AstraZeneca

Amended Clinical Study Protocol	
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A 52-Week International, Multi-centre, Randomized, Parallel-group, Double-blind, Active-controlled, Phase III study with a 52-Week Extension Period to Evaluate the Safety and Efficacy of Saxagliptin in Combination with Metformin compared with Sulphonylurea in Combination with Metformin in Adult Patients with Type 2 Diabetes who have Inadequate Glycaemic Control on Metformin Therapy Alone.

Sponsor:

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

Amendment No.	Date of Amendment	Local Amendment No.	Date of local Amendment

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

PROTOCOL SYNOPSIS

A 52-Week International, Multi-centre, Randomized, Parallel-group, Double-blind, Active-controlled, Phase III study with a 52-Week Extension Period to Evaluate the Safety and Efficacy of Saxagliptin in Combination with Metformin compared with Sulphonylurea in Combination with Metformin in Adult Patients with Type 2 Diabetes who have Inadequate Glycaemic Control on Metformin Therapy Alone.

International Co-ordinating Investigator

The International coordinating investigator has been chosen for particular active contribution, active recruitment and for signing the clinical study reports (52-week and 104-week) of this study.

Study centre(s) and number of patients planned

This international study will be conducted at approximately 160 study centres. Approximately 2200 patients will be enrolled to reach the target of 838 randomized patients and at least 544 patients for evaluation during an enrolment period of approximately 8 months. It is expected that approximately 5 patients will be randomized per centre.

Study period		**Phase of development**
Estimated date of first patient enrolled	Q4 2007 - Q1 2008	III
Estimated date of last patient completed	Q3 2010	

Objectives

The primary efficacy objective of this study is to compare that, after a 52-week oral administration of double-blind treatment, the absolute change from baseline in glycosylated haemoglobin A1c (HbA1c) level with saxagliptin plus metformin is non-inferior to glipizide (sulphonylurea) plus metformin in patients with type 2 diabetes who have inadequate glycaemic control on 1500 mg or higher doses of metformin alone.

Three secondary objectives, among all secondary objectives, are identified a priori for special attention to compare the effects of saxagliptin versus glipizide given as add-on therapy to metformin after a 52-week double-blind treatment period by evaluation of:

- Proportion of patients reporting at least one episode of hypoglycaemic event at Week 52.
- Change from baseline in body weight at Week 52.
- Durability of HbA1c effect based on Week 24 over the 52 weeks as an efficacy objective.

Other secondary objectives are:

Efficacy: To compare the effects of saxagliptin versus glipizide given as add-on therapy to metformin after a 52-week double-blind treatment period by evaluation of:

- Change from baseline in fasting plasma glucose (FPG), insulin, C-peptide, glucagon and proinsulin.
- Proportion of patients achieving a therapeutic glycaemic response defined as HbA1c ≤6.5%.
- Change from baseline in HbA1c in patients with baseline HbA1c ≥7.0%.
- Proportion of patients achieving a therapeutic glycaemic response defined as HbA1c <7.0% in patients whose baseline HbA1c is ≥7.0%.
- Change from baseline in β-cell function (as measured by homeostasis model assessment (HOMA-2).
- Change from baseline in the area under curve (AUC) from 0 to 180 minutes for postprandial glucose, insulin, C-peptide and glucagon during an oral glucose tolerance test (OGTT) on a subset of patients.
- Change from baseline in insulinogenic index on a subset of patients.
- Change from baseline in insulin sensitivity as measured by oral glucose insulin sensitivity model (OGIS) and Matsuda Index on a subset of patients.
- Change from baseline in total cholesterol (TC), low-density lipoprotein-cholesterol (LDL-C), high-density lipoprotein-cholesterol (HDL-C) and triglycerides (TG).
- The population pharmacokinetic profile of saxagliptin and its pharmacologically active metabolite, BMS-510849, in patients assigned to

saxagliptin treatment groups from a total of approximately 50 randomized patients who will undergo OGTT assessment.

Safety: Safety and tolerability will be evaluated by assessment of adverse events (AEs) (including AEs of special interest, such as oedema and skin-related AEs, and hypoglycaemic events), laboratory values, electrocardiogram (ECG), pulse, blood pressure, body weight and physical examination.

The tertiary objectives are:

- To assess the long-term safety, tolerability and efficacy effects of saxagliptin versus glipizide given as add-on therapy to metformin after a 104-week double-blind treatment period, assessed as those identified for the Week 52 period, except the evaluations are for the entire 104 weeks.

Study design

This study is a 52-week, international, multi-centre, randomized, parallel-group, double-blind, active-controlled Phase III study with a 52-week double-blind extension period to study the efficacy and safety of saxagliptin in combination with metformin compared with sulphonylurea (glipizide) in combination with metformin in adult patients with type 2 diabetes who have inadequate glycaemic control (HbA1c >6.5% and ≤10.0%) on metformin therapy alone.

Target patient population

Males and females with type 2 diabetes from 18 years of age, with inadequate glycaemic control defined as HbA1c >6.5% and ≤10.0% are eligible to enter the placebo lead-in period (Period B). Patients should be on a stable dose (1500 mg or higher) of metformin monotherapy for at least 8 weeks prior to enrolment. Females must be postmenopausal or have undergone successful surgical sterilization or, if of childbearing potential, use adequate method of contraception.

Investigational product, dosage and mode of administration

Matching placebo tablets for saxagliptin 5 mg oral for the 2-week placebo lead-in period, the 52-week double-blind period and the 52-week double-blind extension period.

Matching placebo capsules for glipizide (sulphonylurea) 5 mg oral for the 2-week placebo lead-in period, 52-week double-blind period (dosing 5 to 20 mg) and the 52-week double-blind extension period (dosing 5 to 20 mg).

Saxagliptin tablets 5 mg oral for the 52-week double-blind period and the 52-week double-blind extension period.

Glipizide (sulphonylurea) 5 mg capsule oral (dosing 5 to 20 mg) for the 52-week double-blind period and the 52-week double-blind extension period.

Additional drug, dosage and mode of administration

Open-label metformin 500 mg tablets oral at a daily dose of 1500 mg – 3000 mg tablets from Visit 2 throughout the study period.

Duration of treatment

The randomization treatment period will be 104 weeks. Patients will have an enrolment and lead-in period of 2 weeks before day of randomization for 52 weeks of Period C and an extension of additional 52 weeks of Period D. The total planned study duration is 106 weeks.

Outcome variables

Primary outcome variables:

Efficacy

- The primary endpoint is change from baseline to Week 52 in HbA1c level.

Secondary outcome variables:

Secondary outcome variables at Week 52 are:

- Proportion of patients reporting at least one episode of hypoglycaemic event over 52 weeks, a safety outcome variable.
- Change from baseline in body weight at Week 52, a safety outcome variable.
- Mean slope of the regressions of change from Week 24 in HbA1c on treatment duration after Week 24.

Other secondary outcome variables are:

- Change from baseline in FPG, insulin, C-peptide, glucagon and proinsulin.
- Proportion of patients achieving a therapeutic glycaemic response defined as HbA1c $\leq$6.5%.
- Change from baseline in HbA1c in patients with baseline HbA1c $\geq$7.0%.
- Proportion of patients achieving a therapeutic glycaemic response defined as HbA1c <7.0% in patients whose baseline HbA1c is $\geq$7.0%.
- Change from baseline in β-cell function (as measured by HOMA-2).
- Change from baseline in AUC from 0 to 180 minutes for glucose, insulin, C-peptide and glucagon during an OGTT on a subset of patients.

- Change from baseline in insulinogenic index on a subset of patients.
- Change from baseline in insulin sensitivity as measured by OGIS and Matsuda Index on a subset of patients.
- Change from baseline in TC, LDL-C, HDL-C and TG.

Tertiary outcome variables

Tertiary endpoints at Week 104 are:

- To compare the long-term safety, tolerability and efficacy effects of saxagliptin versus glipizide given as add-on therapy to metformin after a 104-week double-blind treatment period, assessed as those identified for the Week 52 period, except the evaluations are for the entire 104 weeks.

Safety

Safety and tolerability will be evaluated by assessment of:

- AEs
- Hypoglycaemic events
- Incidence of oedema and skin-related AEs
- Serious adverse events (SAEs)
- Laboratory values
- ECG
- Vital signs (pulse and blood pressure)
- Physical examination
- Weight
- Plasma concentration of saxagliptin and metabolite BMS-510849 in patients who experience some predefined AEs or discontinue due to an AE

No hypotheses are proposed a priori for these safety-related variables.

Patient reported outcomes (PROs) – Not applicable

Health economics – Not applicable

Pharmacokinetic

To examine the pharmacokinetic characteristics of saxagliptin in a subset of the population enrolled in this study. Data analysis for population pharmacokinetics will be outlined in a separate analysis plan and the results will be reported in a separate report.

Pharmacodynamic – Not applicable

Genetics

Blood samples will be taken from patients who separately consent to optional blood sample donation for deoxyribonucleic acid (DNA) analysis. The purpose is to enable future exploratory pharmacogenetic research studies. DNA obtained from the blood sample and health information collected from the main clinical study will be used to study the causes and further progression on type 2 diabetes and other metabolic disease. Samples from this and other clinical studies may also be used in conjunction to accomplish this objective. The samples will be destroyed after 15 years or handled according to local legislation.

Statistical methods

The primary efficacy analysis to establish non-inferiority with 0.35% non-inferiority limit on the change in HbA1c from baseline to Week 52 will be performed on a per protocol analysis set using an analysis of covariance model (ANCOVA). The model will use treatment group as a fixed effect and baseline value as a covariate. Within the framework of the ANCOVA model, point estimates and the two-sided 95% confidence intervals for the mean change within each treatment group as well as for the differences in mean change between the saxagliptin plus metformin treatment arm and the glipizide plus metformin treatment arm will be performed.

Hypoglycaemic events and body weight changes are considered as safety variables and are specified as important secondary variables supporting the treatment of saxagliptin. Proportion of patients reporting at least one episode of hypoglycaemic event over the 52-week treatment period will be compared between the two treatment groups using a two-sided Fisher's exact test. ANCOVA method comparing the two treatment groups will be used for change from baseline in body weight at Week 52, where the model will include treatment as a fixed effect and baseline as a covariate.

Durability of HbA1c will be assessed for each of the two treatment groups from mean slopes of the regressions of change from Week 24 in HbA1c on treatment duration from Week 24 to Week 52. All patients with a pair of HbA1c levels at Week 24 and post Week 24 will be included. Weeks on randomized treatment period will be used as a regressor. Only observed values between the two visits, inclusive, will be used for the analysis.

For the safety endpoints, the data set utilized will be the safety analysis set, which will include observed data only. This data set will include patients who have taken at least one dose of double-blind investigational product.

For all changes (or percent changes) from baseline to a specific time point post-baseline for the primary and secondary efficacy, analysis will be based on the per protocol analysis set. These analyses will be supplemented by using the full analysis set.

Three secondary variables (proportion of patients reporting hypoglycaemic events, change from baseline in body weight and mean slope of the regressions of change from baseline in HbA1c on treatment duration after Week 24) have been identified for special consideration in this study, in addition to the primary efficacy variable (non-inferior (NI) HbA1c). In order to control overall type 1 error rate of the study, a fixed-sequence test will be adopted with respect to the four hypotheses, ie, the testing will be sequentially performed for non-inferiority comparison of HbA1c, superiority tests for hypoglycaemic event and then weight changes and mean slope for durability. All comparisons will be two-sided at the 5% significance level.

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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
AE	Adverse Event (see definition in Section 4.7.1.1)
ANCOVA	Analysis of covariance model
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
Anti-HAV	Hepatitis A viral antibody – IgM, IgG
Anti-HBs	Antibody hepatitis B surface antigen
Anti-HCV	Hepatitis C virus antibody
AUC	Area Under the Curve
BMI	Body Mass Index
BUN	Blood urea nitrogen
CBC	Complete blood count
CD4	Cluster designation: cell surface marker expressed by lymphocytes
CD8	Cluster designation: cell surface marker expressed by lymphocytes
CK	Creatine kinase
CL/F	Apparent oral clearance
Cmin	Minimum observed concentration
CPMP	Committee for Proprietary Medicinal Products. CPMP has changed name to Committee for Medicinal Products for Human Use (CHMP).
CRO	Contract Research Organization
CSA	Clinical Study Agreement
CYP450 3A4	Cytochrome P450 3A4
DMC	Data Monitoring Committee
DNA	Deoxyribonucleic acid
DPP-4	Dipeptidyl peptidase 4
ECG	Electrocardiogram
E-code	Enrolment code
eCRF	electronic Case Report Form

Abbreviation or special term	Explanation
Ethics Committee	Synonymous to Institutional Review Board and Independent Ethics Committee
EU	European Union
FPG	Fasting plasma glucose
FSH	Follicle Stimulating Hormone
GCP	Good Clinical Practice
GIP	Glucose dependent insulinotropic peptide
GLP-1	Glucagon-like peptide-1
GMP	Good Manufacturing Practice
HbA1c	Glycosylated haemoglobin A1c
HBsAg	Hepatitis B surface antigen
hCG	Human chorionic gonadotropin
HDL-C	High-density lipoprotein-cholesterol
HIV	Human immunodeficiency virus
HOMA	Homeostasis model assessment
HRT	Hormone replacement therapy
IB	Investigator's Brochure
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
IWRS	Interactive Web Response System
ka	Absorption rate constant
Kg	Kilogram
LC-MS/MS	Liquid chromatography-tandem mass spectrometry
LDL-C	Low-density lipoprotein-cholesterol
LOCF	Last observation carried forward
MedDRA	Medical Dictionary for Regulatory Activities
NI	Non-inferior
NYHA	New York Heart Association
OGIS	Oral glucose insulin sensitivity model

Abbreviation or special term	Explanation
OGTT	Oral glucose tolerance test
PP	Per protocol
RIBA HCV	Immunoassay for Hepatitis C RNA
SAE	Serious Adverse Event (see definition in Section 4.7.1.1).
SAP	Statistical Analysis Plan
SCr	Serum Creatinine
SDV	Source Data Verification
SGOT	Serum glutamic oxaloacetic transaminase
SGPT	Serum glutamic pyruvic transaminase
TC	Total cholesterol
TG	Triglycerides
ULN	Upper limit of normal
Vd/F	Apparent oral volume of distribution
WBDC	Web Based Data Capture
WOCBP	Women of Childbearing Potential

1. INTRODUCTION

1.1 Background

Type 2 diabetes is associated with long-term microvascular complications such as retinopathy, nephropathy, and neuropathy as well as cardiovascular events. Intensive treatment to reduce blood glucose to within normal levels can minimize the risk of developing these complications. Current therapeutic agents have limited efficacy and are associated with side effects including hypoglycaemia, weight gain, oedema, and changes in the blood lipid profile. Agents with new mechanisms of action for the treatment of type 2 diabetes are being explored. Inhibition of dipeptidyl peptidase 4 (DPP-4) is emerging as a new therapeutic approach for type 2 diabetes. AstraZeneca and Bristol-Myers Squibb are jointly developing saxagliptin, a novel DPP-4 inhibitor, as a once daily oral therapy for the treatment of hyperglycaemia in patients with type 2 diabetes.

Saxagliptin (BMS-477118) is a synthetic, potent, reversible, orally active DPP-4 inhibitor. DPP-4 is an enzyme that selectively cleaves dipeptides from the N-terminus of oligopeptides with proline or alanine in the penultimate position. DPP-4 actively converts the key insulinotropic hormone glucagon-like peptide-1 (GLP-1) from active to inactive form, and is responsible for the short half-life of GLP-1 in vivo. Inhibitors of DPP-4 increase levels of endogenous intact GLP-1 thereby potentiating its physiological actions, augmenting postprandial insulin secretion and improving the glycaemic profile in patients with type 2 diabetes. Because DPP-4 inhibitors lead to enhanced glucose dependent insulin secretion, they are expected to present low risk of hypoglycaemia and may not lead to weight gain.

Several lines of evidence indicate that preservation of active GLP-1 by treatment with a DPP-4 inhibitor will improve the insulin secretion pattern from pancreatic β-cells, enhance postprandial glucose control, and result in long term improvements in both fasting and postprandial glycaemia and the diabetic state. Furthermore, experimental data suggest that DPP-4 inhibitors may protect and/or promote pancreatic β-cell function and capacity and may have pleiotropic effects on glucose homeostasis and/or pancreatic β-cell function. Possible mechanisms include inhibiting inactivation of other incretins, such as glucose dependent insulinotropic peptide (GIP), and effects on other relevant targets, such as decreasing levels of the ‘counter-regulatory’ hormone glucagon.

Proof of concept for saxagliptin has been established in a Phase II study over a dose range of 2.5 mg to 40 mg for 12 weeks and 100 mg for 6 weeks. When tested for 12 weeks, doses of 2.5 mg, 5 mg, and 10 mg achieved a dose-dependent 24-hour inhibition of plasma DPP-4 activity, and similar glucose lowering that was statistically significant compared with placebo. The statistically significant and clinically relevant glucose lowering was associated with a safety and tolerability profile similar to placebo. Data from two 24-week Phase III studies

with ongoing long-term treatment period support safety and efficacy of the 2.5 mg, 5 mg, and 10 mg doses.

For additional details, see the Investigator's Brochure (IB).

1.2 Rationale

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

This 52+52-week Phase III clinical study investigates the safety and efficacy of saxagliptin in combination with metformin compared with glipizide (sulphonylurea) in combination with metformin in patients with type 2 diabetes. The study is required to demonstrate that saxagliptin is effective in the treatment of type 2 diabetes and at least as effective as other antidiabetic medication.

2. STUDY OBJECTIVES

2.1 Primary objective

The primary efficacy objective of this study is to compare that, after a 52-week oral administration of double-blind treatment, the absolute change from baseline in glycosylated haemoglobin A1c (HbA1c) level with saxagliptin plus metformin is non-inferior to glipizide (sulphonylurea) plus metformin in patients with type 2 diabetes who have inadequate glycaemic control on 1500 mg or higher doses of metformin alone.

2.2 Secondary objectives

Three secondary objectives, among all secondary objectives, are identified a priori for special attention to compare the effects of saxagliptin versus glipizide given as add-on therapy to metformin after a 52-week double-blind treatment period by evaluation of:

- Proportion of patients reporting at least one episode of hypoglycaemic event at Week 52.
- Change from baseline in body weight at Week 52.
- Durability of HbA1c effect based on Week 24 over the 52 weeks as an efficacy objective.

Other secondary objectives are:

Efficacy: To compare the effects of saxagliptin versus glipizide given as add-on therapy to metformin after a 52-week double-blind treatment period by evaluation of:

- Change from baseline in fasting plasma glucose (FPG), insulin, C-peptide, glucagon and proinsulin.

- Proportion of patients achieving a therapeutic glycaemic response defined as HbA1c ≤6.5%.

- Change from baseline in HbA1c in patients with baseline HbA1c ≥7.0%.

- Proportion of patients achieving a therapeutic glycaemic response defined as HbA1c <7.0% in patients whose baseline HbA1c ≥7.0%.

- Change from baseline in β-cell function (as measured by homeostasis model assessment (HOMA-2).

- Change from baseline in the area under curve (AUC) from 0 to 180 minutes for postprandial glucose, insulin, C-peptide and glucagon during an oral glucose tolerance test (OGTT) on a subset of patients.

- Change from baseline in insulinogenic index on a subset of patients.

- Change from baseline in insulin sensitivity as measured by oral glucose insulin sensitivity model (OGIS) and Matsuda Index on a subset of patients.

- Change from baseline in total cholesterol (TC), low-density lipoprotein-cholesterol (LDL-C), high-density lipoprotein-cholesterol (HDL-C) and triglycerides (TG).

- The population pharmacokinetic profile of saxagliptin and its pharmacologically active metabolite, BMS-510849, in patients assigned to saxagliptin treatment groups from a total of approximately 50 randomized patients who will undergo OGTT assessment.

Safety: Safety and tolerability will be evaluated by assessment of adverse events (including AEs of special interest, such as oedema and skin-related AEs, and hypoglycaemic events), laboratory values, electrocardiogram (ECG), pulse, blood pressure, body weight and physical examination.

2.3 Tertiary objectives

- To assess the long-term safety, tolerability and efficacy effects of saxagliptin versus glipizide given as add-on therapy to metformin after a 104-week double-blind treatment period, assessed as those identified for the Week 52 period, except the evaluations are for the entire 104 weeks.

3. STUDY PLAN AND PROCEDURES

3.1 Overall study design and flow chart

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

> This study is a 52-week, international, multi-centre, randomized, parallel-group, double-blind, active-controlled Phase III study with a 52-week extension period to evaluate the efficacy and safety of saxagliptin in combination with metformin compared with glipizide in combination with metformin in adult patients with type 2 diabetes who have inadequate glycaemic control on metformin therapy alone.

Patients with type 2 diabetes and inadequate glycaemic control (HbA1c >6.5% and ≤10.0%) and currently on a stable dose (1500 mg or higher per day) of metformin therapy alone for at least 8 weeks prior to enrolment will be eligible to enter the study (Period A). Period B is a 2-week single-blinded dietary and exercise placebo lead-in period. Patients will be provided open-label metformin upon Visit 2 (Period B) and maintain their current dose for the duration of the study. Patients will be randomized (1:1) to one of the following two treatment groups in the 52-week double-blind treatment period (Period C): saxagliptin 5 mg plus open-label metformin or glipizide 5 mg plus open-label metformin. In patients in the glipizide plus metformin arm, glipizide dose will be titrated to optimal effect (FPG ≤6.1 mmol/L, ≤110mg/dL) or the highest tolerable dose during a period of 18 weeks. Patients who complete the double-blind Period C will be eligible for an additional 52 weeks of treatment, Period D (double-blind extension period), with the same treatment given throughout this study period as was given at time for last visit in Period C.

This study will be conducted at approximately 160 centres. Approximately 2200 patients will be enrolled to randomize 838 patients in order to reach 544 evaluable patients. It is expected that approximately 5 patients will be randomized per centre.

The study will consist of the following five parts:

The enrolment visit (Period A):

Patients with type 2 diabetes and inadequate glycaemic control (HbA1c >6.5% and ≤10.0%) and currently on a stable dose (1500 mg or higher per day) of metformin therapy alone for at least 8 weeks prior to Visit 1 will be eligible to the study. The patient should continue taking the prescribed dose of metformin to the next visit, Visit 2. Laboratory assessments will be performed.

Lead-in period (Period B):

Eligible patients will be given placebo in a single-blind fashion (blind to the patient only) at Visit 2 and start open-label metformin during the 2-week lead-in period. Patients on metformin will be treated with 1500, 2000, 2500 or 3000 mg of open-label metformin for the

duration of the study (see Section 3.4.2 for metformin doses to be used). The aim is that the open-label metformin dose should remain stable throughout the study.

The patients will be counselled on dietary and life-style modifications according to usual clinical routine. A glucometer and a patient diary will be handed out and the patients will be instructed to monitor their blood glucose at least every second day. Information about hypoglycaemic events should be entered into the patient diary.

Visit 2 should preferably be done at the clinic, but may be performed as a telephone visit if it is clear before the scheduled visit that the patient is not eligible due to the laboratory results from Visit 1.

Randomized treatment period (Period C):

The patients will be randomized at Visit 3 (baseline) and the double-blind treatment period will start. Either saxagliptin 5 mg plus open-label metformin or glipizide 5 mg plus open-label metformin will be given using a double-dummy technique. During the randomized treatment period dietary and life-style modification will be reinforced.

Titration period (Visits 4-9)

Patients in the glipizide plus metformin arm will be titrated to optimal effect (FPG ≤6.1 mmol/L, ≤110 mg/dL) or the highest tolerable dose during 18 weeks. Glipizide (4 doses) will be initiated at 5 mg per day (morning dose), and titrated in 3-week intervals to a maximum of 20 mg per day. The titration steps will be 10 mg per day (morning dose) followed by 15 mg per day (10 mg as morning dose and 5 mg as evening dose) and 20 mg (10 mg as morning dose and 10 mg as evening dose). In patients for whom titration was not medically indicated at Week 3, re-assessment for titration will occur at Week 6, 9, 12, 15, and 18. The decision for titration will be based on FPG measured at the study centre, using a glucose analyser provided by AstraZeneca. The investigational product (IP) glipizide can be down-titrated once during the titration period if hypoglycaemic events occur. Treatment may thereafter be up-titrated once during the titration period.

Patients on saxagliptin will remain on 5 mg throughout the study, no titration will be possible.

Assessment of glycaemic parameters (based on results from central laboratory) will be done to determine if criteria for discontinuation are met during the period.

The patients will be instructed to monitor their blood glucose at least every second day. Hypoglycaemic events should be entered into the patient diary. The evaluation at each of the titration visits and final decision by the investigator on dose increase (or decrease) should take into account both the plasma glucose measurements made by the patients prior to visits and the investigator's measurements at the titration visits.

Maintenance treatment period (Visits 10-13)

After the titration period, the patient will return for visits to assess efficacy and safety of the treatment. At any time during the study, investigational product glipizide can be down-titrated to mitigate recurrent hypoglycaemic events at the discretion of the investigator, no up-titration is allowed. The patients will continue to monitor their blood glucose at least once a week. Hypoglycaemic events should be entered into the patient diary. Assessment of glycaemic parameters (based on results from central laboratory) will be done at each visit to determine if criteria for discontinuation are met during the period.

Randomized patients in the Titration or Maintenance treatment period who do not complete the entire study should complete the procedures described for Visit 13 (end of Period C).

Extension period (Period D) (Visits 14-17)

After 52 weeks, eligible patients will continue in the randomized extension treatment period with the same treatment given at the end of Period C. The patient will return for visits approximately every thirteenth week to assess efficacy and safety of the treatment. The patients will continue to monitor their blood glucose at least once a week. Hypoglycaemic events should be entered into the patient diary. At any time during the study, investigational product glipizide can be down-titrated to mitigate recurrent hypoglycaemic events at the discretion of the investigator, no up-titration is allowed. Assessment of glycaemic parameters (based on results from central laboratory) will be evaluated at Visit 14 to 16 to determine eligibility for discontinuation during the period. The patients will stop taking investigational product at the end of treatment visit, Visit 17.

Randomized patients in the Extension period who do not complete the entire study should complete the procedures described for Visit 17 (end of Period D).

Figure 1 Study flow chart for Enrolment, Lead-in and Treatment period (Period A, B, and C)

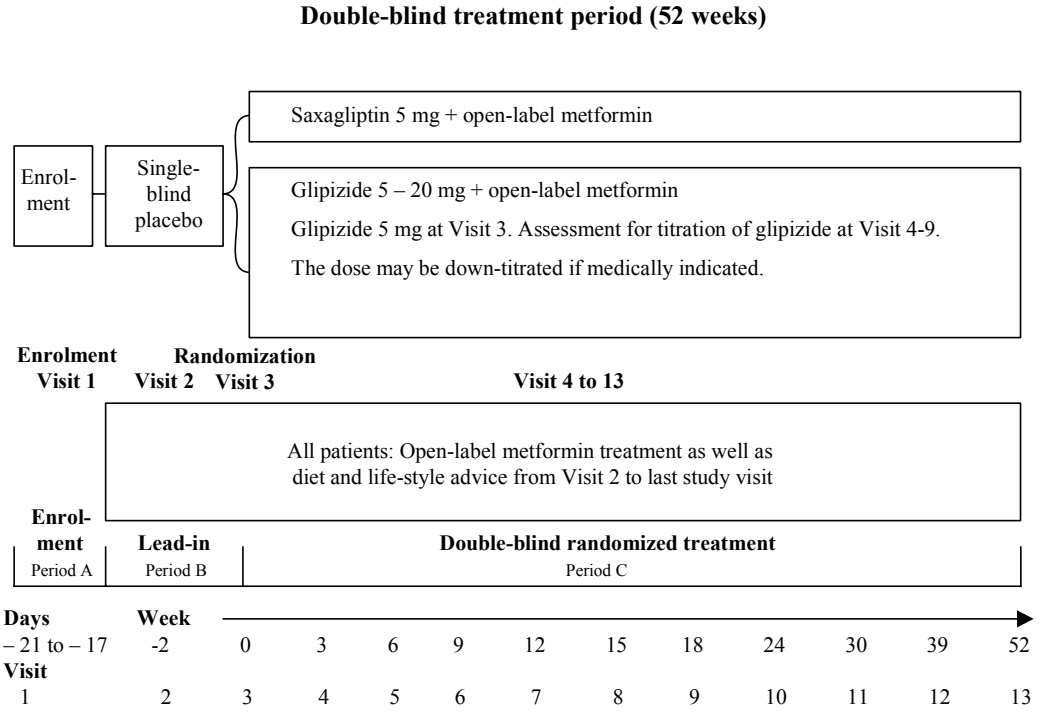

Figure 2 Study flow chart for Extension period (Period D)

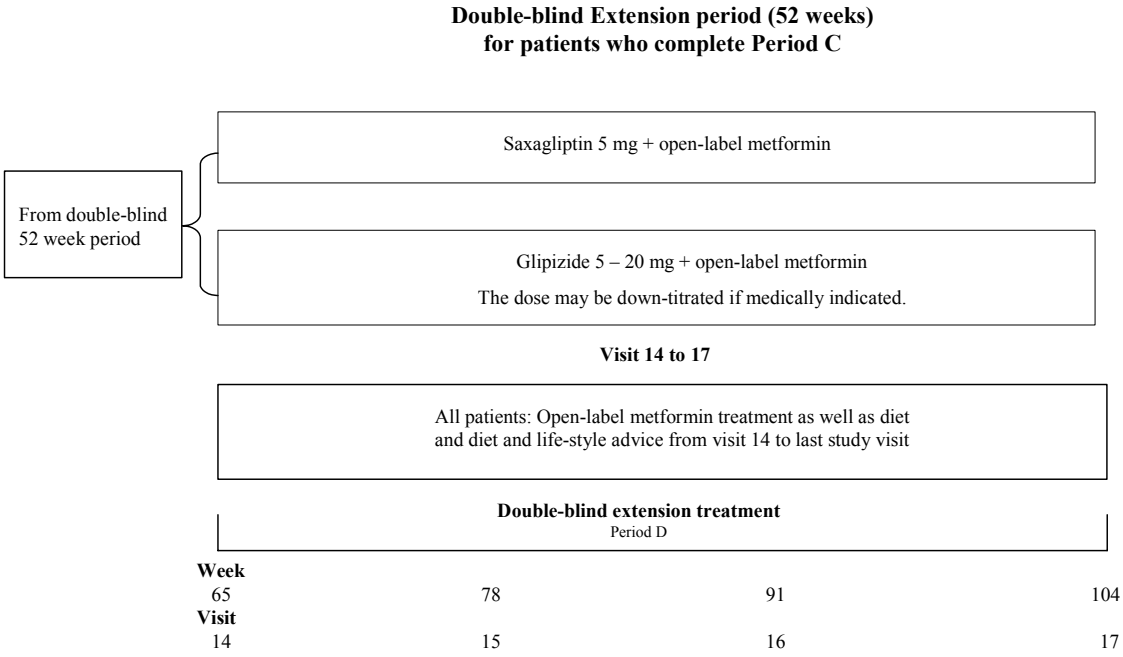

Table 1 Study plan for Enrolment, Lead-in and Treatment period (Period A, B and C)

	Enrolment (A)	Lead-in (B)[a]	Treatment period (C)[b]										
Visit number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**
Study week	**-21 - 17 days**	**-2 w**	**0 w**	**3 w**	**6 w**	**9 w**	**12 w**	**15 w**	**18 w**	**24 w**	**30 w**	**39 w**	**52 w**
Informed consent	X												
Randomization[b]			X										
Demography and Medical history	X												
Inclusion/exclusion criteria	X	X	X										
Physical examination	X		X			X		X		X	X	X	X
Vital signs	X		X			X		X		X	X	X	X
Weight	X		X	X		X	X	X	X	X	X	X	X
Height			X										
Waist circumference			X							X			X
ECG			X										X
Concomitant medication	X	X	X	X		X		X	X	X	X	X	X
Laboratory assessments[c]	X		X	X	X	X	X	X	X	X	X	X	X
Laboratory samples for exploartive research[d]			X										X
Pharmacokinetic sample[e, f]										X			X

Table 1 Study plan for Enrolment, Lead-in and Treatment period (Period A, B and C)

	Enrolment (A)	Lead-in (B)[a]	Treatment period (C)[b]										
Visit number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**
Study week	**-21 - 17 days**	**-2 w**	**0 w**	**3 w**	**6 w**	**9 w**	**12 w**	**15 w**	**18 w**	**24 w**	**30 w**	**39 w**	**52 w**
Pregnancy test[g]	X		X	X	X	X	X	X	X	X	X	X	X
Local FPG (site based glucose analyser)				X	X	X	X	X	X				
Extended OGTT[h]			X										X
AEs		X	X	X	X	X	X	X	X	X	X	X	X
Serious adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X
Diet and life-style advice		X	X	X	X	X	X	X	X	X	X	X	X
Obtain enrolment code (E-code) from interactive web response system (IWRS)	X												
Register titration during Titration period (if applicable) in IWRS				X	X	X	X	X	X				
Register down-titration during Maintenance period (if applicable) in IWRS										X	X	X	X

Table 1 Study plan for Enrolment, Lead-in and Treatment period (Period A, B and C)

	Enrolment (A)	Lead-in (B)[a]	Treatment period (C)[b]										
Visit number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**
Study week	**-21 - 17 days**	**-2 w**	**0 w**	**3 w**	**6 w**	**9 w**	**12 w**	**15 w**	**18 w**	**24 w**	**30 w**	**39 w**	**52 w**
Dispensation of investigational product and/or open-label metformin through IWRS		X	X	X	X	X	X	X	X	X	X	X	X
Dispensation of glucometer and/or supplies/provide instruction		X	X	X	X	X	X	X	X	X	X	X	X
Dispensation of patient diary (if applicable)		X	X	X	X	X	X	X	X	X	X	X	X
Patient diary review for hypoglycaemic events/check glucose values in glucometer			X	X	X	X	X	X	X	X	X	X	X
Drug accountability			X	X	X	X	X	X	X	X	X	X	X
Informed consent and blood sample for genetic research[i]			X	→	→	→	→	→	→				

[a] Visit 2 may be performed as a telephone visit if it is clear before the visit that the patient is not eligible due to the laboratory results
[b] Randomized patients who do not complete the entire study should complete the procedures described for end of Period C (Visit 13)

[c] Specification of laboratory parameters are shown in Table 4 and Table 6
[d] A blood sample and an urine sample will be taken for future analyses
[e] Pharmacokinetic samples (6 samples per visit) will be taken from 50 of the randomized patients who will undergo OGTT assessment. Note that no OGTT assessment will be carried out at Visit 11.
[f] One blood sample for plasma concentration of saxagliptin and BMS-510849 will be taken if a patient experiences any predefined AE or discontinues from the study due to an AE (See section 4.7.1.3)
[g] Pregnancy test will be done on all female patients who are not surgically sterile or postmenopausal
[h] Extended OGTT will be carried out on patients in a selection of countries (50 patients)
[i] Genetic informed consent (IC) must be obtained before genetic blood sample is taken, when patient eligibility for the study has been confirmed. Blood sample donation is optional and can be done from randomization Visit 3 to Visit 9.

Table 2 Study plan for Extension period (Period D)

Visit number[a, b]	**14**	**15**	**16**	**17**
Study week	**65 w**	**78 w**	**91 w**	**104 w**
Physical examination		X		X
Vital signs	X	X	X	X
Weight	X	X	X	X
Waist circumference		X		X
ECG				X
Concomitant medication	X	X	X	X
Laboratory assessments[c]	X	X	X	X
Laboratory samples for explorative research[d]				X
Pharmacokinetic sample[e, f]				X
Pregnancy test[g]	X	X	X	X
Extended OGTT[h]				X
AEs	X	X	X	X
Serious adverse events	X	X	X	X
Diet and life-style advice	X	X	X	
Dispense of glucometer and/or supplies/provide instruction	X	X	X	
Dispense of patient diary (if applicable)	X	X	X	
Patient diary review for hypoglycaemic events/check glucometer values	X	X	X	X
Register down-titration during Extension period (if applicable) in IWRS	X	X	X	
Dispense of investigational product and/or open-label metformin through IWRS	X	X	X	
Drug accountability	X	X	X	X

[a] Randomized patients who do not complete the entire study should complete the procedures described for end of Period D (Visit 17)
[b] Only patients that have completed Period A, B, and C are eligible to Period D
[c] A blood sample and an urine sample will be taken for future analyses
[d] Specification of laboratory parameters is shown in Table 5 and Table 7
[e] Pharmacokinetic samples (6 samples per visit) will be taken from 50 of the randomized patients who will undergo OGTT assessment

[f] One blood sample for plasma concentration of saxagliptin and BMS-510849 will be taken if a patient experiences any predefined AE or discontinues from the study due to an AE (See section 4.7.1.3)
[g] Pregnancy test will be done on all female patients who are not surgically sterile or postmenopausal
[h] Extended OGTT will be carried out on patients in a selection of countries

Table 3 Visit design and visit windows

Visit ID	Visit description		Visit window
Visit 1	Enrolment (Period A)		-21 to -17 days
Visit 2	Lead-in (Period B)		-2 weeks (±1 day)
Visit 3	Randomization/Treatment (Period C)		0 weeks
Visit 4	Treatment (Period C)	**Titration period**	3 weeks (+7 days) after Visit 3
Visit 5	Treatment (Period C)		6 weeks (±3 days) after Visit 3
Visit 6	Treatment (Period C)		9 weeks (-7 days) after Visit 3
Visit 7	Treatment (Period C)		12 weeks (±3 days) after Visit 3
Visit 8	Treatment (Period C)		15 weeks (+7 days) after Visit 3
Visit 9	Treatment (Period C)		18 weeks (±3 days) after Visit 3
Visit 10	Treatment (Period C)		24 weeks (±3 days) after Visit 3
Visit 11	Treatment (Period C)		30 weeks (±5 days) after Visit 3
Visit 12	Treatment (Period C)		39 weeks (±5 days) after Visit 3
Visit 13	Treatment/End of Period C		52 weeks (±5 days) after Visit 3
Visit 14	Extension (Period D)		65 weeks (±7 days) after Visit 3
Visit 15	Extension (Period D)		78 weeks (±7 days) after Visit 3
Visit 16	Extension (Period D)		91 weeks (±7 days) after Visit 3
Visit 17	Extension/End of Period D		104 weeks (±7 days) after Visit 3

Any slippage in time must not accumulate. The randomized double-blind treatment period (Period C) must be at least 359 days and maximum 369 days. The total treatment period including the extension period (Period C and D) must be at least 721 days. The maximum treatment period will be 735 days.

3.2 Rationale and risk/benefit assessment

3.2.1 Rationale for study design, doses, control groups, outcome variables and study population

3.2.1.1 Study design and regulatory requirement

The purpose of the study is to investigate if treatment with saxagliptin as add-on to metformin is beneficial for patients with type 2 diabetes as compared to the current standard therapy. A non-inferiority comparison is designed in this randomized, double blind, active-controlled study. This protocol incorporates the main features of the Committee for Proprietary Medicinal Products' guidance for investigations of diabetes (CPMP 2002).

3.2.1.2 Study doses and control groups

Many patients with type 2 diabetes do not reach glycaemic control goals with metformin monotherapy. The addition of a glucose-lowering agent, with a different mechanism of action, is indicated. The patients must be on a stable treatment of at least 1500 mg of metformin. No titration of metformin is included in the design since 1500 mg of metformin is in general a dose with the best efficacy/risk of side effect profile. Sulphonylureas are commonly used as add-on therapy in patients with inadequate glycaemic control on metformin alone and is the current standard therapy in the treatment of type 2 diabetes. Glycaemic efficacy is similar across sulphonylurea agents and glipizide was chosen as a representative sulphonylurea agent (Riddle 2005, DeFronzo 1999). The hypoglycaemic potency of sulphonylureas is related to the baseline glycaemic control, in patients with a higher Hba1c baseline level a larger reduction is seen than in patients with baseline HbA1c levels close to normal range (Rosenstock et al 1996, Simonson et al 1997, Nauck et al 2007). Thus, the patient population included in this study will give guidance for evaluation of the assay sensitivity.

The dose regimen and titration procedure for glipizide are according to clinical practice. The combination of an agent that decreases hepatic glucose output (such as metformin) and an agent that improves insulin secretion (such as saxagliptin) may have a synergistic glucose lowering effect. The current study is designed to demonstrate that saxagliptin is effective in the treatment of type 2 diabetes and at least as effective as glipizide add-on to metformin standard therapy.

The dose of saxagliptin used in the study is 5 mg. This is the dose that was generally associated with maximal efficacy in a Phase II clinical study evaluating doses of saxagliptin in the range 2.5 mg to 40 mg as monotherapy in drug-naïve subjects with type 2 diabetes. In this study, maximal decrease in both HbA1c as well as in FPG was seen with 5 mg of saxagliptin. Comparable decreases were seen with 5, 10, 20, and 40 mg saxagliptin.

3.2.1.3 Choice of outcome variables

In the regulatory guidelines for type 2 diabetes (CPMP 2002), HbA1c is the prescribed measure for determination of glycaemic control and is therefore chosen as the primary variable. As a member of DPP-4 inhibitors, saxagliptin leads to enhanced glucose dependent insulin secretion: low risk of hypoglycaemia and even weight loss may be expected. The

incidence of hypoglycaemia over time and weight changes from baseline are therefore chosen as important secondary safety endpoints in part to characterise the saxaglipin therapy.

It is strongly believed that saxagliptin treatment may protect and/or promote pancreatic ß-cell function; hence the saxagliptin therapy may be more durable and the patients may be more efficient in insulin secretion over time than the glipizide add-on therapy to metformin. The mean slopes of linear regressions of change from Week 24 in HbA1c after Week 24 will address the durability, or the rate of rise of HbA1c, over the 52 weeks of randomized treatment period. It is assumed that the nadir of HbA1c reduction may be observed as early as 24 weeks post first dose.

Other measures attempted in this protocol to better understand the mechanistic effects of saxagliptin are these other secondary efficacy outcome variables: The ß-cell function will also be measured by HOMA-2 and insulinogenic index; insulin sensitivity will be measured by OGIS and Matsuda Index; OGTT responses; and the lipids variables (TC, LDL-C, HDL-C and TG).

3.2.1.4 Choice of study population

The study population was selected to balance demands on representation of the future patient population and limit bias caused by confounding factors. The prevalence of type 2 diabetes increases with age and since there is no upper age limit the study will include also elderly patients. Women are not allowed to be or to become pregnant since saxagliptin has not been tested in pregnant women and the risk to the embryo, foetus, or infant are unknown.

In order to ensure that the study population is representative of the future target population, the limit for HbA1c is set to >6.5 to ≤10% (value from the enrolment visit). The HbA1c criterion was selected to permit patients with a wide range of glycaemic control, thereby helping to broaden the potential applicability of the study. The lower bound in this interval (ie, >6.5%) reflects continually evolving treatment guidelines such as the International Diabetes Federation Global Guideline for type 2 diabetes 2005 (International Diabetes Federation 2005), The National Institute for Clinical Excellence Guideline Management of type 2 diabetes – Management of Blood Glucose (National Institute for Clinical Excellence 2002), American Diabetes Association Position Statement on Standard of Medical Care in Diabetes 2006 (American Diabetes Association 2006), and the American Association of Clinical Endocrinologist Medical guidelines for the management of diabetes mellitus (American Association of Clinical Endocrinologists 2002). Although individual guidelines recommend treatment to normal HbA1c levels, the risk of hypoglycaemia may limit the possibility to achieve this in clinical practice. Treatment with a compound with the mode of action as saxagliptin with low risk of hypoglycaemia may, however, offer the possibility to normalise blood glucose and achieve an optimal glycaemic control. The upper bound of this interval (ie, ≤10%) is a commonly used and accepted value employed in studies of patients with diabetes.

Measures are taken to ensure that not more than approximately 25% of the population has HbA1c <7 %. The HbA1c levels of the randomized patients will be monitored closely so that when the cohort is estimated to have reached the aimed number, further enrolment to the >6.5

to <7 % cohort will be discontinued and the lower bound of HbA1c for enrolment will be set at HbA1c ≥7% for the remainder of the study.

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

The purpose of the remaining inclusion and exclusion criteria is to limit confounding factors that would complicate the interpretation of the results (eg, corticosteroid-induced type 2 diabetes, haemoglobinopathies that would interfere with the HbA1c analyses) or to exclude patients whose safety could be compromised by participation in the study.

3.2.2 Risk/benefit and ethical assessment

See the IB for an overall risk/benefit assessment of saxagliptin.

In a Phase II proof-of-concept study, all doses of saxagliptin were associated with a statistically significant and clinically relevant improvement in glycaemic control. Data from two phase III studies have also been evaluated. In summary, the safety and efficacy data collected to date from clinical studies in healthy volunteers and patients with type 2 diabetes indicate that the clinical safety and efficacy profile of saxagliptin support studies with 5 mg as the anchor dose. Studies on the long-term safety profile of saxagliptin are currently ongoing.

3.3 Selection of study population

3.3.1 Study selection record

Investigator(s) must keep a record of patients who were considered for enrolment but were never enrolled eg, a patient screening log. This information is necessary to establish that the patient population was selected without bias.

3.3.2 Inclusion criteria

For inclusion in the study patients must fulfil all of the following criteria:

Inclusion criteria at enrolment (Visit 1):

1. Provision of informed consent.

2. Diagnosed with type 2 diabetes.

3. Men or women who are ≥18 years of age at time of consenting upon Visit 1.

4. Women of childbearing potential (WOCBP) must be using an adequate method of contraception to avoid pregnancy throughout the study and for up to 4 weeks after the study in such manner that the risk of pregnancy is minimized.

   WOCBP include any female who has experienced menarche and who has not undergone successful surgical sterilization (hysterectomy, bilateral tubal ligation or bilateral oophorectomy) or is not postmenopausal (defined as amenorrhea ≥12

consecutive months; or women on hormone replacement therapy (HRT) with documented serum follicle stimulating hormone (FSH) level >35mIU/mL).

Even women who are using oral, implanted or injectable contraceptive hormones or mechanical products such as an intrauterine device or barrier methods (diaphragm, condoms, spermicides) to prevent pregnancy or practicing abstinence or where partner is sterile (eg, vasectomy), should be considered to be of child bearing potential.

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

5. Treatment with metformin alone on stable doses of 1500 mg or higher per day for at least 8 weeks prior to Visit 1.

Inclusion criteria at lead-in (Visit 2, laboratory values from Visit 1):

6. HbA1c >6.5% and ≤10.0%. NB Enrolment of patients having HbA1c >6.5% to <7 % will be stopped when the cohort of randomised patients having HbA1c <7 % is approximately 25% and the lower bound of HbA1c for enrolment will be set at HbA1c ≥7% for the remainder of the study.

3.3.3 Exclusion criteria

Any of the following is regarded as a criterion for exclusion from the study:

Exclusion criteria at enrolment (Visit 1):

1. Type 1 diabetes, history of diabetic ketoacidosis or hyperosmolar non-ketonic coma.

2. Pregnant or breastfeeding patients.

3. Insulin therapy within one year of enrolment (with the exception of insulin therapy during a hospitalization or use in gestational diabetes).

4. Previous treatment with any DPP-4 inhibitor.

5. Treatment with thiazolidindione within 12 weeks prior to Visit 1.

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

7. Treatment with cytochrome P450 3A4 (CYP450 3A4) inducers (carbamazepine, dexamethasone, phenobarbital, phenytoin, rifampin).

8. Treatment with human immunodeficiency virus (HIV) treatment/antiviral drugs (delavirdine, indinavir, nelfinavir, ritonavir, saquinavir).

9. Potential allergy to metformin, saxagliptin, glipizide, or placebo or formulation excipients.

10. Contraindications to therapy as outlined in the saxagliptin IB, metformin package insert, or glipizide package insert.

11. Congestive heart failure with functional deficit defined as New York Heart Association (NYHA) class III or IV (see Appendix C) and/or left ventricular ejection fraction of ≤ 40%.

12. Significant cardiovascular history within the past 6 months upon Visit 1 defined as: myocardial infarction, coronary angioplasty or bypass graft(s), valvular disease or repair, unstable angina pectoris, transient ischemic attack, or cerebrovascular accident.

13. History of haemoglobinopathies (sickle cell anaemia or thalassemias, sideroblatic anaemia).

14. History of alcohol abuse or illegal drug abuse within the past 12 months.

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

16. Previous enrolment or randomization of treatment in the present study.

17. Participation in a clinical study during the last 90 days prior to Visit 1.

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

19. Any condition where, in the opinion of the investigator, participation in this study may pose a significant risk to the patient or could render the patient unable to successfully complete the study.

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

Exclusion criteria at lead-in (Visit 2, laboratory values from Visit 1):

21. Serum creatinine ≥133 µmol/L (≥1.5 mg/dL) for men, ≥124 µmol/L (≥1.4 mg/dL) for women.

22. Active liver disease and/or significant abnormal liver function defined as aspartate aminotransferase (AST) >2x upper limit of normal (ULN) and/or alanine aminotransferase (ALT) >2xULN and/or total bilirubin >34 µmol/L (2 mg/dL).

23. Creatine kinase (CK) ≥3xULN.

24. History of positive serologic evidence of current infectious liver disease including hepatitis A viral antibody (anti-HAV), hepatitis B surface antigen (HBsAg), or hepatitis C virus antibody (anti-HCV). Patients who may have isolated positive antibody hepatitis B surface antigen (anti-HBs) can be included.

25. Any clinically significant abnormality identified on physical examination or laboratory tests, which in the judgement of the investigator would compromise the patients' safety or successful participation in the clinical study.

Exclusion criteria at randomization (Visit 3):

26. Any clinically significant abnormality identified on physical examination or ECG, which in the judgement of the investigator would compromise the patients safety or successful participation in the clinical study.

3.3.4 Restrictions

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

Restricted concomitant medications are listed in Section 3.7; restrictions before performing an OGTT (applicable in a selection of countries (50 patients)) are detailed in Section 4.6.2, and fasting prior to laboratory assessments is detailed in Section 4.7.2.1.

3.3.5 Discontinuation of patients from treatment or assessment

3.3.5.1 Criteria for discontinuation

Patients may be discontinued from study treatment and assessments at any time. Specific reasons for discontinuing a patient from this study are:

1. Voluntary discontinuation by the patient who is at any time free to discontinue his/her participation in the study, without prejudice to further treatment.

2. Safety reasons as judged by the investigator, AstraZeneca and/or Bristol-Myers Squibb Pharmacovigilance.

3. Severe non-compliance to protocol as judged by the investigator and/or AstraZeneca.

4. Incorrect enrolment or randomization, ie, the patient does not meet the required inclusion/exclusion criteria for the study.

5. Patient lost to follow-up (as defined by, unable to reach the patient after 3 documented phone calls, fax, e-mail, or attempts to contact him/her through patient

locator agencies (if allowed per national regulation) and having sent one letter by registered/certified mail; all should be documented in the patients medical records).

Study specific discontinuation criteria are listed below. The FPG and HbA1c values will be measured at the central laboratory.

6. Use of (need for) any antihyperglycaemic medication other than investigational product or open-label metformin for more than 14 consecutive days, however insulin during hospitalisation is allowed.

7. Treatment with chronic systemic glucocorticoids. However, two temporary periods no longer than 7 days each are allowed.

8. Severe and/or frequent hypoglycaemic events, defined as ≥ 1 major event or recurring minor events and the possibility of down-titration and contributing factors (eg, excessive physical activity) has been evaluated.

9. Patients whose double blind treatment codes are broken by the investigator.

10. Pregnancy.

11. FPG >15.0 mmol/L (>270 mg/dL) at Visit 4 (Week 3) confirmed at a repeated measurement.

12. FPG >13.3 mmol/L (>240 mg/dL) at Visit 7 (Week 12) and on maximum titrated tolerated dose for at least two weeks confirmed at a repeated measurement.

13. FPG >12.2 mmol/L (>220 mg/dL) at Visit 9 (Week 18) and on maximum titrated tolerated dose for at least two weeks confirmed at a repeated measurement.

14. FPG >11.1 mmol/L (>200 mg/dL) at Visit 10 (Week 24) confirmed at a repeated measurement.

15. HbA1c >8.0% at Visit 11 (Week 30) and Visit 12 (Week 39).

16. HbA1c >7.5% at Visit 13 (Week 52), Visit 14 (Week 65) and Visit 15 (Week 78).

17. HbA1c >7.0% at Visit 16 (Week 91).

18. Absolute lymphocyte count ≤ 400 cells/µL confirmed at a repeated measurement, see Appendix D.

19. Thrombocyte count <75 000 cells/µL confirmed at a repeated measurement, see Appendix E.

20. Increase in serum creatinine to a level of ≥133 µmol /L (≥1.5 mg/dL) for men, ≥124 µmol/L (≥1.4 mg/dL) for women confirmed at a repeated measurement, see Section 3.3.5.2.

3.3.5.2 Procedures for discontinuation

Patients who discontinue should always be asked about the reason(s) for their discontinuation and the presence of any AEs. If possible, they should be seen and assessed by an investigator(s). AEs should be followed up; diary cards and investigational products should be returned by the patient.

Patients discontinuing due to an AE will be asked to provide a blood sample for assessment of plasma concentrations (see section 4.5.1) at the next visit in conjunction with completion of other protocol specified procedures. In addition, the time of last intake of study medication along with an accurate time of obtaining the blood sample should be recorded.

Patients with an increased serum creatinine will have their metformin held and a repeated serum creatinine test within one week. If this repeated serum creatinine still is increased, despite temporary coexisting contributing factors have been overcome, the patient should discontinue the clinical study.

Randomized patients in the Randomized treatment period (Period C) who do not complete the entire study should complete the procedures described for Visit 13 (end of Period C). Randomized patients in the Extension period (Period D) who do not complete the entire study should complete the procedures described for Visit 17 (end of Period D).

3.3.5.3 Procedures for handling incorrectly enrolled patients

Patients not meeting the inclusion/exclusion criteria for the study should, under no circumstances, be enrolled into the study - there can be no exceptions to this rule. Where patients not meeting the study criteria are enrolled in error or incorrectly randomized, procedures for discontinuation of such patients should be followed.

3.3.5.4 Criteria for entering the action plans

If any of the following criteria is fulfilled, the patients must enter the action plan, Appendix D or E, respectively.

Absolute lymphocyte count ≤500 cells/µL, see Appendix D.

Thrombocyte count <75 000 cells/µL, see Appendix E.

3.4 Treatments

3.4.1 Identity of investigational products and additional drug

The following investigational products and additional drug will be supplied by Bristol-Myers Squibb Pharmaceutical Research Institute. The tablets may contain lactose, which may cause discomfort in lactose-intolerant individuals.

Treatment	Dosage form and strength	Manufacturer
Saxagliptin	Plain, yellow, biconvex, round, film coated tablet, 5 mg	Bristol-Myers Squibb
Placebo for saxagliptin	Plain, yellow, biconvex, round, film coated tablet to match saxagliptin 5 mg	Bristol-Myers Squibb
Glipizide	Opaque grey, size 0, two piece, hard gelatine capsule containing commercial glipizide, 5 mg	Commercial drug manufactured by Generics and encapsulated by Fisher
Placebo for glipizide	Opaque grey, size 0, two piece, hard gelatine capsule containing white to off-white powder to match glipizide 5 mg	Fisher
Glucophage® (metformin hydrochloride)	Filmcoated, white to off-white round tablet, 500 mg	Merck Serono

3.4.2 Doses and treatment regimens

The blinding is ensured by using double-dummy technique. The investigational products saxagliptin or placebo and glipizide or placebo will be taken orally, immediately before or together with a meal. Saxagliptin or placebo should be taken once daily and glipizide or placebo should be taken once or twice daily depending on the dose directed by the investigator. The investigational product 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 each clinical visit; however, drinking water is allowed. In the morning prior to each visit, acceptable concomitant medications can be taken with water only.

- Matching placebo tablets for saxagliptin 5 mg oral for the 2-week placebo lead-in period, the 52-week double-blind period and the 52-week double-blind extension period.
- Matching placebo capsules for glipizide (sulphonylurea) 5 mg oral for the 2-week placebo lead-in period, 52-week double-blind period (dosing 5 to 20 mg) and the 52-week double-blind extension period (dosing 5 to 20 mg).
- Saxagliptin tablets 5 mg oral for the 52-week double-blind period and the 52-week double-blind extension period.
- Glipizide (sulphonylurea) 5 mg capsule oral (dosing 5 to 20 mg) for the 52-week double-blind period and the 52-week double-blind extension period.

- Open-label metformin 500 mg tablets oral at a daily dose of 1500 mg - 3000 mg tablets from Visit 2 throughout the study period.

During the lead-in period, each patient will receive one single-blind kit with:

1 bottle containing 35 tablets of placebo to match saxagliptin and 1 bottle containing 140 capsules of placebo to match glipizide

Each patient will during the randomized treatment receive from 1 up to 3 double-blind kits at each visit with:

1 bottle containing 35 tablets of saxagliptin 5 mg and 1 bottle containing 140 capsules of placebo to match glipizide,

or

1 bottle containing 35 tablets of placebo to match saxagliptin and 1 bottle with 140 capsules of glipizide 5 mg.

or

1 bottle containing 35 tablets of placebo to match saxagliptin and 1 bottle with 140 capsules of placebo to match glipizide.

During the titration period the patients will titrate either active or placebo glipizide. Each patient will also receive open-label boxes with 100 tablets of metformin 500 mg, 1 to 7 boxes at each visit.

See Section 3.1 for titration procedures of glipizide.

Treatment doses**:**

Saxagliptin 5 mg: Morning dose: 1 tablet. Evening dose: N/A

Glipzide 0 mg (placebo). Morning dose: 1 capsule. Evening dose: N/A

Glipizide 5 mg: Morning dose: 1 capsule. Evening dose: N/A

Glipizide 10 mg: Morning dose: 2 capsules. Evening dose: N/A

Glipizide 15 mg: Morning dose: 2 capsules. Evening dose: 1 capsule

Glipizide 20 mg*:* Morning dose: 2 capsules. Evening dose: 2 capsules

The following guideline should be used if metformin therapy must be modified due to available open-label drug supply.

Current metformin therapy at Visit 2	Metformin dose (500 mg tablets)

1500 - 1999 mg	1500 mg (3 tablets)
2000 – 2499 mg	2000 mg (4 tablets)
2500 – 2550 mg	2500 mg (5 tablets)
>2550 mg	3000 mg (6 tablets)

3.4.3 Labelling

Packing of the investigational product will be carried out by Bristol-Myers Squibb, AstraZeneca and Contract Research Organization (CRO) in accordance with current Good Manufacturing Practice (GMP). Labelling of the investigational product will be carried out by AstraZeneca or CRO in accordance with current GMP. The labels will be translated into local language in accordance with local regulations for each participating country.

All investigational products will be packed in bottles. The saxagliptin/placebo bottles will contain 35 tablets and the glipizide/placebo bottles will contain 140 capsules. One bottle of each type will be placed into a clampacks to form a kit. The bottles will be labelled with labels or booklets, depending on availability, without a tear off part. The labels will fulfil GMP Annex 13 requirements and local regulatory guidelines.

3.4.4 Storage

All investigational products must be kept in a secure place under appropriate storage conditions. A description of the appropriate storage conditions is specified on the investigational product labels and in the IB.

3.5 Method of assigning patients to treatment groups

After written informed consent has been obtained the patient will be assigned an E-code (country, centre, and patient specific). Patient eligibility will be established before treatment randomization. Patients will be randomized strictly sequentially, as patients are eligible for randomization.

Randomization to study treatment will be done via IWRS on Visit 3 in balanced blocks in order to ensure approximate balance among treatment groups.

The E-code will be used to identify the patient throughout study participation.

The number and size of tablets and capsules distributed will be identical for the 2 treatment arms. Clinical supplies will contain a kit number that is allocated to the treatment arm through a separate randomization and will be used to provide kits of packaged drugs to the centres. The IWRS will sequentially allocate the treatment through the AstraZeneca prepared randomization scheme and provide the randomization number and the appropriate kit number from those available at the centre for the treatment assignment. The Randomization Code will be prepared by study statistician and available for IWRS use.

The randomization is carried out at the study level and the assigned randomization number and the associated kit numbers will not be sequential within a centre. Forced randomization is not allowed. If a patient is dispensed with a wrong drug supply, the patient should continue to take the medication with no attempt to correct the error. The IWRS company will be informed, if possible. The randomization system will ensure balance approximately between groups.

If a patient discontinues from the study, the patient E-code or patient randomization number will not be reused, and the patient will not be allowed to re-enter the study.

3.6 Blinding and procedures for unblinding the study

3.6.1 Methods for ensuring blinding

All packaging of active tablets/capsules and the respective placebo tablets/capsules will be identical in size, colour, smell, and taste.

No member of the extended study delivery team at AstraZeneca or Bristol-Myers Squibb, personnel at investigational centres or any CRO handling data will have access to the randomization scheme during the conduct of the study, with the exception of the IWRS company, Investigational Products department at AstraZeneca and the Drug Safety department at Bristol-Myers Squibb.

3.6.2 Methods for unblinding the study

Patients in the study can be unblinded through the IWRS. This can be carried out in emergencies by the investigator(s) at the study centre and the personnel who are independent to the study evaluation at the Drug Safety Department, Bristol-Myers Squibb.

The treatment code must not be broken except in medical emergencies when the appropriate management of the patient necessitates knowledge of the treatment randomization. In such an emergency, the Investigator will, if time and circumstances permit, contact the local AstraZeneca representative prior to breaking the treatment code. The investigator(s) must document and report to AstraZeneca any breaking of the treatment code. Patients whose double blind treatment codes are broken should be discontinued from the study as soon as possible.

Bristol-Myers Squibb retains the right to break the code for serious adverse events (SAEs) that are unexpected and are suspected to be causally related to an investigational product and that potentially require expedited reporting to regulatory authorities.

Treatment codes will not be broken for the planned analyses of data at Week 52 (Period C) and separately at Week 104 (Period D) until all decisions on the evaluability of the data from each individual patient at the end of each period have been made and documented. Study period D is considered as the extension of study period C as the participating patients will receive the same randomized IP treatment as in Period C. The code breaking at the end of Week 52 will allow AstraZeneca and Bristol-Myers Squibb personnel to complete the planned

primary analysis for registration and other activities that need not to reveal the patients' individual treatment code. Analysis at Week 104 is supplemental. However, the treatment code will be strictly kept within AstraZeneca and Bristol-Myers Squibb to safeguard the integrity of the double-blind treatment and hence to avoid possible bias in data handling to the greatest extent. Except for safety reasons, patients, investigators and study monitors in the field will have no access to the individual treatment code until the end of Period D.

3.7 Pre-study, concomitant and post-study treatment(s)

3.7.1 General medication

Other medication than described in Exclusion Criteria Section 3.3.3 and Discontinuation Criteria Section 3.3.5.1, which is considered necessary for the patient's safety and well-being (eg, to treat illnesses or complaints that occur during the study), may be given at the discretion of the Investigator(s). The administration of all medication (including investigational product, metformin and other medication) must be recorded in the appropriate sections of the electronic case report form (eCRF). The specific type of medication (trade or generic name), the indication for use, and the dates of usage should be reported. The total daily dose of metformin should also be recorded.

3.7.2 Prohibited and restricted medication and herbal/over-the-counter therapy

For prohibited and restricted medication, see Exclusion Criteria Section 3.3.3 and Discontinuation Criteria Section 3.3.5.1.

3.8 Treatment compliance

Patients will be asked to return all unused investigational products and additional drug including empty packages to the clinic at each visit. Compliance will be discussed at each study visit and assessed based on returned tablet counts. The patient's compliance will be assessed by the investigator and recorded in the eCRF. Patients judged to be non-compliant (non-compliance is defined as patients taking less than 80% or more than 120% of their prescribed dose of investigational product and additional drug), may continue in the study, but should be counselled on the importance of taking their study medication as prescribed.

4. MEASUREMENTS OF STUDY VARIABLES AND DEFINITIONS OF OUTCOME VARIABLES

4.1 Primary variable

The primary endpoint is change from baseline to Week 52 in HbA1c level. The HbA1c is used as the basis for the sample size calculation, see Section 6.5.

4.2 Screening and demographic measurements

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

- Date of signed informed consent.
- Inclusion and exclusion criteria.
- Date of birth, sex and race.
- Laboratory assessments.
- Pregnancy test.
- Information about exercise, smoking, alcohol, medical history, surgical history, family history and specific disease history.
- Physical examination including, height, weight and waist circumference, see Section 4.7.3.
- Blood pressure, pulse and 12-lead ECG, see Section 4.7.3.
- Prior and concomitant medication.

4.3 Patient-Reported Outcomes (PROs) - Not applicable

4.4 Health Economic measurements and variables - Not applicable

4.5 Pharmacokinetic measurements and variables

The methods for collection of biological samples and derivation of pharmacokinetic variables are presented below in Sections 4.5.1 and 4.5.2.

4.5.1 Collection of biological samples

Venous blood samples for the determination of saxagliptin in plasma will be drawn on 50 randomized patients and labelled according to the laboratory manual at visits 10, 13, and 17. These patients will be instructed to record in the patient diary the time of dose intake in the morning the day before the visit day.

If the patient can't specify the time of the intake of investigational product in the diary or if the patient hasn't taken the investigational product the day before visit day, the blood sampling should not be performed as scheduled. The patient must be rescheduled for a new visit.

The venous blood samples will be drawn at the same time as some of the OGTT will be done. In addition to this, the samples will also be taken at Visit 10 (when no OGTT will be carried out). The samples will be taken at the following time points –30 min (just prior to intake of investigational product and metformin), 0 min (just prior to glucose administration), +30 min, +60 min, +120 min and +180 min relative to targeted ingestion of 75 grams of glucose, see Section 4.6.2.1.

Further, a blood sample assessment of saxagliptin and BMS-510849 plasma concentrations will be obtained if a patient experiences an AE, including skin disorders, edema, cardiovascular events, lymphocytopenia and/or thrombocytopenia or an AE that results in discontinuation from the study. See definitions given in Section 4.7.1.1. Such blood samples should be taken at the visit following awareness by the investigator that such an AE occurred. The time of last intake of study medications should be recorded along with an accurate time of obtaining the blood samples.

4.5.2 Drug concentration measurements, and derivation or calculation of pharmacokinetic parameters

Drug concentrations of saxagliptin and BMS-510849 in human plasma will be quantitated by a validated liquid chromatography-tandem mass spectrometry (LC-MS/MS) method. Model-based population pharmacokinetic techniques will be employed to derive individual estimates of saxagliptin and BMS-510849 pharmacokinetic parameters, see Section 6.4.2.

4.6 Efficacy and pharmacodynamic measurement and variables

The baseline is defined as the assessment at randomization visit (Visit 3). The baseline for durability is defined as Week 24 (Visit 10). The laboratory parameters that will be measured to assess efficacy and at which visits they are measured are shown in Table 4 and Table 5. The results from baseline and onwards will not be reported to the investigator unless the values are meeting the defined discontinuation criteria in Section 3.3.5.1, except for TC, HDL-C, LDL-C and TG which will be reported.

Table 4 Efficacy laboratory variables Period A, B, C

Visit number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**
Study week	**-21 – 17 days**	**-2 w**	**0 w**	**3 w**	**6 w**	**9 w**	**12 w**	**15 w**	**18 w**	**24 w**	**30 w**	**39 w**	**52 w**
HbA1c[a]	X		X	X	X	X	X	X	X	X	X	X	X
FPG[a]	X		X	X		X	X	X	X	X	X	X	X
Insulin[a]			X							X			X
Proinsulin[a]			X							X			X
C-peptide[a]			X							X			X
Glucagon[a]			X							X			X
TC[a]	X		X							X			X
LDL-C[a]	X		X							X			X
HDL-C[a]	X		X							X			X

Table 4 Efficacy laboratory variables Period A, B, C

Visit number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**
Study week	**-21 – 17 days**	**-2 w**	**0 w**	**3 w**	**6 w**	**9 w**	**12 w**	**15 w**	**18 w**	**24 w**	**30 w**	**39 w**	**52 w**
TG[a]	X		X							X			X
OGTT – Glucose[b]			X										X
OGTT – Insulin[b]			X										X
OGTT – Glucagon[b]			X										X
OGTT - C-Peptide[b]			X										X

[a] Fasting
[b] 50 patients in a selection of countries

Table 5 Efficacy laboratory variables Period D

Visit number	14	15	16	17
Study week	**65 w**	**78 w**	**91 w**	**104 w**
HbA1c[a]	X	X	X	X
FPG[a]	X	X	X	X
Insulin[a]		X		X
Proinsulin[a]		X		X
C-peptide[a]		X		X
Glucagon[a]		X		X
TC[a]		X		X
LDL-C[a]		X		X
HDL-C[a]		X		X
TG[a]		X		X
OGTT – Glucose[b]				X
OGTT – Insulin[b]				X
OGTT – Glucagon[b]				X
OGTT - C-Peptide[b]				X

[a] Fasting
[b] 50 patients in a selection of countries

4.6.1 Blood and urine samples

4.6.1.1 Methods of assessment

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

Sample collection
The central laboratory will provide the 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 centre prior to the start of the Clinical Study. The investigator should follow the procedures defined in this manual.

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

Sample labelling
All samples will be labelled with a bar code containing a number which references the study code, centre number, E-code and visit number. These labels will be prepared and supplied by

the central laboratory for all tubes and containers which are used to collect, treat, store or ship aliquots of the samples to the central laboratory. The centre staff will record the patient information on the label, as instructed in the laboratory manual.

Sample shipment
Shipment of samples will be carried out according to the manual provided by the central laboratory.

4.6.2 Extended Oral glucose tolerance test (OGTT)

4.6.2.1 Methods of assessment

Extended Oral glucose tolerance test

Extended OGTT will be carried out in a selection of countries (approximately 50 patients). OGTTs are scheduled to occur at Randomization (Visit 3), and Visit 13, and 17.

Reschedule the visit within three days if the patient did not comply with all of the following:

- Confirm that the patient's overall dietary intake for the three days prior to OGTT has been normal (to assure at least 150 grams of carbohydrates per day).
- Confirm that the patient fasted for at least 8 hours prior to the visit (including abstaining from tobacco, alcohol and caffeine for 24 hours prior to the OGTT).
- Confirm that the patient did not take a dose of investigational product and open-label metformin on the day of the visit.
- If the administration of investigational product is contraindicated (eg, discontinuation due to adverse event (AE), pregnancy, elevated serum creatinine, lymphocytopenia and thrombocytopenia as per action plans), the OGTT should NOT be performed.

If administration of investigational product has been interrupted for more than 24 hours prior to a scheduled OGTT (eg, due to potential safety concern or SAE), the OGTT should not be performed as scheduled and the Study Team Physician should be contacted to discuss appropriate follow-up testing.

- Just prior to Time -30 minutes (relative to targeted ingestion of 75 grams of glucose), draw fasting specimens for glucose, insulin, C-peptide, and glucagon.
- At Time -30 minutes (relative to targeted ingestion of 75 grams of glucose) administer:
  - Visit 3 (baseline): Open-label metformin,

ie, administer randomized investigational product *after* the OGTT has been carried out.

- Visit 13 and 17: Open-label metformin and randomized investigational product.

- Just prior to Time 0 minutes (ingestion of 75 grams of glucose) draw specimen for glucose, insulin, C-peptide, and glucagon.

- At Time 0 minutes, administer 75 grams of oral glucose solution.

- Timing of samples: +30, +60, +120 and +180 minutes after Time 0 (start of ingestion of 75 grams of oral glucose solution).

At each time point: Draw specimens for glucose, insulin, C-peptide, and glucagon.

4.6.3 Exploratory analyses

4.6.3.1 Collection of blood and urine for exploratory research.

The purpose of the exploratory research is to perform additional investigational studies in type 2 diabetes and related metabolic disorders including, but not limited to, obesity, dyslipidaemia, microvascular complications, macrovascular (cardiac) diseases, inflammatory conditions, or bone, kidney and nerve disorders, and the like. Blood and urine samples will be collected at baseline (Visit 3), Week 52 (Visit 13) and Week 104 (Visit 17). The samples will be frozen and stored for future research. All samples will be destroyed within 2 years after the sample collection date or according to local legislation. Samples may be destroyed prior to this timeframe if the patient has withdrawn consent.

Such studies will attempt to achieve one or more of the following, using samples from the current as well as other clinical studies within the AstraZeneca and Bristol-Myers Squibb partnership:

- Use current or new biomarkers to stratify patient population based on drug response or lack thereof;

- Discovery of new biomarkers to better assess safety, efficacy, tolerability, as well as correlate with pharmacogenetic data generated in parallel;

- Initiate biomarker discovery efforts using novel state-of-the-art;

- Improve the discovery and development of future drug candidates and therapies based on correlative analyses of both clinical outcomes and retrospective biomarker data sets, such as beneficial effects on target organs pancreas, kidney, or peripheral nervous system.

4.7 Safety measurements and variables

The methods for collecting safety data by AstraZeneca and Bristol-Myers Squibb are described below.

4.7.1 Adverse events

4.7.1.1 Definitions

The definitions of AEs, SAEs, and AEs of special interest are given below. It is of the utmost importance that all staff involved in the study is familiar with the content of this section. The principal investigator is responsible for ensuring this.

Adverse event

An AE is the development of an undesirable medical condition or the deterioration of a pre-existing medical condition following or during exposure to a pharmaceutical product, whether or not considered causally related to the 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, including run-in, lead-in, or washout periods, even if no study treatment has been administered.

Serious adverse event

A serious adverse event is an AE occurring during any study period (ie, run-in, lead-in treatment, washout, follow-up), and at any dose of the investigational products (including placebo) or additional drug, that fulfils one or more of the following criteria:

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

The causality of SAEs (ie, their relationship to study treatment) will be assessed by the investigator(s), who in completing the relevant case report form must answer “yes” or “no” to the question “Do you consider that there is a reasonable possibility that the event may have

been caused by any of the following – study medication – other medication?". For further guidance on the definition of an SAE and a guide to the interpretation of the causality question, see Appendix B to the Clinical Study Protocol.

Note that SAEs that could be associated with any study procedure should also be reported. For such events the causal relationship is implied as "yes".

AEs of special interest

Significant AEs of particular clinical importance, other than SAEs and those AEs leading to discontinuation of the patient from study treatment, may include skin disorders, infections, lymphocytopenia and symptomatic hand and foot oedema. Following occurrence of such AEs the Investigator will be informed by the Sponsor and requested to obtain a plasma concentration sample from the patient.

A narrative may be written for these events, as determined by the Study Team Physician in consultation with the Global Drug Safety Physician, and included in the Clinical Study Report.

4.7.1.2 Recording of AEs

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

mild (awareness of event but easily tolerated)

moderate (discomfort enough to cause some interference with usual activity)

severe (inability to carry out usual activity)

very severe (debilitating, significantly incapacitates subject despite symptomatic therapy)

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria in Section 4.7.1.1. 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.

Diagnosis

If a diagnosis of the patient's condition has been made, then the diagnosis should be recorded as the SAE or the AE. In instances of well-recognized symptoms, they can be recorded as the commonly used diagnosis (eg, fever, runny nose, and cough can be recorded as "flu"). However, if a diagnosis of the patient's condition has not been made, or if the individual symptoms are not well recognized, then the individual symptoms should be recorded separately.

Causality

A causality assessment must be recorded for all SAEs and AEs. The eCRF asks the question, "In your medical judgment, is there 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 investigational product 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 one AE is identified, a causality assessment must be made for each AE. For SAEs the causality will also be assessed with regard to concomitant medication. For further guidance on the definition of an SAE and a guide to the interpretation of the causality question, see Appendix B to the Clinical Study Protocol.

Note that SAEs that could be associated with any study procedure should also be reported. For such events the causal relationship is implied as "yes".

Abnormal laboratory tests/ECGs/vital signs

Individual protocol-mandated laboratory and other safety-related test results should not be recorded as AEs unless they fulfil the criteria as described below. These test results will be evaluated in the overall safety analysis.

The following laboratory abnormalities should be captured on the non-serious or serious AE pages of the eCRF as appropriate:

- Any laboratory test result that meets the criteria for an SAE.
- Any laboratory abnormality that requires the patient to have investigational product discontinued or interrupted.
- Any laboratory abnormality that requires the patient to receive specific corrective therapy.

It is expected that wherever possible, the clinical, rather than the laboratory term would be used by the reporting Investigator (eg, anaemia versus low haemoglobin value).

Follow-up of ongoing AEs

All AEs of special interest and SAEs, including those that are ongoing at the end of the study or at discontinuation, will be followed up until resolution or until the Investigator decides that no further follow-up is necessary. AstraZeneca retains the right to request additional information for any patient with ongoing AEs/SAEs at the end of the study, if judged necessary. The requirement to follow-up is not intended to delay database lock or production of the clinical study report. Both these activities should proceed as planned with ongoing AEs if necessary.

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

AEs reported after end of treatment

All AEs will be collected up to and including the final visit. Only unsolicited SAEs will be collected for a period of up to 30 days after the last dose of investigational product. All SAEs and associated concomitant medications will be recorded in the appropriate sections of the eCRF and reported to the Bristol-Myers Squibb Pharmacovigilance as described in Section 4.7.1.4.

Hypoglycaemic events

Hypoglycaemic events (see Section 4.7.4.1) should be reported in a separate "Hypoglycaemic adverse event" section in the eCRF.

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

Overdose

For the purposes of this study, before the randomization code is broken, an overdose (of active or placebo) is defined as a dose exceeding 8 tablets for each day. After code break, an overdose is defined as a dose exceeding 40 mg of saxagliptin per day. Should an overdose (accidental or deliberate) occur, it must be reported in accordance with the procedures described in Section 9.3, regardless of whether the overdose was associated with any symptom or not. All symptoms associated with the overdose should be reported as AEs.

Pregnancy

Should a pregnancy occur, it must be reported in accordance with the procedures described in Section 9.4. Pregnancy in itself is not regarded as an AE unless there is a suspicion that an investigational product may have interfered with the effectiveness of a contraceptive medication.

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 at the Bristol-Myers Squibb Pharmacovigilance database and coded using MedDRA.

4.7.1.3 Single blood sample for plasma concentration assessments associated with an AE

In cases where an AE results in discontinuation of the study or an AE, including skin disorders, edema, cardiovascular events, lymphocytopenia and/or thrombocytopenia, is reported, it is desirable to obtain a blood sample for possible assessment of saxagliptin and BMS-510849 plasma concentration. The blood sample should be obtained at the visit following awareness by the investigator that such an AE occurred or, if not possible, at the following visit. The time of the last intake of study treatment dose and an accurate time of

obtaining the blood sample should be recorded. Section 4.5.1 details blood sampling instructions.

4.7.1.4 Reporting of serious adverse events

Investigators and other centre personnel must inform appropriate AstraZeneca representatives via the web based data capture (WBDC) system of any SAE that occurs in the course of the study 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.

Follow-up information on SAEs must also be reported by the Investigator within the same time frames.

If follow-up indicates a change in the SAE serious criteria to fatal or life-threatening, this information needs to be available in the WBDC system within 1 calendar day.

If a non-serious AE becomes serious, this and other relevant follow-up information must also be provided to AstraZeneca within 1 calendar day as described above.

The AstraZeneca representative will work with the Investigator to compile all the necessary information and ensure that AstraZeneca receives a report by day 1 for **all** SAEs. The AstraZeneca representative will notify the appropriate Bristol-Myers Squibb Pharmacovigilance contact to ensure regulatory compliance.

All SAEs have to be reported, whether or not considered causally related to the investigational product or to the study procedure(s). All SAEs will be recorded and reported to AstraZeneca in the eCRF as described in Section 4.7.1.2. 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 Bristol-Myers Squibb.

For studies in countries implementing the European Union (EU) Clinical Trials Directive, safety updates/reports to Ethic Committees and Principal Investigators will be taken care of by AstraZeneca, see Section 8.1.

SAE handling using WBDC

SAE information will be entered and submitted into the WBDC system on the relevant eCRF modules. An automated e-mail alert will be sent to the designated AstraZeneca representative who will work with the Investigator to ensure that all the necessary information is available in the system within the required time frames, but taking advantage of the time allocated in those timelines. AstraZeneca representative will send a completed SAE report to the appropriate Bristol-Myers Squibb Pharmacovigilance representative via fax or e-mail.

If the system is unavailable, the Investigator should fax a paper back-up SAE report to the AstraZeneca representative immediately, recognising that the same reporting time frames still apply. The Investigator is responsible for completing the eCRF as soon as the system becomes available again.

4.7.2 Laboratory safety measurements and variables

4.7.2.1 Methods of assessment

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.

Due to the fasting laboratory assessments, all patients will visit the clinic on a fasting stomach in the morning, before 1100. The patients will be instructed not to have ingested any food or beverages 8 hours before visiting the clinic (however, drinking water is allowed). Also, the patients will be instructed to not take the investigational product and metformin in the morning before visiting the clinic. Allowed medications can be taken with water only.

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

For information on how AEs based on laboratory tests should be recorded and reported, see Section 4.7.1.2.

The complete list of safety laboratory tests is displayed in Table 6 and Table 7 below. The laboratory tests are conducted following the assessment schedule outlined in Section 4.7.2.1.

Table 6 Safety laboratory variables Period A, B, C

Visit number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**
Study week	**-21 - 17 days**	**-2 w**	**0 w**	**3 w**	**6 w**	**9 w**	**12 w**	**15 w**	**18 w**	**24 w**	**30 w**	**39 w**	**52 w**
Haematology													
Haemoglobin	X		X		X		X		X	X	X	X	X
Haematocrit	X		X		X		X		X	X	X	X	X
Red blood cell count	X		X		X		X		X	X	X	X	X
White blood cell count and differential	X		X		X		X		X	X	X	X	X
Platelet count	X		X		X		X		X	X	X	X	X
Clinical chemistry													
Aspartate Aminotransferase (AST, serum glutamic oxaloacetic transaminase (SGOT))	X		X		X		X		X	X	X	X	X
Alanine Aminotransferase (ALT, serum glutamic pyruvic transaminase (SGPT))	X		X		X		X		X	X	X	X	X
Alkaline Phosphatase	X		X		X		X		X	X	X	X	X

Table 6 Safety laboratory variables Period A, B, C

Visit number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**
Study week	**-21 - 17 days**	**-2 w**	**0 w**	**3 w**	**6 w**	**9 w**	**12 w**	**15 w**	**18 w**	**24 w**	**30 w**	**39 w**	**52 w**
CK	X		X		X		X		X	X	X	X	X
Total Bilirubin	X		X		X		X		X	X	X	X	X
Blood Urea Nitrogen (BUN)	X		X		X		X		X	X	X	X	X
Electrolytes: - Sodium - Potassium - Chloride	X		X		X		X		X	X	X	X	X
Total protein	X		X		X		X		X	X	X	X	X
Albumin	X		X		X		X		X	X	X	X	X
TSH[a]	X												
Serum Creatinine (SCr), calculated Creatinine Clearance[b]	X		X		X		X		X	X	X	X	X
FSH[c]	X												
Hepatitis Screen Panel[d]	X												
Urinalyses													
PH	X		X				X			X		X	X
Protein[e]	X		X				X			X		X	X
Glucose	X		X				X			X		X	X

Table 6 Safety laboratory variables Period A, B, C

Visit number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**
Study week	**-21 - 17 days**	**-2 w**	**0 w**	**3 w**	**6 w**	**9 w**	**12 w**	**15 w**	**18 w**	**24 w**	**30 w**	**39 w**	**52 w**
Leukocyte esterase[e]	X		X				X			X		X	X
Blood by dipstick[e]	X		X				X			X		X	X
Pregnancy test[f]	X		X	X	X	X	X	X	X	X	X	X	X
Albumin:creatinine ratio	X		X				X			X		X	X
Additional laboratory tests													
If elevated Serum Creatinine (SCr): - SCr	X		X				X			X		X	X

Table 6 Safety laboratory variables Period A, B, C

Visit number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**
Study week	**-21 - 17 days**	**-2 w**	**0 w**	**3 w**	**6 w**	**9 w**	**12 w**	**15 w**	**18 w**	**24 w**	**30 w**	**39 w**	**52 w**
If lymphocytopenia[g]													
- Absolute lymphocyte count	X		X		X		X		X	X	X	X	X
- Complete Blood Count (CBC) with differential	X		X		X		X		X	X	X	X	X
- Lymphocyte subsets including:	X		X		X		X		X	X	X	X	X
- Cluster designation: cell surface marker expressed by lymphocytes (CD4) + counts													
- Cluster designation: cell surface marker expressed by lymphocytes (CD8) + counts													

Table 6 Safety laboratory variables Period A, B, C

Visit number	1	2	3	4	5	6	7	8	9	10	11	12	13
Study week	**-21 - 17 days**	**-2 w**	**0 w**	**3 w**	**6 w**	**9 w**	**12 w**	**15 w**	**18 w**	**24 w**	**30 w**	**39 w**	**52 w**
If thrombocytopenia[h]													
- Thrombocyte count	X		X		X		X		X	X	X	X	X
- CBC with differential	X		X		X		X		X	X	X	X	X
- Peripheral blood smear	X		X		X		X		X	X	X	X	X
- Antiplatelet antibodies	X		X		X		X		X	X	X	X	X
- Test for faecal occult blood	X		X		X		X		X	X	X	X	X

[a] If abnormal, reflex to free T4
[b] Creatinine clearance will be estimated by the method of Cockcroft and Gault
[c] For women on hormone replacement therapy
[d] Includes HBsAg and anti-HCV (if positive, reflex to immunoassay for hepatitis C RNA (RIBA HCV)).
[e] Microscopy if dipstick positive for blood, leukocyte esterase or protein
[f] Urine hCG pregnancy test for WOCBP (hCG minimum sensitivity of 25 IU/L) (dipstick analysed at the study centre)
[g] See Appendix D
[h] See Appendix E

Table 7 Safety laboratory variables Period D

Visit number	**14**	**15**	**16**	**17**
Study week	**65 w**	**78 w**	**91 w**	**104 w**
Haematology				
Haemoglobin	X	X	X	X
Haematocrit	X	X	X	X
Red blood cell count	X	X	X	X
White blood cell count and differential	X	X	X	X
Platelet count	X	X	X	X
Clinical chemistry				
AST	X	X	X	X
ALT	X	X	X	X
Alkaline Phosphatase	X	X	X	X
CK	X	X	X	X
Total Bilirubin	X	X	X	X
BUN	X	X	X	X
Electrolytes: - Sodium - Potassium - Chloride	X	X	X	X
Total protein	X	X	X	X
Albumin	X	X	X	X

Table 7 Safety laboratory variables Period D

Visit number	**14**	**15**	**16**	**17**
Study week	**65 w**	**78 w**	**91 w**	**104 w**
SCr, calculated Creatinine Clearance[a]	X	X	X	X
Urinalyses				
PH	X	X	X	X
Protein[b]	X	X	X	X
Glucose	X	X	X	X
Leukocyte esterase[b]	X	X	X	X
Blood by dipstick[b]	X	X	X	X
Albumin:creatinine ratio	X	X	X	X
Pregnancy test[c]	X	X	X	X
Additional laboratory tests				
If elevated SCr: - SCr	X	X	X	X
If lymphocytopenia[d] - Absolute lymphocyte count - CBC with differential - Lymphocyte subsets including: - CD4 + counts - CD8 + counts	X X X	X X X	X X X	X X X

Table 7 Safety laboratory variables Period D

Visit number	14	15	16	17
Study week	**65 w**	**78 w**	**91 w**	**104 w**
If thrombocytopenia[e]				
- Thrombocyte count	X	X	X	X
- CBC with differential	X	X	X	X
- Peripheral blood smear	X	X	X	X
- Antiplatelet antibodies	X	X	X	X
- Test for faecal occult blood	X	X	X	X

[a] Creatinine clearance will be estimated by the method of Cockcroft and Gault
[b] Microscopy if dipstick positive for blood, leukocyte esterase or protein
[c] Urine hCG pregnancy test for WOCBP (hCG minimum sensitivity of 25 IU/L) (dipstick analysed at the study centre)
[d] See Appendix D
[e] See Appendix E

4.7.2.2 Derivation or calculation of outcome variables

Creatinine clearance will be estimated by the method of Cockcroft and Gault.

4.7.3 Vital signs, ECG and physical examination

4.7.3.1 Methods of assessment

Pulse and blood pressure
One pulse measurement will be taken after the patient has been sitting and resting for at least 5 minutes and before blood samples are taken. The pulse measurement will be followed by three blood pressure measurements, using a standardized cuff adapted to the size of the patient's arm.

ECG
A 12-lead ECG will be taken (supine position, standard ECG with a paper speed of 50 mm/second covering at least 6 sequential beats) after the patient has been lying down resting for at least 5 minutes. The ECG will be evaluated by the investigator and entered as 'Normal' or 'Abnormal' in the eCRF.

Weight and height
The patient's weight will be recorded in kilogram (kg), to one decimal place, on a fasting stomach with light clothing and no shoes. The patient's height will be recorded in centimetres, with no shoes.

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.

Physical examinations
The physical examination includes the following: General appearance including skin inspection, lymph nodes, thyroid, musculoskeletal/extremities, cardiovascular, lungs, abdomen, and reflexes. Baseline data is collected at Visit 3, and new findings at the following physical examinations are recorded as change from baseline.

4.7.3.2 Derivation or calculation of outcome variables

The mean blood pressure measurements (diastolic and systolic blood pressure) will be computed by AstraZeneca for each patient at each visit. Body Mass Index (BMI) will be computed using the formula weight/height^2.

4.7.4 Other safety measurements and variables

4.7.4.1 Methods of assessment

Self-monitoring of plasma glucose should be done in order to reduce risk of prolonged periods of undetected hyperglycaemia or to confirm hypoglycaemia. Patients will be asked to do self-

monitoring of plasma glucose using glucometers provided by AstraZeneca. The patients will receive instruction on the use of the glucometer, according to the manufacturer's instruction.

Fasting plasma glucose concentrations

FPG should be self-monitored at least every second day during the lead-in and titration period, and at least once a week during the remaining treatment and extension periods. The patient diary will be collected from Visit 3 and kept in the investigator study file and a new diary for the next period will be handed over to the patient, if needed.

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

Hypoglycaemic events

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

A hypoglycaemic event can be either

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

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

Major hypoglycaemic events, defined as symptomatic events requiring external assistance due to severe impairment in consciousness or behaviour, with blood glucose level <3.0 mmol/L, <54 mg/dL, and prompt recovery after glucose or glucagon administration.

Minor hypoglycaemic event, defined as either a symptomatic event with blood glucose level <3.0 mmol/L, <54 mg/dL, and no need for external assistance, or an asymptomatic blood glucose measurement <3.0 mmol/L, <54 mg/dL.

Events suggestive for hypoglycaemia, with symptoms that the patient experiences as hypoglycaemia and no confirmative measurement.

Plasma glucose values, not blood glucose values, will be obtained from the central laboratory and when using the site based glucose analyser and glucometers provided by AstraZeneca.

Therefore, the corresponding plasma glucose values will be used to define hypoglycaemia, ie, plasma glucose <3.5 mmol/L, <63 mg/dL.

Data to be collected for each hypoglycaemic event:

- Date of start and stop and time of the day for start
- If symptoms are present or not and which symptoms
- If fingerstick value obtained and the plasma glucose value
- Intervention needed for recovery, max intensity, action taken, causality and possible contributing factors

The patient diary will be reviewed and data regarding hypoglycaemic events transcribed into the eCRFs at each clinical visit. A new diary for the next period will be handed over to the patient if needed. If a major hypoglycaemic event occurs, or more than one minor since last visit, the patient should contact the investigator. For recording of hypoglycaemic events/symptoms suggestive of hypoglycaemic events as AEs, see Section 4.7.1.2.

4.7.5 Independent Adjudication Committee

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

4.8 Volume of blood sampling and handling of biological samples

The total volume[a] of blood that will be drawn from each patient in this study is as follows:

Assessment		**Total volume (mL)**
Efficacy and safety	Clinical chemistry	200
	Haematology	74 (146)
Exploratory		30
Pharmacokinetic		(72)
Plasma concentration		(3)
OGTT		(210)
Genotyping		10
Total		314 (671)

[a] Pharmacokinetic and OGTT samples will be carried out on patients in a selection of countries (50 patients). The blood volume stated within brackets for haematology may be applicable for patients in the algorithm for trombocytophenia and/or lymphocytophenia (depending on number of blood sample visits). One plasma

concentration sample taken if the patient experience any of the predefined AEs (see 4.7.1.3) or discontinue from the study due to an AE.

4.8.1 Analysis of biological samples

4.8.1.1 Clinical chemistry samples

The analyte stability limits defined by the contracted central clinical laboratory will be applied to all analyses performed on behalf of AstraZeneca. The central laboratory will not analyse samples that fall outside these stability limits. Analytical data will not be reported if found to have been derived from a sample that fell outside these stability limits. The standards of procedure followed by the central laboratory may be amended in accordance with its Standard Operating Procedures. The central laboratory will inform AstraZeneca of the stability limits relevant to this study before the first patient gives informed consent to take part in the study.

If the contracted central clinical laboratory chooses to sub-contract the analytical work to another laboratory, the contracted central clinical laboratory must assure itself and provide assurance to AstraZeneca that the other laboratory will apply defined stability limits to all analyses performed on behalf of AstraZeneca. Samples falling outside these limits must not be analysed or data reported. The other laboratory will inform AstraZeneca of the stability limits relevant to this study before the first patient gives informed consent to take part in the study.

4.8.1.2 Pharmacokinetic samples

The long-term stability of the analyte(s) will be documented in method validation reports produced by AstraZeneca and Bristol-Myers Squibb. Results from analyses of samples stored longer than the time period for which stability has been demonstrated should not be reported unless complementary analyte(s) stability data is acquired and amended to the relevant method validation report.

4.9 Genetic measurements and co-variables

Patients who provide written informed consent related to genetic research will provide a blood sample according to the Study Plan, see Table 1. Individual patients will not be identified. Samples and data will be kept confidential and stored separately. For more information, see Appendix F.

5. DATA MANAGEMENT

Data must be entered into the WBDC system at the investigational centre within 2 business days after the scheduled visit (except for SAEs that should be entered within 1 calendar day). Trained study personnel will be responsible for entering data into the WBDC system according to the Instructions for the Investigator including the data entry instructions. Data includes observations, tests and assessments specified in the protocol. Data entered in the WBDC system will immediately be saved at a central database and changes tracked to provide an audit trail. When data has been entered, reviewed, edited and Source Data Verification

(SDV) performed, the Investigator will electronically sign the eCRF and the data will be locked to prevent further editing. A copy of the eCRF will be provided to the investigational centre after the study database has been locked for archiving at the investigational centre.

Data from the central laboratory assessments will be returned to AstraZeneca directly as datasets, and validated to ensure that it is consistent with the clinical data. Any queries on the data will be raised and resolved within the WBDC system or other designated systems.

Data verification and validation will be performed. The Investigator should answer any external queries raised by AstraZeneca in a timely manner, and query resolutions will be saved in the central database. Prior to breaking the treatment codes at Week 52 and separately at Week 104, all decisions on the evaluability of the data from each individual patient must have been made and documented. The Study Delivery Team at AstraZeneca R&D will document the date of clean file and database lock.

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

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

Concomitant medications will be coded using the Bristol-Myers Squibb Drug Dictionary. AEs will be coded using MedDRA.

6. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

6.1 Statistical evaluation – general aspects

All statistical evaluation, as well as summaries and tabulations and the pharmacokinetic evaluation will be done by qualified personnel at AstraZeneca and Bristol-Myers Squibb. The pharmacokinetic data derived from this study may be pooled with similar data from other studies and the results described in a separate report. Before breaking the treatment codes for Week 52 and separately for Week 104 analyses, all decisions on the evaluability of the data from each individual patient at end of both Study Period C and D will be made and documented and each patient will be assigned to the appropriate analysis data set.

A comprehensive Statistical Analysis Plan (SAP) for both study periods C and D will be prepared before unblinding of the Week 52 and Week 104 data.

6.2 Description of outcome variables in relation to objectives and hypotheses

The primary objective of this study is to assess whether saxagliptin plus metformin is non-inferior (NI) to glipizide (sulphonylurea) plus metformin in improving glycaemic control in patients with type 2 diabetes. The primary outcome variable is the change from baseline in HbA1c at 52 weeks of treatment.

When evaluating NI of saxagliptin plus metformin against glipizide plus metformin, the null hypothesis is the mean of the saxagliptin plus metformin in question is inferior to the mean of the glipizide plus metformin in question by a fixed amount or more (the NI limit) with respect to absolute change from baseline in HbA1c at Week 52 of treatment. Per Committee for Proprietary Medicinal Products (CPMP) scientific discussion, a NI limit of 0.35% for change from baseline has been selected for comparisons against glipizide add-on to metformin. Assay sensitivity can be achieved if the attainment of 0.6% in HbA1c reduction from baseline at Week 52 (Section 3.2.1.2) is observed from the glipizide add-on to metformin treatment arm.

The key secondary outcome variables at Week 52 are:

- Proportion of patients reporting at least one episode of hypoglycaemic event over 52 weeks, a safety outcome variable.
- Change from baseline in body weight at Week 52, a safety outcome variable.
- Mean slope of the regressions of change from Week 24 in HbA1c on treatment duration after Week 24.

The above three secondary variables (proportion of patients reporting at least one episode of hypoglycaemic events, change from baseline in body weight and mean slope of the regressions of change from baseline in HbA1c on treatment duration after Week 24) have been identified for special consideration in this study, in addition to the primary efficacy variable (NI HbA1c). Multiple comparisons procedure will be applied in order to control the type I error rate to support secondary superior claims of saxagliptin plus metformin treatment over glipizide plus metformin therapy. When evaluating superiority of saxagliptin add-on to metformin to glipizide add-on to metformin with respect to each of the above secondary endpoints, the hypotheses and statistical methods are:

1. Hypoglycaemic event: the null hypothesis is the equality of the two proportions of patients with at least one hypoglycaemic event against the alternative hypothesis of the inequality of the two proportions of patients with at least one hypoglycaemic event. Fisher's exact test will be used to compare the association of two proportions with the treatment on the safety analysis set.

2. Change from baseline to Week 52 in body weight: The null hypothesis is the equality of the two mean weight changes from baseline to Week 52 against the alternative hypothesis of the inequality of the two mean weight changes are not

equal. Analysis of covariance model (ANCOVA) method will be used on safety analysis set, where mean changes from baseline to Week 52 will be the response variable and the model will include treatment as a fixed effect and baseline weight as a covariate.

3. Durability: the null hypothesis is the equality of the two mean slopes against the alternative hypothesis of the inequality of the two slopes. Student's t-test will be use on patients who have HbA1c levels recorded for Week 24 and at least a second one recorded on or before Week 52. Missing values will not be imputed for visits between Week 24 and Week 52.

Other secondary efficacy variables are:

- Change from baseline in FPG, insulin, C-peptide, glucagon and proinsulin.
- Proportion of patients achieving a therapeutic glycaemic response defined as HbA1c ≤6.5%.
- Change from baseline in HbA1c in patients with baseline HbA1c ≥7.0%.
- Proportion of patients achieving a therapeutic glycaemic response defined as HbA1c <7.0% in patients whose baseline HbA1c is ≥7.0%.
- Change from baseline in β-cell function (as measured by HOMA-2 (Wallace et al 2004)).
- Change from baseline in AUC from 0 to 180 minutes for glucose, insulin, C-peptide and glucagon during an OGTT on a subset of patients.
- Change from baseline in insulinogenic index (Phillips et al 1994)) on a subset of patients.
- Change from baseline in insulin sensitivity as measured by OGIS (Mari et al 2001) and Matsuda Index (Matsuda and DeFronzo 1999) on a subset of patients.
- Change from baseline in TC, LDL-C, HDL-C and TG.

Data analysis for population pharmacokinetics will be outlined in a separate analysis plan and the results will be reported in a separate report.

Safety and tolerability will be evaluated by assessment of adverse events (including AEs of special interest, such as oedema and skin-related AEs, and hypoglycaemic events), laboratory values, ECG, pulse, blood pressure, body weight and physical examination. No hypotheses are proposed a priori for these safety-related variables.

Tertiary endpoints at Week 104 are:

- To compare the long-term safety, tolerability and efficacy effects of saxagliptin versus glipizide given as add-on therapy to metformin after a 104-week double-blind treatment period, assessed as those identified for the Week 52 period, except the evaluations are for the entire 104 weeks.

6.3 Description of analysis sets

The primary outcome and selected secondary efficacy endpoints analyses will be performed on the Per Protocol (PP) analysis sets. All efficacy endpoints will also be analysed using the full analysis sets. The safety endpoints will be analysed from the safety analysis set.

6.3.1 Lead-In analysis set

For the summary of patients enrolled to the lead-in period (Period B), all patients who enrolled to the Period B with an E-code and took at least one placebo dose during the lead-in period will be included in the analysis set.

6.3.2 Randomized analysis set

For the summary of baseline characteristics, all patients with a randomization code will be included in the analysis set.

6.3.3 Per protocol analysis set

For the analysis of Week 52 primary efficacy endpoint and all secondary efficacy endpoints, the PP analysis set is a subset of full analysis set including patients who have completed the 52 weeks of randomized treatment period and have no reasons for exclusions.

These exclusions from the PP analysis set will include but not be limited to the patients who took prohibited concomitant medications, non-compliance to investigational product and major deviations of study procedures. The exclusions from the PP analysis set will be explicitly defined in SAP prior to Week 52 database locking. The non-inferiority conclusion pertaining to the primary endpoint will be drawn primarily based on results from per protocol analysis set and complementally based on full analysis set (see Section 6.3.4).

6.3.4 Full analysis set last observation carried forward (LOCF)

For the analysis of all Week 52 efficacy endpoints, the full analysis set is a subset of randomized analysis set including patients who take at least one randomized investigational product dose, have non-missing baseline and a post baseline efficacy data. The missing Week 52 efficacy endpoints will be replaced by last observed value after baseline. Missing baseline (Visit 3) data will be estimated by a single value assessed at Visit 1, if one exists. Analysis of efficacy variables at Week 52 will be supplemented by the results from the full analysis set.

6.3.5 Safety analysis set

The safety analysis set is a subset of randomized analysis set including patients who take at least one IP dose and have any safety records that can be found in the study database. Actual

treatment will be re-assigned to any patient who has taken IP dose other than what they were randomized to for the duration of the entire 52 weeks. Analysis will only use values that are actually measured.

6.4 Method of statistical analysis

6.4.1 Analysis of double-blind treatment Period C

The primary efficacy analysis to establish non-inferiority with 0.35% non-inferiority limit on the change in HbA1c from baseline to Week 52 will be performed on a per protocol analysis set using ANCOVA. The model will use treatment group as a fixed effect and baseline value as a covariate. Within the framework of the ANCOVA model, point estimates and the two-sided 95% confidence intervals for the mean change within each treatment group as well as for the differences in mean change between the saxagliptin plus metformin treatment arm and the glipizide plus metformin treatment arm will be performed. Saxagliptin plus metformin will be considered not inferior to glipizide plus metformin if the upper limit of the two-sided 95% confidence interval of the difference in change in HbA1c from baseline to Week 52 between saxagliptin plus metformin and glipizide plus metformin is less than 0.35%.

Analyses of the secondary efficacy endpoints will be performed using ANCOVA methods for change from baseline in glucose related endpoints, β-cell functions, and insulin sensitivity. The ANCOVA model will use treatment group as a fixed effect and baseline value as a covariate. Within the framework of the ANCOVA model, point estimates and the two-sided 95% confidence intervals for the mean change within each treatment group as well as for the differences in mean change between the two treatment groups will be reported.

Repeated measures analysis may be performed on selected efficacy variables over time as sensitivity analysis.

Hypoglycaemic events and body weight changes are considered as safety variables and are specified as important secondary variables supporting the treatment of saxagliptin. Proportion of patients reporting at least one episode of hypoglycaemic event over the 52-week treatment period will be compared between the two treatment groups using a two-sided Fisher's exact test. ANCOVA method comparing the two treatment groups will be used for change from baseline in body weight at Week 52, where the model will include treatment as a fixed effect and baseline as a covariate.

Durability of HbA1c will be assessed for each of the two treatment groups from mean slopes of the regressions of change from Week 24 in HbA1c on treatment duration from Week 24 to Week 52. All patients with a pair of HbA1c levels at Week 24 and post Week 24 will be included. Weeks on randomized treatment period will be used as a regressor. Only observed values between the two visits, inclusive, will be used for the analysis.

Three secondary variables (proportion of patients reporting hypoglycaemic events and change from baseline in body weight, and mean slopes of the regressions of change from baseline in HbA1) have been identified for special consideration in this study, in addition to the primary efficacy variable (NI HbA1c). In order to control overall type 1 error rate of the study, a fixed-

sequence test will be adopted with respect to the 4 hypotheses, ie, the testing will be sequentially performed in the following order:

1. Non-inferiority comparison of HbA1c, if NI is demonstrated then statistical inference proceed step 2, otherwise inference will stop.

2. Superiority tests for hypoglycaemic event if significant ($p<0.05$) in favour of saxagliptin and metformin treatment group then statistical inference proceed step 3, otherwise inference will stop.

3. Superiority test for weight changes, if significant ($p<0.05$) in favour of saxagliptin and metformin treatment group then statistical inference proceed step (4), otherwise inference will stop.

4. Superiority inference for durability.

All comparison will be two-sided at the 5% significance level.

All other secondary efficacy variables are supplemental and not included in the multiple comparison scheme as outlined above.

Summary tables will be presented for proportions of patients achieving glycaemic therapeutic response.

Change from baseline in AUC from 0 to 180 minutes for glucose, insulin, C-peptide and glucagon will be analyzed by ANCOVA method similar for the primary endpoint. The lipid endpoints will be log-transformed before ANCOVA analysis. In which case log baseline will be used as a covariate and treatment as a fixed effect in the model. Within the framework of the ANCOVA model, point estimates and the two-sided 95% confidence intervals will be first constructed in the logarithmic scale. By taking the anti-logarithms, estimates and confidence intervals for the true geometric means and ratios of true geometric means will be displayed.

In general, analyses of all secondary efficacy endpoints, other than durability as specified variable of special interest, will be carried out by means of linear models using baseline value as a covariate as for the primary variable. Results will be reported as point estimates, 95% confidence intervals.

Subgroup analyses will be described in the SAP.

Analysis for safety and tolerability endpoints, other than proportion of patients with at least one hypoglyceamic event and weight changes, will be summarized by descriptive statistics or frequency tables and/or graphic method. There are no hypotheses proposed a priori for these safety endpoints.

6.4.2 Pharmacokinetic measurements and variables

The plasma concentrations obtained by sampling of individual patients will be used to build a pharmacokinetic model to estimate pharmacokinetic parameters (eg, apparent oral clearance (CL/F), apparent oral volume of distribution (Vd/F), and absorption rate constant (ka)). Possible covariate effects on pharmacokinetic parameters (eg, gender effect on CL/F) may be identified and quantified. Using model-based simulations, the pharmacokinetic parameters will be used to compute individual exposure measures (eg, AUC, minimum observed concentration (Cmin)). Relationships between these exposure measures and various efficacy and safety endpoints may be explored. The pharmacokinetic data derived from this study may be pooled with similar data from other studies and the results described in a separate report.

6.4.3 Analysis of double-blind treatment Period D

Efficacy variables for the Period D are similar to those defined for Week 52, and will be summarized over the entire 104 weeks of randomized treatment.

Durability of effect will be assessed using descriptive and graphical presentations of efficacy variables over time. A summary of the number of patients who maintain desirable HbA1c levels at each time point in Period D will be generated. The same methods used to investigate the slopes of HbA1c after Week 24 in the Period C will be employed to compare the HbA1c slopes from Week 24 through Period D in the two treatment regimens. A repeated measures analysis may also be performed on change from baseline in HbA1c.

Safety variables for the long-term period are similar to those defined in Period C, and will be summarized over the entire 104 weeks of randomized treatment.

6.4.4 Safety measurements and variables

Descriptive statistics will be provided for the safety laboratory variables. AEs will be tabulated. Other safety-related variables, such as pulse, physical examination and ECG tests, will be summarised with descriptive statistics, tabulations and/or listings.

6.5 Determination of sample size

With a total of 838 patients randomized and treated (or 419 per treatment group), there is 95% power to establish the non-inferiority comparison on change from baseline to Week 52 in HbA1c at the 5% level assuming standard deviation of change from baseline in HbA1c is 1.1%, with a non-inferiority limit set at 0.35% and a zero true difference between the two randomized treatments. The sample size also assumes about 35% of the randomized patients will be excluded from the per protocol analyses set.

For the non-inferiority primary efficacy endpoint, non-inferiority is defined as the upper limit of the two-sided 95% confidence interval of the difference in change in HbA1c from baseline to Week 52 between saxagliptin plus metformin and glipizide plus metformin to be less than 0.35%, where a change of 0.35% or more is considered a clinically relevant difference.

6.6 Interim analyses

Not applicable. The study will declare data base lock after 52 weeks of randomized treatment for the primary analysis. Subsequent analyses for additional data after 104 weeks of randomized therapy is supplemental.

6.7 Data monitoring committee

A Data Monitoring Committee (DMC) will be reviewing safety data on a periodic basis, including the incidence of AEs, laboratory measurements and safety assessments to ensure the ongoing safety of study patients. An independent statistician will be contracted to provide the DMC with essential safety data during the study. The DMC responsibilities, authorities, and procedures will be documented in a DMC charter. The personnel involved in the clinical study at AstraZeneca and at Bristol-Myers Squibb will remain blinded to these analyses and will have no knowledge of the results presented to the DMC.

7. STUDY MANAGEMENT

7.1 Monitoring

Before first patient into the study, a representative of AstraZeneca will visit the investigational study centre to:

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

During the study, a monitor from AstraZeneca or company representing AstraZeneca will have regular contacts with the study centre, including visits to:

- Provide information and support to the investigator(s).
- Confirm that facilities remain acceptable.
- Confirm that the investigational team is adhering to the protocol that data are being accurately recorded in the eCRFs, and that investigational product accountability checks are being performed.
- Perform source data verification (a comparison of the data in the eCRFs with the patient's medical records at the hospital or practice, and other records relevant to

the study). This will require direct access to all original records for each patient (eg, clinic charts).

- Perform source verification of the genetic consent of participating patients and ensure that the investigational team is adhering to the specific requirements of this genetic research.

The monitor or another AstraZeneca representative will be available between visits if the investigator(s) or other staff at the centre needs information and advice.

7.2 Audits and inspections

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

7.3 Training of staff

The principal investigator will maintain a record of all individuals involved in the study (medical, nursing and other staff). He or she will ensure that appropriate training relevant to the study is given to all of these staff, and that any new information of relevance to the performance of this study is forwarded to the staff involved.

Before the first patient is entered into the study, the investigational staff will be trained to use the WBDC system by a web-based learning (ie, self-study) method.

7.4 Changes to the protocol

Study procedures will not be changed without the mutual agreement of the Co-ordinating Investigator (if applicable), AstraZeneca, and Bristol-Myers Squibb.

If it is necessary for the Clinical Study Protocol to be amended, the amendment and/or a new version of the Clinical Study Protocol (Amended Protocol) must be notified to or approved by each Ethics Committee, and if applicable, also the local regulatory authority, before implementation. Local requirements must be followed.

If an administrative change is required, such a change must be notified to or approved by each Ethics Committee according to local requirements.

If a protocol amendment requires a change to a particular centre’s Informed Consent Form, then AstraZeneca and the site’s Ethics Committee must be notified. Approval of the revised

Informed Consent Form by AstraZeneca and by the Ethics Committee is required before the revised form is used.

AstraZeneca will distribute amendments and new versions of the protocol to each principal investigator(s), who in turn is responsible for the distribution of these documents to his or her Ethics Committee, and to the staff at his or her site. The distribution of these documents to the regulatory authority will be handled according to local practice.

7.5 Study agreements

The principal investigator at each site must comply with all the terms, conditions, and obligations of the CSA for this study. In the event of any inconsistency between this Clinical Study Protocol and the CSA, the Clinical Study Protocol shall prevail.

7.6 Study timetable and end of study

Before a patient's enrolment in the study and any study-related procedures are undertaken, the following should be fulfilled:

- Signed Clinical Study Protocol and other agreements between AstraZeneca and the Principal Investigator/Study Site.
- Approval of the study by the Ethics Committee.
- Approval of the study, if applicable, by the regulatory authority.

The planned overall timetable for the study is as follows:

First Patient In	Q4 2007 - Q1 2008
Last Patient In	Q3 2008

For 52 weeks randomized treatment:

Last Patient Last Visit	Q3 2009
Data base lock	Q4 2009

For 104 weeks randomized treatment:

Last Patient Last Visit	Q3 2010
Data base lock	Q4 2010

End of study is defined as database lock, which is the time point after which no patients will be exposed to study related activities.

8. ETHICS

8.1 Ethics review

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

The final Clinical Study Protocol, including the final version of the Informed Consent Form, must be approved or given a favourable opinion in writing by an Ethics Committee as appropriate. The investigator must submit written approval to AstraZeneca before he or she can enrol any patient into the study.

The Principal Investigator is responsible for informing the Ethics Committee of any amendment to the protocol in accordance with local requirements. In addition, the Ethics Committee must approve all advertising used to recruit patients for the study. The protocol must be re-approved by the Ethics Committee annually, as local regulations require.

Progress reports and notifications of serious and unexpected adverse drug reactions will be provided to the Ethics Committee according to local regulations and guidelines.

8.2 Ethical conduct of the study

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

For studies including genetic analysis special precautions are taken as described in Section 4.9.

8.3 Informed consent

The principal investigator(s) at each site will ensure that the patient is given full and adequate oral and written information about the nature, purpose, possible risk and benefit of the study. Patients must also be notified that they are free to discontinue from the study at any time. The patient should be given the opportunity to ask questions and allowed time to consider the information provided.

The patient's signed and dated informed consent must be obtained before conducting any procedure specifically for the study, including the following:

- Withholding or discontinuation of treatment
- Collection of blood and urine samples
- Physical examination including ECG

The principal investigator(s) must store the original, signed Informed Consent Form. A copy of the signed Informed Consent Form must be given to the patient.

If modifications are made according to local requirements, the new version has to be approved by AstraZeneca.

8.4 Patient data protection

The Master Informed Consent Form will incorporate (or, in some cases, be accompanied by a separate document incorporating) wording that complies with relevant data protection and privacy legislation. Pursuant to this wording, patients will authorise the collection, use and disclosure of their study data by the Investigator and by those persons who need that information for the purposes of the study.

The Master Informed Consent Form will explain that study data will be stored in a computer database, maintaining confidentiality in accordance with national data legislation. All data computer processed by AstraZeneca and Bristol-Myers Squibb will be identified by E-code and study code.

The Master Informed Consent Form will also explain that for data verification purposes, authorised representatives of AstraZeneca, a regulatory authority, an Ethics Committee may require direct access to parts of the hospital or practice records relevant to the study, including patients' medical history.

9. PROCEDURES IN CASE OF EMERGENCY, OVERDOSE OR PREGNANCY

9.1 AstraZeneca emergency contact procedure

In the case of a medical emergency you may contact the Study Delivery Team Leader. If the Study Delivery Team Leader is not available, contact the Study Delivery Team Physician at AstraZeneca Research and Development site shown below.

Role in the study	Name	Address & telephone number

9.2 Procedures in case of medical emergency

The principal investigator(s) 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 should be reported as such, see Section 4.7.1.1.**

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 local AstraZeneca 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 3.6.2.

9.3 Procedures in case of overdose

- An overdose with associated AEs should be recorded as the AE diagnosis/symptoms on the relevant AE modules in the eCRF. In addition, the overdose should be reported on the Overdose eCRF module.

- An overdose without associated symptoms should not be recorded as an AE in the eCRF. The overdose should only be reported on the Overdose eCRF module.

9.4 Procedures in case of pregnancy

Pregnancy itself is not regarded as an AE unless there is a suspicion that the investigational product under study may have interfered with the effectiveness of a contraceptive medication. However, the outcome of all pregnancies (spontaneous miscarriage, elective termination, normal birth or congenital abnormality) must be followed up and documented even if the patient was discontinued from the study.

All reports of congenital abnormalities/birth defects are SAEs. Spontaneous miscarriages should also be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs. All pregnancies must be reported on the pregnancy module in the eCRF. All outcomes of pregnancy must be reported to AstraZeneca on the pregnancy outcomes report that will be available in the Investigator Study File.

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Clinical Study Protocol: Appendix B

Drug Substance	Saxagliptin
Study Code	D1680C00001
Appendix Edition Number	1.0
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Appendix B
Additional Safety Information

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 AE as it occurred or that 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).

Hospitalization

Out-patient 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, hospitalization, disability or incapacity but may jeopardize 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 hospitalization

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. Has a specific laboratory investigation (if performed) 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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Clinical Study Protocol Appendix C	
Drug Substance	Saxagliptin
Study Code	D1680C00001
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Appendix C
New York Heart Association (NYHA) Classification

1. NEW YORK HEART ASSOCIATION (NYHA) CLASSIFICATION

The NYHA classification will be based on the following definitions:

Class I — No limitation:
Ordinary physical exercise does not cause undue fatigue, dyspnoea or palpitations.

Class II — Slight limitation of physical activity:
Comfortable at rest but ordinary activity results in fatigue, palpitations, dyspnoea.

Class III — Marked limitation of physical activity:
Comfortable at rest but less than ordinary activity results in symptoms.

Class IV — Unable to carry out any physical activity without discomfort:
Symptoms of congestive heart failure are present even at rest with increased discomfort with any physical activity.

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Clinical Study Protocol: Appendix D	
Drug Substance	Saxagliptin
Study Code	D1680C00001
Appendix Edition Number	1.0
Appendix Date	

Appendix D
Algorithm for Lymphocytopenia

1. ALGORITHM FOR LYMPHOCYTOPENIA

1.1 Overview of procedures

1.1.1 Patients who experience an absolute lymphocyte count >400 and ≤500 cells/µL during Period C or D:

The Investigator, the Sponsor and the AstraZeneca representative will be notified by the central laboratory when any patient experiences an absolute lymphocyte count ≤500 cells/µL. For patients with an absolute lymphocyte count >400 and ≤500 cells/µL the investigational product should be held immediately upon reporting of the laboratory result. Within 72 hours of the report of an absolute lymphocyte count >400 and ≤500 cells/µL, the patient will undergo brief physical examination including blood pressure, heart rate, and temperature determination, and a repeat Complete Blood Count (CBC) with differential will be collected and sent to the central laboratory. In addition a blood sample for assessment of saxagliptin and BMS-510849 plasma concentration should also be obtained, refer to section 4.5.1 and 4.7.1.3 of the Clinical Study Protocol. The Investigator will notify the AstraZeneca representative of the repeat blood count values obtained. If the repeat lymphocyte count is >400 and ≤500 cells/µL, the need for discontinuation should be discussed with the AstraZeneca Study Team Physician.
Patients experiencing an absolute lymphocyte count >400 and ≤500 cells/µL will have continued 72 hour repeat CBC with differential until the absolute lymphocyte count is >500 cells/µL. The blinded investigational product should continue to be held. Thereafter, the patient will be followed as judged by the Investigator until the lymphocytopenia has resolved or stabilized at >750 cells/µL. If the absolute lymphocyte count remains ≤750 cells/µL for two weeks, lymphocyte subsets by flow cytometry, including $CD4_+$ and $CD8_+$ counts, will be obtained.

If the lymphocyte count returns to >750 cells/µL, blinded investigational product may be reinstated unless otherwise contraindicated. If blinded investigational product is reinstated, a CBC with differential should be checked one week after investigational product is restarted.

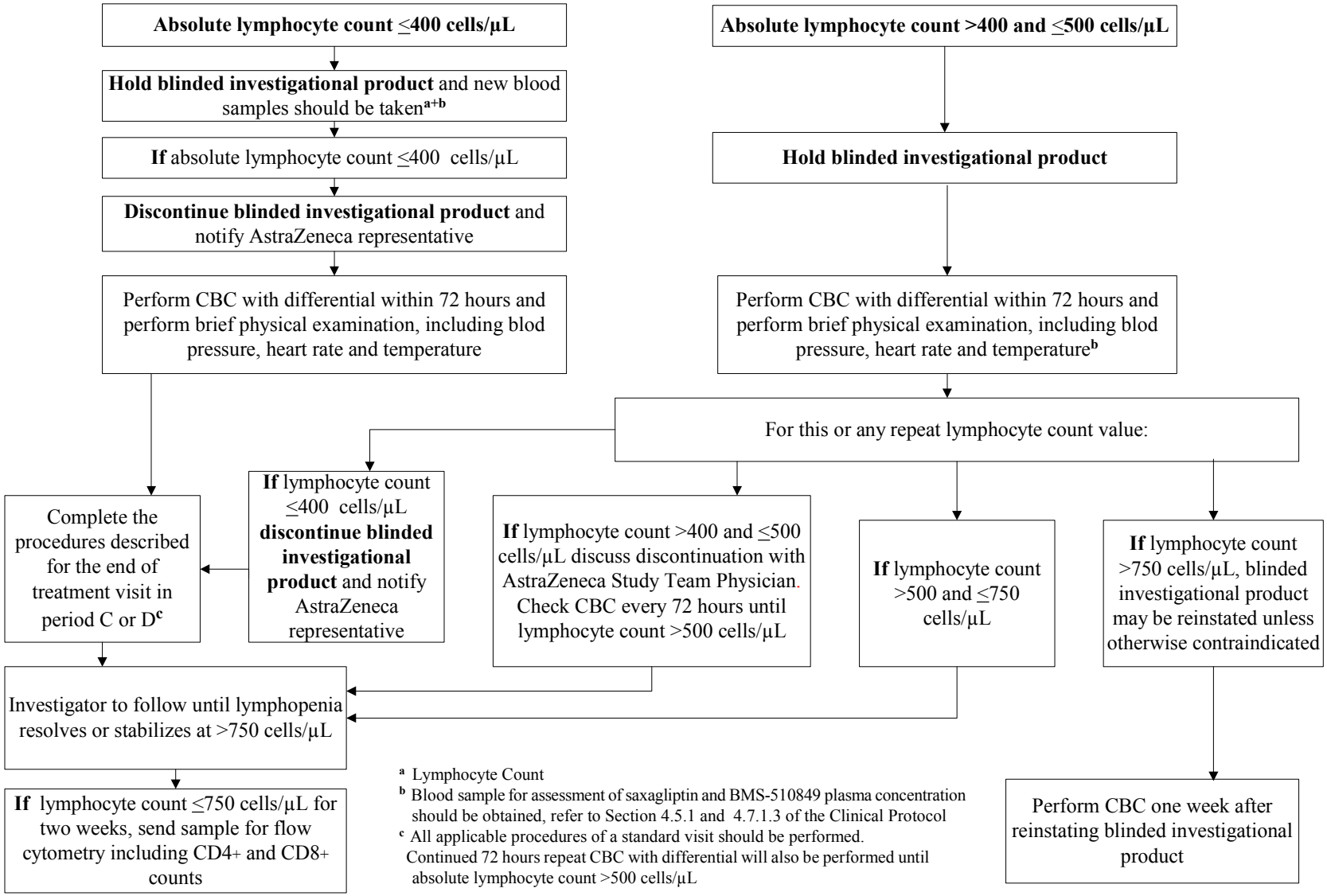
1.1.2 Patients who experience an absolute lymphocyte count ≤400 cells/µL during Period C or D:

The Investigator, the Sponsor and the AstraZeneca representative will be notified by the central laboratory when any patient experiences an absolute lymphocyte count ≤400 cells/µL. For patients with an absolute lymphocyte count ≤400 cells/µL at any time during Period C or D, investigational product should be held immediately and a new blood sample should be taken. In addition a blood sample for assessment of saxagliptin and BMS-510849 plasma concentration should also be obtained, refer to section 4.5.1 and 4.7.1.3 of the Clinical Study Protocol. If this second blood sample confirm an absolute lymphocyte count ≤400 cells/µL the patient must **discontinue from investigational product**. The Investigator will notify the AstraZeneca representative. Within 72 hours of the report of an absolute lymphocyte count ≤400 cells/µL, the patient will undergo brief physical examination including blood pressure, heart rate, and temperature determination, and a repeat CBC with differential will be

collected. The Investigator will notify the AstraZeneca representative of the repeat blood count values obtained. An end-of-study visit will be scheduled. At the end-of-study visit, all applicable procedures of a standard visit will be performed.

Patients experiencing an absolute lymphocyte count ≤400 cells/μL will have continued 72 hour repeat CBC with differential until the absolute lymphocyte count is >500 cells/μL. Thereafter, the patient will be followed as judged by the Investigator until the lymphocytopenia has resolved or stabilized at >750 cells/μL. If the absolute lymphocyte count remains ≤750 cells/μL for two weeks, lymphocyte subsets by flow cytometry, including $CD4_+$ and $CD8_+$ counts, will be obtained.

LYMPHOCYTOPENIA FLOWCHART
Double-Blind Treatment Period C and D



[a] Lymphocyte Count
[b] Blood sample for assessment of saxagliptin and BMS-510849 plasma concentration should be obtained, refer to Section 4.5.1 and 4.7.1.3 of the Clinical Protocol
[c] All applicable procedures of a standard visit should be performed.
Continued 72 hours repeat CBC with differential will also be performed until absolute lymphocyte count >500 cells/µL

Clinical Study Protocol Appendix E	
Drug Substance	Saxagliptin
Study Code	D1680C00001
Appendix Edition Number	1.0
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Appendix E
Algorithm for Thrombocytopenia

1. ALGORITHM FOR THROMBOCYTOPENIA

1.1 Overview of procedures

1.1.1 Patients who experience a platelet count <75,000 cells/µL during the double-blind Period C and D:

The Investigator, the Sponsor and the AstraZeneca representative will be notified by the central laboratory when any patient experiences a platelet count <75,000 cells/µL. The investigational product should be held immediately and a repeated blood sample should be taken. In addition a blood sample for assessment of saxagliptin and BMS-510849 plasma concentration should be obtained, refer to Section 4.5.1 and 4.7.1.3 of the Clinical Study Protocol. If platelet count <75,000 cells/µL is confirmed, the central laboratory will review the peripheral blood smear and notify the Investigator, the Sponsor and the AstraZeneca representative as to whether the smear is compatible with the reported decrease in platelet count.

- If the peripheral blood smear **is not compatible with** the reported decrease in platelet count (eg, clumped platelets), complete blood count (CBC) with differential is to be repeated within 72 hours of notification of the decreased platelet count. The Investigator, the Sponsor and the AstraZeneca representative should be notified of the results.

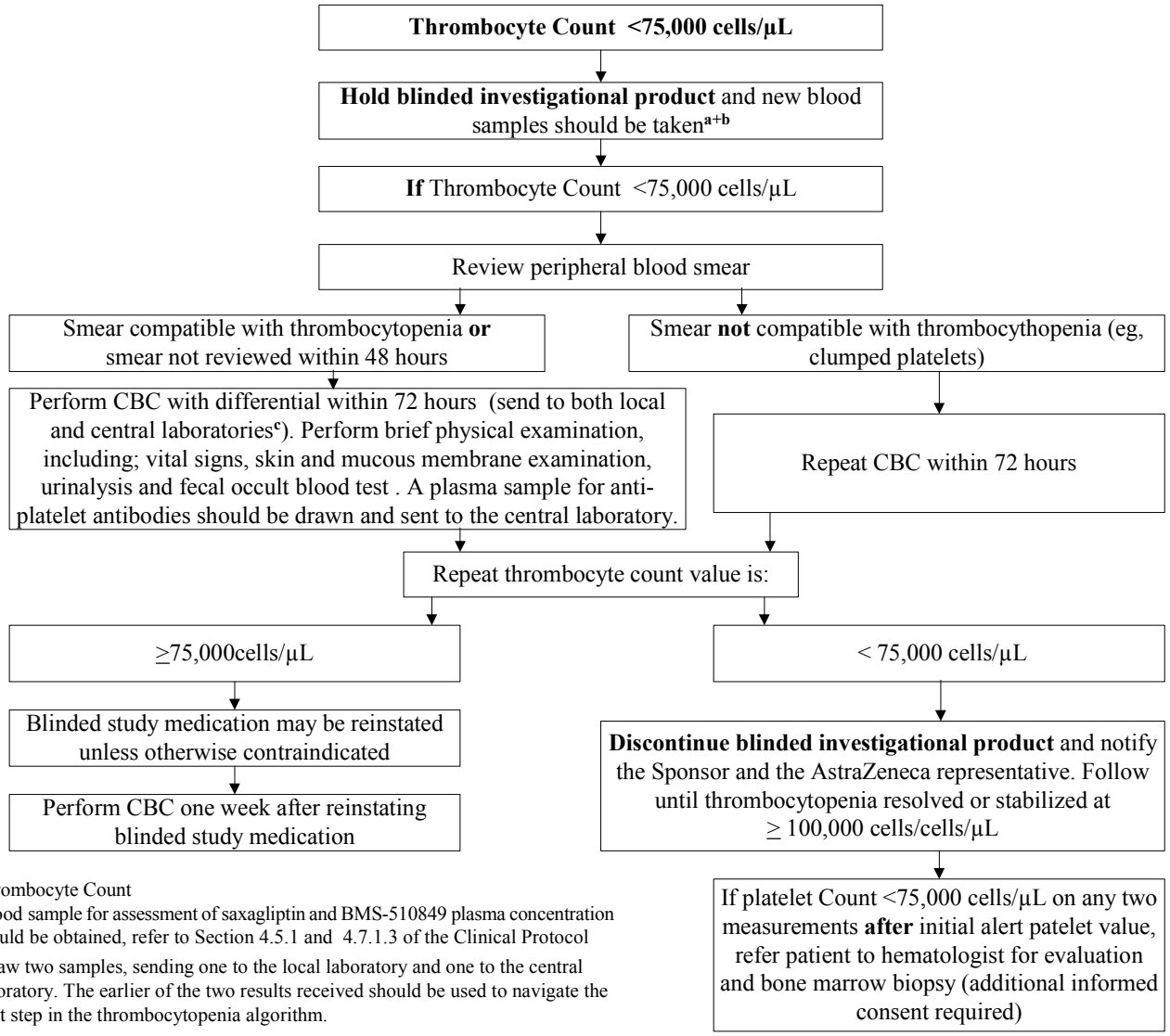
- If the peripheral blood smear **is compatible with** the reported decreased platelet count, or if the peripheral blood smear **is not reviewed within 48 hours** of the notification of the decreased platelet count, within 72 hours two CBCs with differential will be drawn and sent to local and central laboratories, respectively (the local CBC result received will be used to navigate the next step in the thrombocytopenia algorithm). Also within 72 hours, the patient will undergo brief physical examination including vital signs, skin and mucous membrane examination, urinalysis, and assessment for fecal occult blood. A **plasma** sample for anti-platelet antibodies will be drawn and sent to the central laboratory.

- If the repeat platelet count is ≥75,000 cells/µL, the investigational product may be reinstated unless otherwise contraindicated. A follow-up CBC should be performed one week after restarting blinded investigational product.

- If the repeat platelet count is <75,000 cells/µL, the patient will be **discontinued from investigational product**. The Investigator will notify the Sponsor and the AstraZeneca representative. The patient will be followed by the Investigator in consultation with the AstraZeneca Study Team Physician until the thrombocytopenia has resolved or stabilized at ≥100,000 cells/µL. If the platelet count is <75,000 cells/µL on any two measurements **after** the initial alert platelet value, the patient will be referred to a hematologist for evaluation, and, as allowed

per local country requirements, a bone marrow biopsy may be requested to explain the decrease of the platelets.

THROMBOCYTOPENIA FLOWCART
Double-Blind Treatment Period C and D



[a] Thrombocyte Count

[b] Blood sample for assessment of saxagliptin and BMS-510849 plasma concentration should be obtained, refer to Section 4.5.1 and 4.7.1.3 of the Clinical Protocol

[c] Draw two samples, sending one to the local laboratory and one to the central laboratory. The earlier of the two results received should be used to navigate the next step in the thrombocytopenia algorithm.

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Clinical Study Protocol: Appendix F	
Drug Substance	Saxagliptin
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Appendix Edition Number	1.0
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Appendix F
Optional Genetic Research

GENETICS RESEARCH SYNOPSIS

A 52-Week International, Multi-centre, Randomized, Parallel-group, Double-blind, Active-controlled, Phase III study with a 52-Week Extension Period to Evaluate the Safety and Efficacy of Saxagliptin in Combination with Metformin compared with Sulphonylurea in combination with Metformin in Adult Patients with Type 2 Diabetes who have Inadequate Glycaemic Control on Metformin Therapy Alone.

The genetic research activities described in this appendix (including the collection and storage of genetic samples), are optional for study centres as well as for individual patients. These research activities will hereafter be referred to as "this genetic research." The clinical study protocol to which this document is appended will be referred to as "the main study." The term "genetic sample" means a blood sample collected for genetic research and/or deoxyribonucleic acid (DNA) prepared from it.

This genetic research will be performed only after the appropriate Ethics Committee has approved it. Informed consent will be obtained using a form separate from that used for the main study. All sections of the protocol for the main study also apply to this genetic research. This appendix details additional procedures and considerations for inclusion of patients in the genetic component of the clinical study.

Study centre(s) and number of patients who may be enrolled in this genetic research

The main study will be conducted in 838 randomized patients recruited from approximately 160 centres.

Since the pharmacogenetic component of this clinical study is optional the number of patients who will agree to participate in the genetic component of the clinical study is unknown.

Objectives

The purpose of the genetic research is to enable future exploratory pharmacogenetic research studies. DNA obtained from the blood sample and health information collected from the main clinical study may be used to study the causes and progression of type 2 diabetes and other metabolic diseases and response to study treatments. Samples from this and other clinical studies may also be used in conjunction to accomplish this objective.

Study design

The main study comprises a 52-week international, multi-centre, randomized, parallel-group, double-blind, active-controlled, Phase III study with a 52-week extension period to evaluate

the safety and efficacy of saxagliptin (5 mg) in combination with metformin compared with sulphonylurea in combination with metformin in adult patients with type 2 diabetes who have inadequate glycaemic control on metformin therapy alone. A 9 ml (approximately) optional blood sample for genetic research can be collected at a single visit from Visit 3 (randomization visit) to Visit 9.

Target population

Men or women who are ≥18 years of age at the enrolment visit (Visit 1) diagnosed with type 2 diabetes, who fulfil the inclusion criteria for the main study, and who give informed consent for this genetic research.

Co-variables

Those genes putatively important in determining the response to study treatments (where response is defined broadly to include drug disposition, safety, efficacy and tolerability). This includes those genes coding for the drug targets as well as pathways and accessory pathway genes required for drug activity. Genes coding for proteins associated with the absorption, distribution, metabolism and excretion of study drugs from the body eg, specific drug transporters and drug metabolising enzymes. Genes that may influence progression and prognosis of type 2 diabetes and related metabolic, nutritional and endocrine disorders under study within the saxagliptin programme (ie, those diseases and disorders falling into International classification of diseases and related health problems (ICD)-9 multilevel clinical classification software, category 3 –"Endocrine, nutritional and metabolic diseases and immunity disorders"), or genes related to any other outcomes followed up on as part of the clinical study.

Statistical methods

The number of patients who will agree to participate in this genetic research is unknown. It is therefore not possible to establish whether sufficient data will be generated. A statistical analysis plan will be prepared where appropriate.

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation or special term	Explanation
eCRF	electronic Case report form
DNA	Deoxyribonucleic acid
EDTA	Ethylenediamine tetra-acetic acid
ICD	International classification of diseases and related health problems
mL	Millilitre

1. BACKGROUND

AstraZeneca and Bristol-Myers Squibb plan to include investigations into genetic variations and their effect on drug response as part of the drug development program 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.

1.1 Rationale for genetic research

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

Genes that may be investigated include:

Genes encoding drug targets (of study drug(s)), genes encoding proteins which function in drug transport and metabolism as well as 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 saxagliptin clinical study.

3. GENETIC RESEARCH PLAN AND PROCEDURES

3.1 Genetic research plan

This appendix to the Clinical Study Protocol has been subjected to peer review according to AstraZeneca standard procedures.

The patient will be asked to participate in this genetic research at Visit 3. If the patient agrees to participate, a single blood sample will be taken for genetic research at Visit 3. If the sample isn't drawn at Visit 3, it may be drawn at any other scheduled visit after Visit 3 until Visit 9.

3.2 Selection of genetic research population

3.2.1 Study selection record

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.

3.2.2 Inclusion criteria

For inclusion in this genetic research, patients must fulfil all of the inclusion criteria described in the main body of the study protocol **and**:

- Provide informed consent for the genetic sampling and analyses.

3.2.3 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.
- Received blood transfusion in the 120 days preceding the date of genetic sampling collection.

If either of these two exclusion criteria is present, the patient cannot participate in the optional blood sample donation.

3.2.4 Discontinuation of patients from this genetic research

3.2.4.1 Criteria for discontinuation

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

- 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.

3.2.4.2 Procedures for discontinuation

Patients who discontinue from the main study should always be asked specifically whether they are withdrawing or continuing their consent for this genetic research. It must be established whether the patient:

- Agrees to the genetic sample and any DNA extracted from the sample being kept for genetic research in the future.

- Withdraws consent for the sample to be kept for genetic research in the future and wishes the sample to be destroyed. Destruction of the sample (or the DNA extracted from the sample) will only be possible so long as the particular sample is traceable. In the event that genetic research has already been performed, Bristol-Myers Squibb and AstraZeneca will retain the results and associated data for regulatory reasons but these will not be used in any subsequent analyses.

The principal investigator is responsible for providing written notification to AstraZeneca and Bristol-Myers Squibb of any patient who has withdrawn consent for the use of the sample taken for genetic research. AstraZeneca and Bristol-Myers Squibb will provide written confirmation to the investigator of the actions taken with the sample, which must be filed in the investigator study file.

4. GENETIC MEASUREMENTS AND CO-VARIABLES

4.1 Summary of genetics objectives and analysis

The purpose of the genetic research is to generate a resource for future exploratory pharmacogenetic research studies. DNA obtained from the blood sample and health information collected from the main clinical study will be used to study the causes and further progression of type 2 diabetes and other metabolic disease. Samples from this and other clinical studies may also be used in conjunction to accomplish this objective.

The joint exploratory data analysis may be performed in the future by Statistical Genetics and Biomarkers in Exploratory Development, Global Biostatistics and Programming and the department of Pharmacogenomics in Clinical Discovery at Bristol-Myers Squibb and/or the AstraZeneca equivalent (including approved external service providers) to investigate if genetic variants (genotypes) are associated with clinical outcomes (phenotypes) such as, but not limited to, drug response, efficacy, safety, toxicity, and overall survival. The following potential analyses may be performed as appropriate:

- Examine demographic factors such as race/ethnicity, age and gender to determine appropriate stratification or adjustment for the analysis.

- Summarize allele and genotype frequencies from the sample with 95% confidence intervals.

- Explore the associations among genetic variation, expression of genes and proteins and clinical outcomes using methods like, but not limited to, chi-squared tests, logistic regression, generalized linear models, non-parametric tree-based models, survival models or clustering algorithms. The associations may be expressed, where appropriate, using odds ratios with 95% confidence limits.

4.2 Collection of samples for genetic research

Patients will provide a blood sample as per the inclusion criteria and visit schedule.

A single venous blood sample (9 or 10 mL) will be collected into a vacutainer or similar blood collection tube containing ethylenediamine tetra-acetic acid (EDTA) and gently inverted a minimum of five times to mix thoroughly. Tubes will be labelled with the protocol study number, centre number, enrolment code and/or randomisation number and date of sample collection. No personal identifiers (patient name, initials, or date of birth) will be placed on the tube or accompanying documentation. A record of the date of the patient consent to the genetic research and the date of the blood sample collection will be recorded in the appropriate section of the electronic Case Report Form (eCRF).

Genotype is a stable parameter; therefore if for any reason the blood sample is not drawn at Visit 3, it may be drawn at any other scheduled visit after Visit 3 until Visit 9. The genetic blood sample should ideally be drawn through the same cannula used to draw blood samples required for the main study.

4.2.1 Sample processing and shipping

Samples will be transported in ambient temperature from the centre to the central laboratory where they will be split into two aliquots and stored frozen.

Where possible, blood samples should be shipped daily with other ambient samples and shipment should be coordinated with the receiving centre to ensure arrival within working hours. A requisition sheet, detailing the protocol study number, centre number, enrolment code and/or randomisation number and date of sample collection, should accompany the shipment.

4.2.2 Storage and coding of DNA samples

The processes adopted for the coding and storage of samples for genetic analysis are important to maintain patient confidentiality.

The samples and data for genetic analysis in this study will be de-identified. 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 is 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 AstraZeneca and Bristol-Myers Squibb 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 after the sample collection date or according to local legislation. Samples may be destroyed prior to this timeframe if the patient has withdrawn consent.

5. MANAGEMENT OF GENETIC RESEARCH DATA

In the case of genotypic 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 eCRF and database. The genotypic data will not be merged with the entire clinical dataset collected from the subject population for statistical analysis. However, relevant subsets of clinical data may be replicated for genotype-phenotype analysis.

Genotypic data will be stored in the Bristol-Myers Squibb Sample Bank or another secure database, separate from that used for the main study. Some or all of the dataset from the main study may be duplicated within the Bristol-Myers Squibb Sample Bank to facilitate exploratory genetic analyses.

5.1 Reporting of genotypic results

Any results from this genetic research will be reported separately from the clinical study report for the main study. AstraZeneca and Bristol-Myers Squibb will not provide individual genotype results to patients, their family members, any insurance company, an employer, clinical study investigator, general physician or any other third party, unless required to do so by law. The patient’s DNA will not be used for any purposes other than those described in the study protocol.

Individual patients will not be identified in any report or publication resulting from this work. The data and results of this study may be reviewed with collaborators and published, but neither the patient's name nor any other personal identifiers will appear in any publication or report. De-identification will be done after the genotypic data and clinical data sets have been merged.

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 a statistically relevant number of patients will consent to provide sufficient data to 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.

7. STUDY MANAGEMENT

7.1 Monitoring

Before first patient entry into the study, a representative of AstraZeneca will visit the investigational study centre. In addition to the requirements described in the main study, this genetic research will be discussed.

During the study, a representative of AstraZeneca will have regular contacts with the investigational centre. One of the purposes of these visits will be to perform source verification of the genetic consent of participating patients and to ensure that the investigational team are adhering to the specific requirements of this genetic research.

7.2 Training of staff

Before the first patient is entered into the study the investigational staff will have an opportunity to discuss the procedures associated with the collection of blood samples, extraction of DNA and genetic research with a representative of AstraZeneca. The ethical considerations specific to genotyping and the importance of the informed consent process will be made clear. The requirements for the collections of the patients' sample will also be made clear.

7.3 Changes to the protocol

Any changes to the genetic research will comply with the principles described in Section 7.4 of the main body of the protocol.

7.4 Study agreements

The principal investigator at each centre must 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 Clinical Study Protocol shall prevail. Specific reference to requirements relating to this genetic research will be included in the study agreement(s).

8. ETHICS

8.1 Ethics review

In addition to documenting Ethics Committee approval of the main study, approval must be obtained for this genetic research and the associated genetic informed consent from the relevant Ethics Committee. It must be clearly stated in the approval that this genetic research is approved. The investigator must submit written approval to AstraZeneca before any patients participates in this genetic research.

8.2 Ethical conduct of the study

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

For studies including genetic analysis special precautions are taken as described in section 4.2.2 of this Appendix.

8.3 Informed consent

The genetic component of this study is optional and the patient may participate in other components of the 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 (non-genetic components of the 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 patients understand that they may freely discontinue from the genetic aspect of the study at any time.

8.4 Patient data protection

All data protection and confidentiality principles, described in the main study protocol, are applicable to this genetic research.

Reference to participation in this genetic research should not be recorded into the patients' general medical records, unless required by local regulations. Instead, all notes should be kept within the clinical study records.

Due to the exploratory nature of this genetic research, there will be no routine communication of results to patients. Bristol-Myers Squibb or AstraZeneca will not provide individual genotype results to patient, 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 to prevent genetic data from being linked to the identity of the patient. However, it must be recognised that there are exceptional circumstances where individuals may see both genetic data and a patients personal identifier, for example in the case of a medical emergency, when AstraZeneca Physicians and investigators might know the patient's identity and might have access to the genetic data, or during regulatory audit where designated authorities must be permitted access to the relevant files.

With respect to optional blood sample donation, the only information that will be recorded in the eCRF and clinical database will be information related to the provision of informed consent for genetic research and sample collection information. No genotypic data derived from samples collected in this study will be stored in the main clinical database. Genotypic data will be stored in the Bristol-Myers Squibb secure database or another secure database, separate from that used for the main study. Some or all of the dataset from the main study may be duplicated within the Bristol-Myers Squibb secure database to facilitate exploratory genetic analyses.

9. REFERENCES - NOT APPLICABLE

Clinical Study Protocol Amendment	
Amendment Number	1
Drug Substance	Saxagliptin
Study Code	D1680C00001
Date	

A 52-Week International, Multi-centre, Randomized, Parallel-group, Double-blind, Active-controlled, Phase III study with a 52-Week Extension Period to Evaluate the Safety and Efficacy of Saxagliptin in Combination with Metformin compared with Sulphonylurea in Combination with Metformin in Adult Patients with Type 2 Diabetes who have Inadequate Glycaemic Control on Metformin Therapy Alone.

Sponsor:

AstraZeneca AB

151 85 Södertälje, Sweden.

Centres affected by the Amendment:

All centres in the study

The protocol for the study is to be amended as follows:

Section of protocol affected:

International Co-ordinating Investigator

Previous text:

International Co-ordinating Investigator

The International coordinating investigator will be chosen for particular active contribution, active recruitment and for signing the clinical study reports (52-week and 104-week) of this study.

Revised text:

International Co-ordinating Investigator

The International coordinating investigator ***has been*** chosen for particular active contribution, active recruitment and for signing the clinical study reports (52-week and 104-week) of this study.

Reason for Amendment:

International Co-ordinating Investigator has been chosen

Persons who initiated the Amendment:

Extended Study Delivery Team

Section of protocol affected:

3.4.1 Identity of investigational products and additional drug

Previous text:

Treatment	Dosage form and strength	Manufacturer
Glucophage® (metformin hydrochloride)	Filmcoated, white to off-white round tablet, 500 mg	Bristol-Myers Squibb

Revised text:

Treatment	Dosage form and strength	Manufacturer
Glucophage® (metformin hydrochloride)	Filmcoated, white to off-white round tablet, 500 mg	***Merck Serono***

Reason for Amendment:

Supplier of Glucophage® (metformin hydrochloride) changed

Persons who initiated the Amendment:

Extended Study Delivery Team

Section of protocol affected:

3.4.2 Doses and treatment regimens

Previous text:

The blinding is ensured by using double-dummy technique. The investigational products saxagliptin or placebo and glipizide or placebo will be taken orally, immediately before or together with a meal. Saxagliptin or placebo should be taken once daily and glipizide or placebo should be taken once or twice daily depending on the dose directed by the investigator. The investigational product 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 each clinical visit; however, drinking water is allowed. In the morning prior to each visit, acceptable concomitant medications can be taken with water only.

- Matching placebo tablets for saxagliptin 5 mg oral for the 2-week placebo lead-in period, the 52-week double-blind period and the 52-week double-blind extension period.
- Matching placebo capsules for glipizide (sulphonylurea) 5 mg oral for the 2-week placebo lead-in period, 52-week double-blind period (dosing 5 to 20 mg) and the 52-week double-blind extension period (dosing 5 to 20 mg).
- Saxagliptin tablets 5 mg oral for the 52-week double-blind period and the 52-week double-blind extension period.
- Glipizide (sulphonylurea) 5 mg capsule oral (dosing 5 to 20 mg) for the 52-week double-blind period and the 52-week double-blind extension period.
- Open-label metformin 500 mg tablets oral at a daily dose of 1500 mg - 3000 mg tablets from Visit 2 throughout the study period.

During the lead-in period, each patient will receive one single-blind kit with:

> 1 bottle containing 35 tablets of placebo to match saxagliptin and 1 bottle containing 140 capsules of placebo to match glipizide

Each patient will during the randomized treatment receive from 1 up to 3 double-blind kits at each visit with:

> 1 bottle containing 35 tablets of saxagliptin 5 mg and 1 bottle containing 140 capsules of placebo to match glipizide,
>
> or
>
> 1 bottle containing 35 tablets of placebo to match saxagliptin and 1 bottle with 140 capsules of glipizide 5 mg tablets.

During the titration period the patients will titrate either active or placebo glipizide. Each patient will also receive open-label bottles with 100 tablets of metformin 500 mg, 1 to 6 bottles at each visit.

See Section 3.1 for titration procedures of glipizide.

Treatment doses**:**

Saxagliptin 5 mg: Morning dose: 1 tablet. Evening dose: N/A

Glipizide 5 mg: Morning dose: 1 capsule. Evening dose: N/A

Glipizide 10 mg: Morning dose: 2 capsules. Evening dose: N/A

Glipizide 15 mg: Morning dose: 2 capsules. Evening dose: 1 capsule

Glipizide 20 mg*:* Morning dose: 2 capsules. Evening dose: 2 capsules

The following guideline should be used if metformin therapy must be modified due to available open-label drug supply.

Current metformin therapy at Visit 2	Metformin dose (500 mg tablets)
1500 - 1999 mg	1500 mg (3 tablets)
2000 – 2499 mg	2000 mg (4 tablets)
2500 – 2550 mg	2500 mg (5 tablets)
>2550 mg	3000 mg (6 tablets)

Revised text:

The blinding is ensured by using double-dummy technique. The investigational products saxagliptin or placebo and glipizide or placebo will be taken orally, immediately before or together with a meal. Saxagliptin or placebo should be taken once daily and glipizide or placebo should be taken once or twice daily depending on the dose directed by the investigator. The investigational product 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 each clinical visit; however, drinking water is allowed. In the morning prior to each visit, acceptable concomitant medications can be taken with water only.

- Matching placebo tablets for saxagliptin 5 mg oral for the 2-week placebo lead-in period, the 52-week double-blind period and the 52-week double-blind extension period.

- Matching placebo capsules for glipizide (sulphonylurea) 5 mg oral for the 2-week placebo lead-in period, 52-week double-blind period (dosing 5 to 20 mg) and the 52-week double-blind extension period (dosing 5 to 20 mg).

- Saxagliptin tablets 5 mg oral for the 52-week double-blind period and the 52-week double-blind extension period.

- Glipizide (sulphonylurea) 5 mg capsule oral (dosing 5 to 20 mg) for the 52-week double-blind period and the 52-week double-blind extension period.

- Open-label metformin 500 mg tablets oral at a daily dose of 1500 mg - 3000 mg tablets from Visit 2 throughout the study period.

During the lead-in period, each patient will receive one single-blind kit with:

1 bottle containing 35 tablets of placebo to match saxagliptin and 1 bottle containing 140 capsules of placebo to match glipizide

Each patient will during the randomized treatment receive from 1 up to 3 double-blind kits at each visit with:

1 bottle containing 35 tablets of saxagliptin 5 mg and 1 bottle containing 140 capsules of placebo to match glipizide,

or

1 bottle containing 35 tablets of placebo to match saxagliptin and 1 bottle with 140 capsules of glipizide 5 mg ~~tablets~~.

or

1 bottle containing 35 tablets of placebo to match saxagliptin and 1 bottle containing 140 capsules of placebo to match glipizide.

During the titration period the patients will titrate either active or placebo glipizide. Each patient will also receive open-label ***boxes*** with 100 tablets of metformin 500 mg, ***1 to 7 boxes*** at each visit.

See Section 3.1 for titration procedures of glipizide.

Treatment doses**:**

Saxagliptin 5 mg: Morning dose: 1 tablet. Evening dose: N/A

Glipizide 0 mg (placebo): Morning dose: 1 capsule. Evening dose**: N/A**

Glipizide 5 mg: Morning dose: 1 capsule. Evening dose: N/A

Glipizide 10 mg: Morning dose: 2 capsules. Evening dose: N/A

Glipizide 15 mg: Morning dose: 2 capsules. Evening dose: 1 capsule

Glipizide 20 mg*:* Morning dose: 2 capsules. Evening dose: 2 capsules

The following guideline should be used if metformin therapy must be modified due to available open-label drug supply.

Current metformin therapy at Visit 2	Metformin dose (500 mg tablets)
1500 - 1999 mg	1500 mg (3 tablets)
2000 – 2499 mg	2000 mg (4 tablets)
2500 – 2550 mg	2500 mg (5 tablets)
>2550 mg	3000 mg (6 tablets)

Reason for Amendment:

Clarification to study conduct and procedures

Persons who initiated the Amendment:

Extended Study Delivery Team

Clinical Study Protocol Amendment 1: Appendix A

Drug Substance	Saxagliptin
Study Code	D1680C00001
Appendix Edition Number	1
Appendix Date	

Appendix A
Signatures

ASTRAZENECA SIGNATURE(S)

A 52-Week International, Multi-centre, Randomized, Parallel-group, Double-blind, Active-controlled, Phase III study with a 52-Week Extension Period to Evaluate the Safety and Efficacy of Saxagliptin in Combination with Metformin compared with Sulphonylurea in Combination with Metformin in Adult Patients with Type 2 Diabetes who have Inadequate Glycaemic Control on Metformin Therapy Alone.

This Clinical Study Protocol and all Amendments to the CSP have been subjected to an internal AstraZeneca peer review.

I agree to the terms of this study protocol/amendment.

AstraZeneca Research and Developmen
site representative

ASTRAZENECA SIGNATURE(S)

A 52-Week International, Multi-centre, Randomized, Parallel-group, Double-blind, Active-controlled, Phase III study with a 52-Week Extension Period to Evaluate the Safety and Efficacy of Saxagliptin in Combination with Metformin compared with Sulphonylurea in Combination with Metformin in Adult Patients with Type 2 Diabetes who have Inadequate Glycaemic Control on Metformin Therapy Alone.

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AstraZeneca Research and Developmen
site representative