erosion

Vulvovaginal ulceration

10 RENAL ABNORMALITIES

Renal abnormalities are identified by:

Doubling of creatinine levels

Development of end-stage renal disease (eg, dialysis or renal transplantation)

And/or by the following PTs covering acute renal failure:

Acute prerenal failure

Anuria

Azotaemia

Continuous haemodiafiltration

Dialysis

Haemodialysis

Nephropathy toxic

Oliguria

Peritoneal dialysis

Renal failure

Renal failure acute

Renal impairment

Renal transplantation