AstraZeneca

Revised Clinical Study Protocol	
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A 52-Week, Randomised, Double Blind, Active-Controlled, Multi-Centre Phase IIIb/IV Study to Evaluate the Efficacy and Tolerability of Saxagliptin Compared to Glimepiride in Elderly Patients with Type 2 Diabetes Mellitus Who Have Inadequate Glycaemic Control on Metformin Monotherapy

Sponsor: AstraZeneca AB, SE-151 85 Södertälje, Sweden

AstraZeneca representative

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

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

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

AstraZeneca

PROTOCOL SYNOPSIS

A 52-Week, Randomised, Double Blind, Active-Controlled, Multi-Centre Phase IIIb/IV Study to Evaluate the Efficacy and Tolerability of Saxagliptin Compared to Glimepiride in Elderly Patients with Type 2 Diabetes Mellitus Who Have Inadequate Glycaemic Control on Metformin Monotherapy

International Co-ordinating Investigator

Prof. Dr. Guntram Schernthaner

Study centre(s) and number of patients planned

This is a multinational study and will be conducted at approximately 175 study centres. Approximately 975 patients will be enrolled to reach the target of 698 randomised patients. It is expected that approximately 3 to 8 patients will be randomised per study centre.

Study period		Phase of development
Estimated date of first patient enrolled	Q4 2009	IIIb/IV
Estimated date of last patient completed	Q3 2012	IIIb/IV

Objectives

Primary: To show the superiority of saxagliptin compared to glimepiride in bringing elderly patients (≥65 years) with type 2 diabetes to HbA_{1c} target <7% without hypoglycaemia (confirmed or severe) over a 52-week treatment period. Saxagliptin or glimepiride will be administered as an add-on therapy to a background therapy with metformin.

Secondary: To compare the effects of saxagliptin versus glimepiride given as add-on to a metformin therapy after 52 weeks of a double-blind treatment period by evaluation of secondary efficacy and safety endpoints described below.

Secondary, key endpoint (safety analysis):

- Proportion of patients having experienced at least one hypoglycaemic event (confirmed or severe; for definition, see Section 6.4.9) over the 52-week double-blind treatment period

Efficacy:

- Change from baseline to Week 52 in HbA_{1c}
- Proportion of patients achieving a therapeutic glycaemic response at Week 52 defined as HbA_{1c} <7.0% or <6.5%
- Change from baseline to Week 52 in fasting plasma glucose (FPG) and insulin
- Change from baseline to Week 52 in β-cell function (as measured by Homeostasis Model Assessment-β [HOMA-β])

Safety:

- Safety and tolerability will be evaluated by assessment of adverse events, laboratory values, electrocardiogram (ECG), blood pressure, pulse rate, body weight and physical examination

Other relevant endpoints:

- Change from baseline to Week 52 in patient related outcomes using the following validated questionnaires: Diabetes Treatment Satisfaction Questionnaire (DTSQ), Hypoglycaemia Fear Survey II (HFS-II) worry subscale, and EuroQoL-5 Dimension (EQ-5D)
- Change from baseline to Week 52 in total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), and triglycerides

Study design

This study is a 52-week, multi-centre, randomised, parallel-group, double-blind, active-controlled Phase IIIb/IV trial to evaluate the efficacy and safety of saxagliptin compared with glimepiride in elderly patients (≥65 years old) with type 2 diabetes who have inadequate glycaemic control (defined as HbA_{1c} ≥7.0% and ≤9.0%) on a stable dose of metformin monotherapy. Randomisation will be stratified by age (<75 and ≥75 years).

Target patient population

Elderly males and females (≥65 years) with type 2 diabetes, with inadequate glycaemic control on a stable dose of metformin monotherapy, any dose for at least 8 weeks, are eligible to enter the study.

Investigational product, dosage and mode of administration

- Saxagliptin oral tablets, 5 mg once daily.
- Matching placebo oral tablets for saxagliptin 5 mg, once daily.

Comparator, dosage and mode of administration

- Glimepiride, encapsulated oral tablets, dosing 1 to 6 mg, once daily.
- Matching placebo encapsulated oral tablets for glimepiride once daily.

Duration of treatment

The double-blind treatment period will be 52 weeks. Patients will have a 2-week enrolment period and a 2 weeks lead-in period before the day of randomisation. The dose for glimepiride/placebo will be titrated for 12 weeks, and then maintained for another 40 weeks.

Outcome variable(s):

Primary:

- The primary endpoint is the proportion of patients reaching HbA_{1c} target <7% without hypoglycaemia (confirmed or severe) over a 52-week treatment period.

Secondary, key endpoint (safety analysis):

- Proportion of patients having experienced at least one hypoglycaemic event (confirmed or severe) over the 52-week double-blind treatment period.

Secondary, efficacy:

- Change from baseline to Week 52 in HbA_{1c}.
- Proportion of patients achieving a therapeutic glycaemic response at Week 52 defined as HbA_{1c} <7.0% or <6.5% .
- Change from baseline to Week 52 in fasting plasma glucose (FPG) and insulin.
- Change from baseline to Week 52 in β-cell function (as measured by Homeostasis Model Assessment-β [HOMA-β]).

Secondary, safety:

- Safety and tolerability evaluated by assessment of adverse events (AEs), laboratory values, electrocardiogram (ECG), blood pressure, pulse rate, body weight and physical examination.

Other relevant endpoints:

- Change from baseline to Week 52 in patient related endpoints using the following validated questionnaires: Diabetes Treatment Satisfaction Questionnaire(DTSQ), Hypoglycaemia Fear Survey II (HFS-II) worry subscale, and EuroQoL-5 Dimension (EQ-5D)
- Change from baseline to Week 52 in total cholesterol (TC), low-density lipoprotein-cholesterol (LDL-C), high-density lipoprotein-cholesterol (HDL-C), triglycerides

Statistical methods

The proportion of patients reaching HbA_{1c} <7% at Week 52 without confirmed or severe hypoglycaemia (as defined in Section 6.4.9) will be analysed using the Cochran-Mantel-Haenszel (CMH) method for the odds ratio (OR), including a stratification variable for the age group (<75 versus ≥75 years).

The primary efficacy analysis will be performed on the safety analysis set using the above mentioned CMH approach providing statistical test results and 95% confidence intervals for the OR comparing treatments. There will be no re-assignment of treatments for this analysis, each patient will be analysed as randomised.

The key secondary objective, the proportion of patients with hypoglycaemic events during the double-blind treatment period, will be analysed using the same approach as in the analysis of the primary endpoint. Superiority of saxagliptin will be tested in the safety analysis set.

To preserve the type I error rate ≤0.05 (two-sided) across the primary and the key secondary endpoint, a hierarchical testing procedure will be used to interpret the statistical significance of these treatment comparisons. The primary endpoint will be tested first followed by the key secondary endpoint. Both comparisons will be tested at a two-sided significance level of α=0.05. However, a comparison of the key secondary objective will only be confirmed as statistically significant if the preceding primary comparison is statistically significant.

Exploratory analyses of continuous endpoints will be performed using ANCOVA methods for the change from baseline. The ANCOVA model will use the factors treatment group and age (<75 versus ≥75 years) as a fixed effect and the respective baseline value as covariate.

Exploratory analyses of categorical endpoints will use the same approach as for the primary endpoint.

A total of 698 evaluable patients (349 in each treatment arm) is needed to detect superiority of saxagliptin in the primary analysis with a two-sided significance level of α=0.05 and 80% power under the assumption of a 1.55 times higher odds for reaching HbA_{1c} <7% without hypoglycaemia (confirmed or severe, as defined in Section 6.4.9) with saxagliptin treatment, compared to glimepiride. The selected sample size should result in a total number of 140 evaluable patients aged ≥75 years per treatment arm (40% of 349).

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

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

Abbreviation or special term	Explanation
AE	Adverse Event (see definition in Section 6.4.1)
ALT	Alanine Aminotransferase
ANCOVA	Analysis of Covariance model
AST	Aspartate Aminotransferase
AZDD	AstraZeneca Drug Dictionary
BMI	Body Mass Index
BUN	Blood Urea Nitrogen
CK	Creatine Kinase
CMH	Cochran-Mantel-Haenszel
CPMP	Committee for Proprietary Medicinal Products. CPMP has changed name to Committee for Medicinal Products for Human Use (CHMP)
CrCl	Creatinine Clearance
CRO	Contract Research Organization
CSA	Clinical Study Agreement
CSR	Clinical Study Report
CYP450 3A4	Cytochrome P450 3A4
DAE	Discontinuation due to Adverse Event
DM	Data Management
DMC	Data Monitoring Committee
DPP-4	Dipeptidyl Peptidase 4
DTSQ	Diabetes Treatment Satisfaction Questionnaire
EASD	European Association for the Study of Diabetes
EC	Ethics Committee, synonymous to Institutional Review Board (IRB) and Independent Ethics Committee (IEC)
ECG	Electrocardiogram
eCRF	electronic Case Report Form
EQ-5D	EuroQoL-5 Dimension
ESRD	End Stage Renal Disease
EU	European Union
FAS	Full Analysis Set
FPG	Fasting Plasma Glucose
GCP	Good Clinical Practice

Abbreviation or special term	Explanation
GIP	Glucose-dependent Insulinotropic Peptide
GLP-1	Glucagon-Like Peptide-1
GMP	Good Manufacturing Practice
HbA1c	Glycosylated Haemoglobin A1c
HDL-C	High-Density Lipoprotein-Cholesterol
HFS-II	Hypoglycaemia Fear Survey II
HOMA-β	Homeostasis Model Assessment-β
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
Kg	Kilogram
LDL-C	Low-Density Lipoprotein-Cholesterol
LOCF	Last Observation Carried Forward
LSLV	Last Subject Last Visit
MDRD	Modification of Diet in Renal Disease
MedDRA	Medical Dictionary for Regulatory Activities
OAE	Other significant Adverse Event (see definition in Section 11.2.2)
OR	Odds Ratio
PI	Principal Investigator
PP	Per Protocol
PRO	Patient Reported Outcomes
QoL	Quality of Life
RUCD	Recommended Usual Clinical Dose
SAE	Serious Adverse Event (see definition in Section 6.4.2)
SAP	Statistical Analysis Plan
SCr	Serum Creatinine
TB	Total Bilirubin
TC	Total Cholesterol
TSH	Thyroid Stimulating Hormone
ULN	Upper Limit of Normal
WBDC	Web Based Data Capture

1. INTRODUCTION

1.1 Background

Type 2 diabetes is common in the elderly (Meneilly 2006). Unfortunately, currently available medications are not always indicated or well tolerated in the older patient (Asche et al 2008; Rosenstock 2001; Sakharova et al 2005). On one hand, metformin is contraindicated in patients with renal impairment, thiazolidinediones are associated with an increased risk of heart failure and elderly patients have an increased risk for severe hypoglycaemia with the use of sulphonylureas or insulin. These factors may result in reluctance by physicians to titrate or add to background antihyperglycaemic therapies. Overall, because of the above, the elderly may be receiving suboptimal therapy for their diabetes. The higher risk of hypoglycaemic reactions is of particular importance in the elderly patient population. Elderly are less likely to be aware of hypoglycaemia when it occurs due to alterations in the release of counter-regulatory hormones (Mathieu et al 2007; Meneilly 2006). In addition to reduced psychomotor performance during these events, they may lead to falls, which could result in injury or fracture.

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 enhance 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 (PPG) 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.

A total of 4148 patients with type 2 diabetes mellitus have been randomised in 6 double-blind controlled clinical safety and efficacy studies for saxagliptin, including 3021 patients treated with saxagliptin. In these studies, saxagliptin was evaluated at doses of 2.5, 5, and 10 mg once daily. Treatment with saxagliptin at all doses produced clinically relevant and statistically significant improvements in glycosylated haemoglobin A_{1c} (HbA_{1c}), fasting plasma glucose (FPG), and PPG, compared to control. Reductions in HbA_{1c} were seen across subgroups including gender, age, race, and baseline body mass index (BMI). In addition, saxagliptin rarely caused hypoglycaemia.

To date, a total of 508 patients ≥65 years of age, and only 41 patients ≥75 years of age have been treated in the Phase IIb/III program with doses of saxagliptin. On an individual study basis, the efficacy of saxagliptin has not proven to be affected by age. In a pooled efficacy subanalysis in patients ≥65 years of age in which 135 patients were treated with saxagliptin 2.5 mg and 138 patients with saxagliptin 5 mg, no consistent differences in saxagliptin efficacy compared to placebo was shown. There were no apparent differences in adverse event (AE) profiles based on age.

For additional details on the background of saxagliptin, see the Investigator's Brochure (IB).

1.2 Research hypothesis

The hypothesis to be tested is to show the superiority of saxagliptin compared to glimepiride in bringing elderly patients (≥65 years old) with type 2 diabetes to HbA_{1c} target <7% without hypoglycaemia (confirmed or severe) over a 52-week treatment period.

The combined endpoint is of more clinical relevance in this patient population that is difficult to treat. The combined endpoint is aimed at demonstrating that saxagliptin is a safer alternative to glimepiride when bringing patient to the target HbA_{1c} recommended by most guidelines. Hypoglycaemia (as defined in Section 6.4.9) is used for this primary endpoint.

Saxagliptin is superior to glimepiride with regards to the hypoglyceamia endpoint. In other words, saxagliptin treatment leads to fewer patients with hypoglycaemia compared to glimepiride after 52 weeks of treatment.

Saxagliptin has a comparable safety and tolerability profile compared to glimepiride.

1.3 Rationale for conducting this study

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

Very little data is currently available for saxagliptin in elderly diabetic patients especially in patients ≥75 years of age. In the phase IIb/III program, there was a total of 508 patients ≥65 years of age but only 41 patients were ≥75 years of age. Of the included patients in this study, 40% will be above 75 years of age.

This 52-week Phase IIIb/IV clinical study investigates the efficacy and tolerability of saxagliptin compared with glimepiride (sulphonylurea) in elderly patients with type 2 diabetes who have inadequate glycaemic control on metformin monotherapy.

Given the particular mechanism of action of saxagliptin, the current Phase III data and the fact that there will be no insulin secretagogues in the background treatment, it is likely that less hypoglycaemias will be observed with saxagliptin compared to glimepiride. The numbers of confirmed or severe hypoglycaemias, as defined in Section 6.4.9, 11.2.3, will be examined for these secondary safety endpoints.

1.4 Benefit/risk and ethical assessment

For an overall risk/benefit assessment of saxagliptin, see the Investigator Brochure.

A total of 5346 subjects were evaluated in the saxagliptin Phase 1-3 clinical development program, including 423 in a Phase 2b dose ranging study and 4250 subjects in Phase 3 studies. In the development program, saxagliptin was studied at maximum daily doses of 400 mg (80 times the Recommended Usual Clinical Dose [RUCD]) for up to 2 weeks, 100 mg (20 times the RUCD) for up to 6 weeks, 40 mg (8 times the RUCD) and 20 mg (4 times the RUCD) for up to 12 weeks, and 10 mg (2 times the RUCD) for up to 2 years. Saxagliptin doses of 2.5 and 5 mg have also been studied for up to 2 years. As of October 2008, the total number of subjects in the Phase 2b/3 studies exposed to saxagliptin (2.5 mg, 5 mg, or 10 mg) for ≥50 weeks included 652 subjects treated with saxagliptin monotherapy, 902 subjects treated with saxagliptin in combination with metformin, 407 subjects treated with saxagliptin added on to sulphonylurea, and 275 subjects treated with saxagliptin added on to thiazolidinediones.

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 recommended dose. Studies on the long-term safety profile of saxagliptin is currently ongoing.

Increased incidence of hypoglycaemic events have previously been noted with glimepiride therapy. Therefore, hypoglycaemic events will be monitored.

Discontinuation criteria due to lack of efficacy is included to prevent overt hyperglyceamia that is not deemed desirable from a patient safety/tolerability perspective.

2. STUDY OBJECTIVES

2.1 Primary objective

The primary objective of this study will be to show the superiority of saxagliptin compared to glimepiride in bringing elderly patients (≥65 years) with type 2 diabetes to HbA_{1c} target <7% without hypoglycaemia (confirmed or severe) over a 52-week treatment period. Saxagliptin or glimepiride will be administered as an add-on therapy to a background therapy with metformin.

2.2 Secondary objectives

To compare the effects of saxagliptin versus glimepiride given as add-on to a metformin therapy after 52 weeks of a double-blind treatment period by evaluation of secondary efficacy and safety endpoints described below:

Key secondary (safety analysis)

- Proportion of patients having experienced at least one hypoglycaemic event (confirmed or severe) over the 52-week double-blind treatment period

Efficacy

- Change from baseline to Week 52 in HbA_{1c}
- Proportion of patients achieving a therapeutic glycaemic response at Week 52 defined as HbA_{1c} <7.0% or <6.5%
- Change from baseline to Week 52 in fasting plasma glucose (FPG) and insulin
- Change from baseline to Week 52 in β-cell function (as measured by Homeostasis Model Assessment-β [HOMA-β] [Albareda et al 2000; Matthews et al 1985; Wallace et al 2004])

2.3 Safety objective

- Safety and tolerability will be evaluated by assessment of AEs, laboratory values, electrocardiogram (ECG), pulse rate, blood pressure, body weight and physical examination

2.4 Exploratory objectives

Other relevant endpoints

- Change from baseline to Week 52 in patient related outcomes using the following validated questionnaires: Diabetes Treatment Satisfaction Questionnaire (DTSQ), Hypoglycaemia Fear Survey II (HFS-II) worry subscale, EuroQoL-5 Dimension (EQ-5D)

– Change from baseline to Week 52 in total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), and triglycerides

3. STUDY PLAN AND PROCEDURES

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

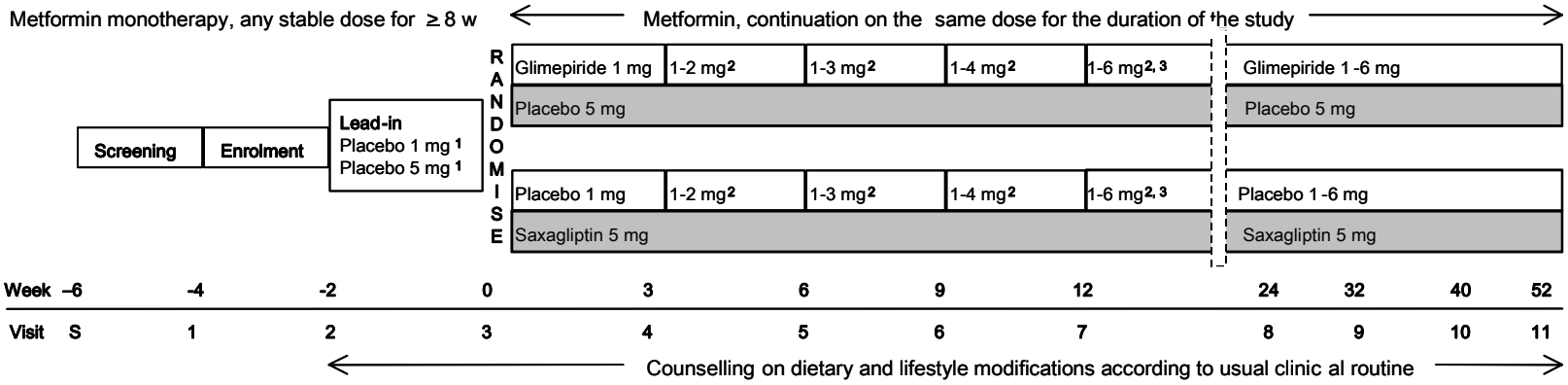
3.1 Overall study design and flow chart

This study is a 52-week, multi-centre, randomised, parallel-group, double-blind, active-controlled Phase IIIb/IV trial to evaluate the efficacy and safety of saxagliptin compared with glimepiride in elderly patients (≥65 years old) with type 2 diabetes who have inadequate glycaemic control (defined as HbA_{1c} ≥7.0% and ≤9.0%) on a stable dose of metformin monotherapy for at least 8 weeks. The randomisation will be stratified by age <75 and ≥75 years. The cohorts will be approximately 60% of the patients for age group 65 years to 75 years and 40% for age group ≥75 years. The enrolment to any of the cohorts will be stopped when the number of patients is reached.

This is a multinational study and will be conducted at approximately 175 study centres, with a recruitment period of approximately 19 months. Approximately 975 patients will be enrolled to reach the target of 698 randomised patients. It is expected that approximately 3 to 8 patients will be randomised per study centre. The overall study flow chart is shown in Figure 1. The Study Plan shown in Table 1 specifies the number, timing and routine assessments for the planned visits.

In order to minimise the number of screening failures among the patients to be enrolled at Visit 1, all potentially eligible patients will attend a screening visit within 14 days prior to Visit 1. A screening informed consent form will be provided by AstraZeneca, and implemented locally, based on all applicable regulatory requirements and laws. A signed informed consent form must be obtained prior to taking the blood sample for determination of HbA_{1c} at the central laboratory. Missing the requested HbA_{1c} range is one of the main screening failure reasons and discrepancies between locally and centrally determined values are well known. All patients who are screened should be listed on a patient screening log.

Figure 1 Study flow chart for Enrolment, Lead-in and Treatment period



1. Lead-in, placebo 1 mg and placebo 5 mg, single blinded treatment for glimepiride and saxagliptin
2. Indicates dose range for the glimepiride/placebo treatment. Should be based on treatment target FPG ≤6.1 mmol/L or ≤110 mg /dL and the patient's self monitored plasma glucose values.
3. The patients reaching the 6 mg dose at Visit 7 will have a follow-up phone call 3 weeks later

The study will consist of 4 periods:

Enrolment Period (Week –4 to –2)

Patients aged 65 years or older with type 2 diabetes with inadequate glycaemic control (HbA_{1c} ≥7.0 % and ≤9.0% based on value from screening visit) and currently on a stable monotherapy of metformin (any doses) for at least 8 weeks will be eligible to enter the study. The patient should maintain the prescribed stable dose of metformin for the duration of the study. Blood sampling and other examinations for assessment of inclusion and exclusion criteria will be performed.

Lead-in Period (Week –2 to 0)

Patients who still meet all inclusion and no exclusion criteria are eligible to enter the 2-week single-blind (blind to patient only) placebo lead-in period. The patients will from this period on, and during the entire study, be counselled on dietary and lifestyle modifications according to usual clinical routine. They will be given a glucometer to check their plasma glucose at home on a regular basis and to register the results in the patient diary during the duration of the study. The glucometer measures capillary glucose, and the measured value is recalculated by the glucometer to show plasma values. Hypoglycaemic events should during the entire study period always be entered into the patient hypoglycaemic event diary. For details on hypoglycaemic events and diaries, see Sections 6.4.9 and 6.5, 6.5.1.

Titration Period (Week 0 to 12)

At the Randomisation Visit (Visit 3), starting the titration period, patients will be randomised (1:1) to one of the following two blinded treatment arms: saxagliptin 5 mg and placebo 1 mg once daily or glimepiride 1 mg and placebo 5 mg once daily. To ensure blinding of the investigational products, the patients will also receive placebo capsules/tablets using a double-dummy technique.

During the first 12 weeks, the glimepiride/placebo dose will be slowly titrated in a stepwise fashion depending on glycaemic control. For the duration of the study, fasting plasma glucose will be measured at the study centre, using a glucose analyser (HemoCue®) provided by AstraZeneca. The investigator's decision on dose increase (or decrease) will take into account both the plasma glucose measurements, made by the patients prior to visits, and the investigator's measurements at the titration visits. The glimepiride/placebo dose will be titrated to optimal effect (FPG ≤6.1 mmol/L or ≤110 mg/dL) or the highest tolerable dose during the first 12 weeks. The starting dose for glimepiride/placebo will be 1 mg per day (once daily), and titrated at 3-week intervals to a maximum of 6 mg per day. The titration steps will be 2 mg per day (once daily) followed by 3 mg, 4 mg or 6 mg (once daily), if needed only. In patients for whom titration was not medically indicated at Week 3 (Visit 4), re-assessment for titration will occur at Week 6 (Visit 5), Week 9 (Visit 6) and Week 12 (Visit 7).

The glimepiride/placebo dose can be down titrated during the titration period if hypoglycaemic events occur. The treatment may thereafter be up titrated once during the titration period. The patients reaching the 6 mg dose at Week 12 will have a follow-up phone call 3 weeks later.

The saxagliptin dose, 5 mg, will remain constant throughout the study.

Blood samples for assessment of glycaemic parameters (based on results from central laboratory) will be taken at each visit to determine if criteria for discontinuation are met. The patients will be instructed to monitor their plasma glucose during the entire study, and if hypoglycaemic events occur, to register into the patient diaries. For details on hypoglycaemic events and patient diaries, see Sections 6.4.9 and 6.5.

Randomised patients, who do not complete the entire study, should complete the procedures described for Visit 11.

Maintenance Treatment Period (Week 12 to 52)

After the titration period, the patient will remain on the patient optimal dose of investigational products for 40 weeks to assess efficacy and safety of the treatment. The dose of glimepiride/placebo can be down titrated at any time during this period to mitigate recurrent hypoglycaemic events at the discretion of the investigator. No up titration will be allowed during the maintenance treatment period (ie, if dose is lowered it will then be left on this lower dose level). 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.

The titration period and the maintenance treatment period are referred to as the double-blind treatment period and is 52 weeks long.

Table 1 Study plan for Enrolment, Lead-in, Titration and Maintenance periods

	Screen.	Enrol.	Lead-in	Rand.	Titration Period				Maintenance Treatment Period			
Visit number	**S**	**1**	**2**[a]	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**[b]
Study Week	**-6**	**-4**	**-2**	**0**	**3**	**6**	**9**	**12**	**24**	**32**	**40**	**52**
Visit Window Day ± No. Days	**-42 ± 7**	**-28 ± 3**	**-14 ± 3**	**0**	**21 ± 3**	**42 ± 3**	**63 ± 3**	**84 ± 3**	**168 ± 3**	**224 ± 3**	**280 ± 3**	**364 ± 3**
Screening Informed consent and blood sample for determination of HbA_{1c}	X											
Informed consent		X										
Medical history and demography		X										
Inclusion/exclusion criteria		X	X	X								
Physical examination		X										X
Brief physical examination				X								
Blood pressure, pulse rate		X		X				X	X	X	X	X
Weight		X		X				X	X	X	X	X
Height		X										
Waist circumference				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
Register titration of glimepiride/placebo during the titration period (if applicable) in IWRS					X	X	X	X				
Patient reported outcomes questionnaires[d]				X					X			X

	Screen.	Enrol.	Lead-in	Rand.	Titration Period				Maintenance Treatment Period			
Visit number	**S**	**1**	**2**[a]	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**[b]
Study Week	**-6**	**-4**	**-2**	**0**	**3**	**6**	**9**	**12**	**24**	**32**	**40**	**52**
Visit Window Day ± No. Days	**-42 ± 7**	**-28 ± 3**	**-14 ± 3**	**0**	**21 ± 3**	**42 ± 3**	**63 ± 3**	**84 ± 3**	**168 ± 3**	**224 ± 3**	**280 ± 3**	**364 ± 3**
Register down titration of glimepiride/placebo during the maintenance period (if applicable) in IWRS									X	X	X	
Dispense investigational products			X	X	X	X	X	X	X	X	X	
Dispense glucometer and/or supplies/provide instruction			X	X	X	X	X	X	X	X	X	
Dispense patient diaries			X	X	X	X	X	X	X	X	X	
Patient diary review for hypoglycaemic events/check glucometer values				X	X	X	X	X	X	X	X	X
Adverse Events (AEs)				X	X	X	X	X	X	X	X	X
Serious Adverse Events (SAEs)[e]		X	X	X	X	X	X	X	X	X	X	X
Drug accountability[f]				X	X	X	X	X	X	X	X	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. Randomised patients who do not complete the entire study should complete the procedures described for Visit 11
c. Specification of laboratory parameters are shown in Table 2 and Table 3
d. Patient reported outcomes questionnaires: DTSQ, HFS-II, EQ-5D
e. From the time when the Informed Consent is obtained (Visit 1) until the first administration of investigational products (Visit 3), only SAEs need to be recorded
f. Returned tablets should be counted and the number of returned tablets and date of return should be registered in the eCRF

3.2 Rationale for study design, doses and control groups

3.2.1 Study design and regulatory requirements

The purpose of the study is to investigate if treatment with saxagliptin as add-on to a background monotherapy of metformin is beneficial in the elderly patients with type 2 diabetes as compared to adding a sulphonylurea (glimepiride). A superiority comparison is designed in this randomised, 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).

The study will be double-blind, double-dummy, to minimize the risk of bias in either direction.

3.2.2 Study doses and control groups

Many elderly 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 usually indicated. Sulphonylureas are commonly used as add-on therapy in patients with inadequate glycaemic control on metformin monotherapy and are the current standard therapy in the treatment of type 2 diabetes. Glycaemic efficacy is similar across sulphonylurea agents, and glimepiride was chosen as it is a commonly used sulphonylurea agent and is considered to result in less hypoglycaemia, compared to earlier generations (Campbell et al 1998; Davis 2004; Dills et al 1996; Draeger et al 1996). Glimepiride is also widely used in the EU.

The dose of saxagliptin used in the study is 5 mg, as this is the recommended dose in patients with a CrCl above 60 ml/min. The dose of 5 mg 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-naive patients with type 2 diabetes. In this Phase II study, maximal decrease in both HbA_{1c} as well as in FPG was seen with 5 mg of saxagliptin. Comparable decreases were seen with 5, 10, 20, and 40 mg saxagliptin.

In the Phase IIb dose-ranging study, administration of saxagliptin 5 mg was associated with significant inhibition of plasma dipeptidyl peptidase 4 (DPP-4) activity at the trough of the dosing interval as well as clinically meaningful decreases in HbA_{1c}, fasting serum glucose and postprandial serum glucose. The results from the short-term periods of the Phase III studies confirmed clinically meaningful benefits of saxagliptin 5 mg on HbA_{1c}, as well as FPG, postprandial glucose, insulin, C-peptide, and glucagon levels. A greater percentage of subjects treated with saxagliptin achieved target glycaemic goals including HbA_{1c} levels <7%, compared to subjects treated with placebo or active comparator. The saxagliptin 5 mg groups generally achieved greater reductions from baseline in HbA_{1c} than the saxagliptin 2.5 mg groups. There was no consistent evidence for an incremental efficacy benefit for 10 mg beyond that seen for the 5 mg dose. In the monotherapy (CV181011) and add-on combination therapy with metformin (CV181014) studies, where data was available for up to 102 weeks, treatment with saxagliptin, at all doses tested, produced sustained reductions in HbA_{1c} relative to control.

The dose regimen and titration procedure for glimepiride are according to clinical practice and the approved label. 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 might bring more elderly patients at HbA_{1c} goal without hypoglycaemia, compared to glimepiride as add-on to metformin therapy.

3.2.3 Study duration

After screening, a 2-week enrolment period will follow to allow assessment of inclusion/exclusion criteria. A 2-week single-blinded (to the patient) placebo lead-in period will allow for a check of patient compliance to study routines.

The 52-week duration of the double-blind treatment with saxagliptin was chosen to address regulatory needs for data on efficacy and safety in elderly patients. It is also an opportunity to be able to better differentiate saxagliptin versus a sulphonylurea, as it is generally considered that there is a higher risk of secondary failure with sulphonylurea over time.

3.2.4 Choice of outcome variables

While HbA_{1c} is traditionally used as a primary endpoint in these types of clinical trials, it was felt that a primary endpoint that would be including both HbA_{1c} and hypoglycaemia (confirmed or severe) would be more appropriate, as the clinical treatment decision ultimately takes into account those two factors in real practice. HbA_{1c} is also a recommended efficacy variable in regulatory diabetes guidelines. As a member of DPP-4 inhibitors, saxagliptin leads to enhanced glucose dependent insulin secretion: low risk of hypoglycaemia and minimal weight gain may be expected. As a result, the present study will be examining other secondary efficacy outcome variables: weight, ß-cell function measured by HOMA-β. It is believed that saxagliptin treatment may protect and/or promote pancreatic ß-cell function, hence the saxagliptin therapy may be more durable and patients may have a better insulin secretion over time compared to glimepiride as an add-on therapy to metformin.

3.2.5 Choice of study population

The study population was selected to balance demands on representation of the future elderly patient population and limit bias caused by confounding factors. The prevalence of type 2 diabetes increases with age, and one of the goals of the present study is to also obtain additional efficacy and safety data with saxagliptin in patients ≥75 years of age. To ensure that a minimum number of patients ≥75 years of age will be randomised, a stratification with 40% of the study population ≥75 years will be performed.

In order to ensure that the study population is representative of the future target population, the limit for HbA_{1c} is set to ≥7% to ≤9% (value from the enrolment visit). The HbA_{1c} 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, ≥7%) reflects most treatment guidelines (Nathan et al 2009; Ryden et al 2007). The upper

bound of this interval (ie, ≤9%) is a commonly used and accepted value, employed in studies of patients with diabetes.

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 HbA_{1c} analyses), or to exclude patients whose safety could be compromised by participation in the study.

4. PATIENT SELECTION CRITERIA

Patient population should be selected without bias.

Investigator(s) should keep a record, the patient screening log, of patients who enter pre-study screening.

Each patient should meet all of the inclusion criteria and none of the exclusion criteria to be eligible for this study. Under no circumstances can there be exceptions to this rule.

4.1 Inclusion criteria

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

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

2. Established clinical diagnosis of type 2 diabetes.

3. Men or women who are ≥65 years of age at time of consenting upon Visit 1.
   NB: The cohorts will be approximately 60% of the patients for age group 65 to 75 years and 40% for age-group ≥75 years. The enrolment to the cohorts will be stopped when the number of patients is reached.

4. Treatment with a stable metformin monotherapy, at any dose, for at least 8 weeks prior to Visit 1.

5. HbA_{1c} ≥7.0% and ≤9.0%.

4.2 Exclusion criteria

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

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

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

3. Current use of any injectable or oral antihyperglycaemic agent excluding metformin.

4. Treatment with any additional oral or injectable antihyperglycaemic agent within 8 weeks prior to Visit 1.

5. Renal impairment as defined by a creatinine clearance <60 mL/min (using the Modification of Diet in Renal Disease [MDRD] equation), as well as patients with End Stage Renal Disease (ESRD) on haemodialysis;

   $CrCl\ (ml/min/1.73\ m^2)=175x(SCr)^{-1.154}x(age)^{-0.203}x(0.742\ if\ female)x(1.21\ if\ African\ American)$

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, eg, carbamazepine, dexamethasone, phenobarbital, phenytoin, rifampin and St. John's Worth.

8. Past history of intolerance, allergy or hypersensitivity to glimepiride, other sulphonylureas or sulphonamides.

9. Past hypersensitivity reaction to a DPP-4 inhibitor.

10. Contraindications to therapy as outlined in the saxagliptin Investigator's Brochure.

11. Contraindications to therapy as outlined in the glimepiride package insert.

12. Contraindications to therapy as outlined in the metformin package insert, including conditions leading to an increased risk of hypoxaemia and lactic acidosis.

13. History of haemoglobinopathies (sickle cell anaemia or thalassemias, sideroblastic 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 AstraZeneca and Bristol-Myers Squibb personnel and study centre personnel).

16. Participation in a clinical study testing a medication during the last 3 months prior to Visit 1.

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

18. Important cognitive function problems.

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

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

Additional exclusion criteria at Visit 2:

21. Active liver disease and/or significant abnormal liver function defined as aspartate aminotransferase (AST) >3x upper limit of normal (ULN) and/or alanine aminotransferase (ALT) >3xULN and/or total bilirubin >34 µmol/L (>2.0 mg/dL).

22. Creatine kinase (CK) >10xULN.

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

Additional exclusion criteria at Visit 3:

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

Procedures for withdrawal of incorrectly enrolled patients, see Section 5.3.

5. STUDY CONDUCT

5.1 Restrictions during the study

There are no restrictions on patients participating in this study with regards to diet, smoking, 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 5.6.

5.2 Patient enrolment, randomisation and initiation of investigational product

The Principal investigator will:

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

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

3. Determine patient eligibility, see Sections 4.1 and 4.2.

4. Assign eligible patient a unique randomisation number.

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

If patients have discontinued their participation in the study, then they cannot re-enter into the study.

5.2.1 Procedures for randomisation

Randomisation to investigational products will be done via Interactive Web Response System (IWRS) at Visit 3 in balanced blocks in order to ensure approximate balance between the two treatment arms.

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

The IWRS will sequentially allocate the investigational products through the AstraZeneca prepared randomisation scheme and provide the randomisation number and the appropriate bottle numbers from investigational products available at the study centre. The study statistician requests the randomisation scheme to be generated using the Grand system at AstraZeneca.

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

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

Where patients that do not meet the selection criteria are randomised in error or incorrectly started on investigational products, or where patients subsequently fail to meet the study criteria post-initiation, a discussion should occur between the AstraZeneca Study Team Physician and the investigator regarding whether to continue or discontinue the patient from investigational products. If a patient is dispensed with a wrong investigational product, the patient should continue to take the medication with no attempt to correct the error. The IWRS company will be informed, if possible.

The AstraZeneca Study Team Physician is to ensure that all such decisions are appropriately documented. In situations where an agreement cannot be reached, the patient should have the treatment with investigational products stopped.

5.4 Blinding and procedures for unblinding the study

5.4.1 Methods for ensuring blinding

Using double-dummy technique will ensure the blinding of the investigational products during the double-blinded treatment period of the study. All packaging of active tablets/capsules and the respective placebo tablets/capsules will be identical in size, colour, smell, and taste. The bottles containing investigational products will be packed into patient kits and the bottles and kits will be labelled with unique identification numbers allocated from the IWRS.

No member of the study delivery team at AstraZeneca or Bristol-Myers Squibb, personnel at study centres or any CRO handling data will have access to the randomisation scheme during the conduct of the study, with the exception of the AstraZeneca personnel generating the randomisation scheme and the CRO company providing the IWRS and carrying out the packaging and labelling of investigational products.

5.4.2 Methods for unblinding the study

Individual treatment codes, indicating the treatment randomisation for each randomised patient, will be available to the investigator(s) from the IWRS. Routines for this will be described in the IWRS user manual that will be provided to each study centre.

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 Pharmacovigilance Department, Bristol-Myers Squibb. If a patient is admitted for an emergency to a clinic that is not participating in the study, AstraZeneca will have an external provider for an unblinding service, 24 hours per day, 7 days a week.

The treatment code should not be broken except in medical emergencies when the appropriate management of the patient requires knowledge of the randomised treatment. The investigator documents and reports the action to AstraZeneca, without revealing the treatment given to patient to the AstraZeneca study personnel. Patients, whose double-blind treatment codes are broken, should be discontinued from the study as soon as possible.

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

Treatment codes will not be broken for the planned analyses of data until all decisions on the evaluability of the data from each individual patient have been made and documented.

5.5 Treatments

5.5.1 Identity of investigational product(s)

The following investigational products and matching placebo will be used in the study:

Investigational product	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
Glimepiride	Opaque grey, two-piece, hard gelatine capsule containing glimepiride tablet, 1, 2 or 4 mg	Commercial glimepiride manufactured by Sanofi-Aventis and encapsulated by CRO/External Provider
Placebo for glimepiride	Opaque grey, two-piece, hard gelatine capsule to match the encapsulated glimepiride tablet	CRO/External Provider

The investigational products contain lactose, which may cause discomfort in lactose-intolerant individuals.

5.5.2 Doses and treatment regimens

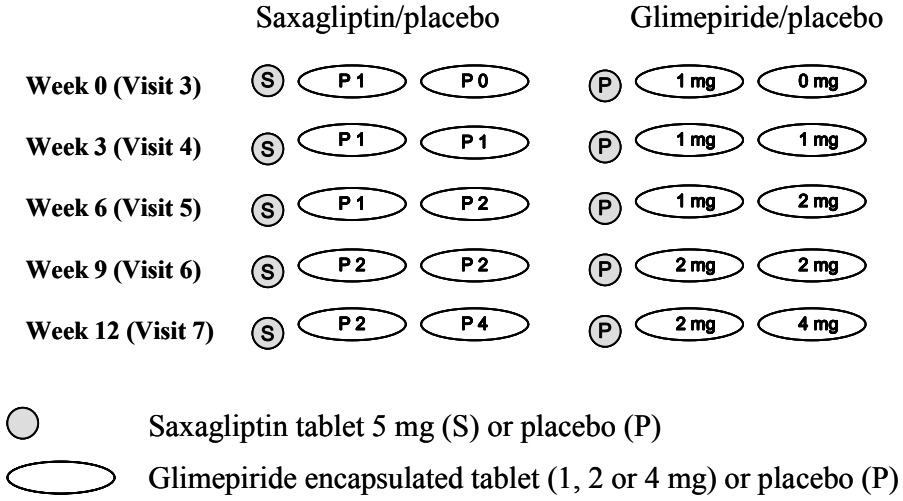
The blinding of the investigational products is ensured by using double-dummy technique. The investigational products saxagliptin or placebo and glimepiride or placebo will be taken orally once daily, immediately before or together with breakfast.

Patients should be instructed to abstain from all food for 8 hours prior to each visit; drinking water is allowed. The investigational products should not be taken in the morning prior to any of the visits, but acceptable concomitant medications can be taken with water only.

The following investigational products/matching placebo and doses will be used:

- Saxagliptin tablet, 5 mg, oral, once daily, for the double-blind treatment period.
- Glimepiride encapsulated oral tablet (1, 2 or 4 mg), dosing 1 to 6 mg, for the double-blind treatment period. The starting dose for glimepride will be 1 mg once daily, as recommended in the product monograph. The dose will be increased slowly at three-week intervals to 2 mg, 3 mg, 4 mg and 6 mg (maximal dose), to reach optimal effect, based on glycaemic control (FPG ≤6.1 mmol/L or ≤110 mg/dL). It will be possible to lower the dose during the study due to hypoglycaemia.

- Matching placebo tablet for saxagliptin 5 mg, oral, once daily, for the 2-week placebo lead-in period and the double-blind treatment period.
- Matching placebo encapsulated oral tablet for glimepiride for the 2-week placebo lead-in period and the double-blind treatment period.



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

- One bottle containing 35 tablets of placebo to match saxagliptin and one bottle containing 35 capsules of placebo to match glimepiride.

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

- One bottle containing 35 tablets of saxagliptin 5 mg and 2 bottles containing 35 capsules of placebo to match glimepiride,

or

- One bottle containing 35 tablets of placebo to match saxagliptin and 2 bottles with 35 capsules of glimepiride 1, 2 or 4 mg, or placebo.

During the titration period, the patients will titrate either active or placebo glimepiride.

For treatment doses of saxagliptin and glimepiride, and for titration procedures of glimepiride, see Section 3.1.

5.5.3 Labelling

Packaging and labelling

Packaging of the investigational products in bottles and the labelling will be carried out by an external provider. The bottles will be labelled with booklets. Labels will be prepared in accordance with Good Manufacturing Practice (GMP) and local regulatory guidelines. The labels will fulfil GMP Annex 13 requirements for labelling. Label text will be translated into local language.

5.5.4 Storage

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

The dispensing and retention of reserve samples of investigational products will be performed with the FDA Code of Federal Regulations 21, Part 320, Bioavailability and Bioequivalence requirements.

5.6 Concomitant and post-study treatment(s)

Other medication than described in Exclusion Criteria, Section 4.2 and Discontinuation of investigational products, Section 5.8, 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) and recorded in the appropriate sections of the electronic Case Report Form (eCRF). The specific type of medication (trade or generic name), the reason for therapy, route of administration and the dates for start and stop of treatment should be reported. For metformin, and if applicable, for other antihyperglycaemic medication, the total daily dose should also be recorded.

Post-study treatment will be given at the discretion of the investigator.

5.7 Treatment compliance

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

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

5.7.1 Accountability

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

The study centre personnel will account for all investigational products dispensed to and returned from the patient, and record data into the eCRF.

AstraZeneca personnel will account for all investigational products received at the study centre, unused investigational products and for appropriate destruction. Certificates of delivery, destruction and return should be signed.

5.8 Discontinuation of investigational products

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

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

Study specific discontinuation criteria are listed below.

1. Use of (need for) additional antihyperglycaemic medication other than investigational products more than 14 consecutive days, however insulin for up to 7 days during hospitalisation is allowed as long as the primary reason for hospitalisation is not management of the patient's glycaemic control.
2. Treatment with glucocorticoids equivalent to oral prednisolone >10 mg/day (two temporary periods but no longer than 7 days each are allowed).
3. Major (or severe) and/or frequent hypoglycaemic events, defined as ≥1 major event or recurring mild or moderate events and the possibility of down titration and contributing factors (eg, excessive physical activity) has been evaluated.
4. Patients whose individual treatment codes are broken by the investigator.
5. FPG >15.0 mmol/L (>270 mg/dL), for at least 2 weeks, during the period from Visit 3 (Week 0) to Visit 5 (Week 6), confirmed by repeated measurements at the central laboratory.
6. FPG >13.3 mmol/L (>240 mg/dL), for at least 2 weeks, during the period from Visit 5 (Week 6) to Visit 7 (Week 12), confirmed by repeated measurements at the central laboratory.

7. FPG >12.2 mmol/L (>220 mg/dL), for at least 2 weeks, during the period from Visit 7 (Week 12) to Visit 11 (Week 52), confirmed by repeated measurements at the central laboratory.
8. HbA_{1c} ≥8.0% at Visit 7 (Week 12), Visit 8 (Week 24), Visit 9 (Week 32) or Visit 10 (Week 40), confirmed at a repeated measurement within 5 days. The HbA_{1c} values will be measured at the central laboratory.
9. Calculated CrCl <60 ml/min or an increase in serum creatinine of ≥44.2 µmol/L (≥0.5 mg/dL) above the baseline value confirmed at a repeated measurement within one week.
10. CK >10x ULN, confirmed at a repeated measurement within 24 hours.
11. Increase of ALT and/or AST >3x ULN and increase of TB ≥1.5x ULN, confirmed at a repeated measurement within one week.
12. Increase of ALT or AST >5x ULN, confirmed at a repeated measurement within one week.
13. Haemoglobin ≤9.0g/dL.
14. Intravascular administration of iodinated contrast agents. Since intravascular administration of iodinated contrast agents in radiologic studies can lead to renal failure, metformin should be temporarily stopped prior to, or at the time of the test and not reinstituted until 48 hours afterwards, and only after renal function has been re-evaluated and found to be normal. Metformin should also be temporarily stopped 48 hours before elective surgery with general anaesthesia and should not be resumed earlier than 48 hours afterwards.

5.8.1 Procedures for discontinuation of a patient from investigational products

A patient that decides to discontinue the investigational products will always be asked about the reason(s) and the presence of any AEs. If possible, they will be seen and assessed according to procedures as in Visit 11 and the eCRF will be completed. AEs will be followed up (See Sections 6.4.3 and 6.4.4); diaries and the investigational products should be returned by the patient.

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

5.9 Withdrawal from study

Patients are at any time free to withdraw from study (investigational products and assessments), without prejudice to further treatment (withdrawal of consent). Such patients will always be asked about the reason(s) and the presence of any AEs. If possible, they will be seen and assessed according to procedures as in Visit 11 and the eCRF will be completed. AEs will be followed up (See Sections 6.4.3 and 6.4.4); diaries and the investigational products should be returned by the patient.

A patient withdrawn from the study will not be replaced.

6. COLLECTION OF STUDY VARIABLES

6.1 Recording of data

The Web Based Data Capture (WBDC) system (Rave from Medidata) will be used for data collection and query handling. Trained study centre personnel will be responsible for entering data specified in the protocol into the WBDC system and according to the eCRF Instructions. The investigator will ensure that data are recorded on the eCRFs as specified in the study protocol and in accordance with the instructions provided.

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

6.2 Data collection and enrolment

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

- Date of signed informed consent.
- Inclusion and exclusion criteria.
- Demography: Date of birth, sex and race.
- Laboratory assessments.
- Medical history, including information about: general medical history, surgical history, lifestyle (tobacco, alcohol, exercise), family history, specific disease history.
- Physical examination, see Section 6.4.6.
- Vital signs (blood pressure, pulse rate), see Section 6.4.8.
- Height, weight and waist circumference, see Section 6.4.8.
- A 12-lead ECG, see Section 6.4.7.
- Prior and concomitant medication.

6.2.1 Follow-up procedures

Which follow-up procedures and when to be assessed are explained in the Study Plan, Table 1. Randomised patients who do not complete the entire study should complete the procedures described for Visit 11.

Unresolved AEs will be followed up according to Section 6.4.3.

6.3 Efficacy

The baseline is defined as the assessment at randomisation visit (Visit 3).

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.

6.3.1 Efficacy laboratory variables

The laboratory variables that will be measured to assess efficacy, and at which visits to be measured, are shown in Table 2. These variables will be assessed at a central laboratory. For information on methods of collection, assessment, labelling, storage and shipment of samples, see the Laboratory Manual.

Table 2 Efficacy laboratory variables

Visit number	**S**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**
Study Week	**-6**	**-4**	**-2**	**0**	**3**	**6**	**9**	**12**	**24**	**32**	**40**	**52**
HbA_{1c}	X			X				X	X	X	X	X
FPG[a]				X	X	X	X	X	X	X	X	X
Insulin[a]				X					X			X
TC, LDL-C, HDL-C, TG[a]				X					X			X

a. Fasting

Patients should be instructed to abstain from all food for 8 hours prior to each visit; drinking water is allowed. The investigational products should not be taken in the morning prior to any of the visits, but acceptable concomitant medications can be taken with water only.

Fasting plasma glucose will for the duration of the study be measured at the study center, using a glucose analyser (HemoCue®) provided by AstraZeneca. For information on methods for collection and assessment of samples, see the manual provided by the manufacturer.

6.4 Safety

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

6.4.1 Definition of adverse events

An Adverse Event (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, electrocardiogram). In clinical studies, an AE can include an undesirable medical condition occurring at any time, including run-in or washout periods, even if no study treatment has been administered.

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

6.4.2 Definitions of serious adverse event

A serious adverse event (SAE) is an AE occurring during any study phase (ie, enrolment, lead-in, titration and maintenance treatment periods), 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

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

SAEs related to bone fracture, skin lesions, infection, lymphocytopenia, thrombocytopenia and symptomatic hand and foot oedema should be given special attention. Regarding bone fractures is should include both non-serious and serious events. Supplemental paper CRF are to be completed by the study investigators for these specific AEs/SAEs.

For the purposes of regulatory reporting, the following events/medical conditions should be reported as described in Section 6.4.4, in the same timelines as SAEs regardless of whether the event/medical condition is classified as serious or non-serious:

- Pancreatitis
- Opportunistic infections (eg, tuberculosis, Herpes zoster, cytomegalovirus, Pneumocystis jirovecii, etc)

Serum AST or ALT greater than or equal to 3 times ULN concomitant with serum total bilirubin greater than 2 times ULN or evidence of jaundice.

6.4.3 Recording of adverse events

6.4.3.1 Time period for collection of adverse events

Adverse Events will be collected from randomization at Visit 3 throughout the double-blind treatment period until and including the last contact, Visit 11.

Serious Adverse Events will be collected from the signature of informed consent throughout the treatment period until and including the last contact, Visit 11.

6.4.3.2 Adverse event 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.

6.4.3.3 Variables

The following variables will be collect for each AE;

- AE (verbatim)
- Date when AE started and stopped
- Maximum intensity, mild, moderate, severe, very severe
- Whether AE is serious or not
- Investigator causality rating against the investigational products (yes or no)
- Action taken with regard to investigational product
- AE caused patient's withdrawal from study *(*yes or no*)*
- Outcome

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

- Date AE met criteria for SAE
- Date investigator became aware of SAE
- AE is serious due to
- Date of hospitalisation
- Date of discharge
- Probable cause of death
- Date of death

- Autopsy performed
- Causality assessment in relation to Study procedure(s)
- Causality assessment in relation to Other medication
- Description of AE

If the intensity of an AE changes, only the maximum intensity of the event will be recorded.

Intensity is defined as one of the following:

- Mild: Awareness of event, but easily tolerated
- Moderate: Discomfort enough to cause some interference with usual activity
- Severe: Inability to carry out usual activity
- Very severe: Debilitating, significantly incapacitates patient despite symptomatic therapy

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria in Section 6.4.2. An AE of severe intensity need not necessarily be considered serious. For example, nausea that persists for several hours may be considered severe nausea, but not a SAE. On the other hand, a stroke that results in only a limited degree of disability may be considered a mild stroke but would be a SAE.

6.4.3.4 Causality collection

The investigator will assess causal relationship between investigational products and each AE, and answer “yes” or “no” to the question “Do you consider that there is a reasonable possibility that the event may have been caused by the investigational products?” If there is any valid reason, even if undetermined or untested, for suspecting a possible cause-and-effect relationship between the investigational products and the occurrence of the AE, then this 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 causal relationship will also be assessed for other medication and study procedures. Note that for SAEs that could be associated with any study procedure the causal relationship is implied as “yes”.

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

6.4.3.5 Adverse events based on signs and symptoms

All AEs spontaneously reported by the patient or reported in response to the open question from the study personnel: “Have you had any health problems since the previous visit?”, or revealed by observation will be collected and recorded in the eCRF. When collecting AEs,

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

6.4.3.6 Adverse events based on examinations and tests

The results from protocol mandated laboratory tests and vital signs will be summarised in the clinical study report (CSR). Deterioration as compared to baseline in protocol-mandated laboratory values, vital signs and other safety variables should therefore only be reported as AEs if they fulfil any of the SAE criteria or are the reason for discontinuation of treatment with the investigational products or meet the requirements for regulatory reporting, as described in Section 6.4.2.

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

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

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

6.4.3.7 Disease progression

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

6.4.3.8 Follow-up of unresolved adverse events

Any AEs that are ongoing at the end of the study (Visit 11) or at discontinuation, will be followed up until resolution by the investigator or until the investigator decides that no further follow-up is necessary, but without further recording in the eCRF. AstraZeneca retains the right to request additional information for any patient with ongoing AEs/SAEs at the end of the study, if judged necessary. The requirement to follow-up is not intended to delay database lock or production of the clinical report. Both these activities should proceed as planned with ongoing AEs if necessary.

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

6.4.3.9 Adverse event reported after the end of treatment

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

6.4.3.10 Reporting of hypoglycaemic events

Hypoglycaemic events (see Section 6.4.9) should be reported in a separate "Hypoglycaemic Adverse Event module" section in the eCRF. Hypoglycaemic events are considered non-AE in this protocol by the nature of the primary endpoint selected for the present study.

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

6.4.4 Reporting of serious adverse events

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

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

The designated AstraZeneca representative works with the investigator to ensure that all relevant information is provided to Bristol-Myers Squibb Global Pharmacovigilance & Epidemiology **within one calendar day** of initial receipt for all SAEs. The AstraZeneca representative will notify the appropriate Bristol-Myers Squibb Pharmacovigilance contact to ensure regulatory compliance.

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

The reference document for definition of expectedness/listedness is the Investigator Brochure for the investigational product, and the EU Summary of Product Characteristics (SPC) for the active comparator product (including any AstraZeneca comparator).

6.4.4.1 Serious adverse event handling using Web Based Data Capture Rave

Serious Adverse Event (SAE) information will be entered and submitted into the Web Based Data Capture (WBDC) system Rave (Medidata) 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. AstraZeneca representative will send a completed SAE report to the appropriate Bristol-Myers Squibb Pharmacovigilance representative via fax or e-mail.

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

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

6.4.5 Laboratory safety assessment

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

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

Table 3 Safety laboratory variables

Visit number	**S**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**
Study Week	**-6**	**-4**	**-2**	**0**	**3**	**6**	**9**	**12**	**24**	**32**	**40**	**52**
Haematology												
Haemoglobin		X							X			X
Haematocrit		X							X			X
Red blood cell count		X							X			X
White blood cell count and differential		X							X			X
Platelet count		X							X			X
Clinical chemistry												
Aspartate Aminotransferase (AST)		X							X			X
Alanine Aminotransferase (ALT)		X							X			X
Alkaline Phosphatase		X							X			X
Creatine Kinase (CK)		X							X			X
Total Bilirubin (TB)		X							X			X

Table 3 Safety laboratory variables

Visit number	**S**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**
Study Week	**-6**	**-4**	**-2**	**0**	**3**	**6**	**9**	**12**	**24**	**32**	**40**	**52**
Total Protein		X							X			X
Albumin		X							X			X
Blood Urea Nitrogen (BUN)		X							X			X
Electrolytes: - Sodium - Potassium - Chloride		X							X			X
TSH[a]		X										
Serum Creatinine (SCr)[b]		X							X			X
Urinalyses												
pH		X							X			X
Protein[c]		X							X			X
Glucose		X							X			X
Leukocyte esterase[c]		X							X			X
Blood by dipstick[c]		X							X			X
Albumin:creatinine ratio		X							X			X

a. If abnormal, reflex to free T4
b. Creatinine clearance (CrCl) will be estimated by the method of MDRD (Levey et al 1999)
c. Microscopy if dipstick positive for protein, leukocyte esterase or blood

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

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

For blood volume, see Section 7.1

6.4.6 Physical examination

The physical examination includes the following: General appearance, lymph nodes, thyroid, cardiovascular, lungs, abdomen, reflexes, musculoskeletal and extremities. Baseline data is collected at Visit 1, and findings are entered into the eCRF. New findings at the physical examination at Visit 11 are recorded as change from baseline.

The brief physical examination includes: General appearance, cardiovascular, lungs, abdomen and extremities to verify the findings from the physical examination at baseline and will be performed at Visit 3, and the eCRF will be completed.

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

6.4.7 ECG

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

ECG will be assessed at Visit 1 and Visit 11.

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

6.4.8 Other variables

Other variables will be assessed following the Study Plan and Time Schedule outlined in Section 3.1, and results are entered into the eCRF.

Blood pressure and pulse rate

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

Weight and height

The patient's weight will be recorded in kilogram (kg) on a fasting stomach with light clothing and no shoes. The patient's height will be recorded (at Visit 1) in centimetres, with no shoes.

Waist circumference

The waist should be measured (in centimetres) in the morning before breakfast in the standing position at the natural waist (smallest waist circumference). If there is no natural waist, the measurement should be made at the level of the umbilicus.

6.4.9 Hypoglycaemic events

The patient will be asked always to self-monitor plasma glucose for symptoms suggestive of hypoglycaemia and to register if a finger-stick value was obtained and the glucose value in the supplied patient diary for hypoglycaemic events (see Section 6.5.2, 6.5.1).

A hypoglycaemic event can be either

- An event with symptoms and confirmed low glucose
- An event with low glucose
- An event 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 (CPMP) guidance on clinical investigation of medicinal products in the treatment of diabetes mellitus, and slightly adapted taking into consideration recent recommendations from the ADA Workgroup on Hypoglycaemia (Diabetes Care, 2005, 28, 1245) for severe hypoglycaemias:

- Confirmed hypoglycaemic event, defined as either a symptomatic event with plasma glucose level <3.0 mmol/L (<54 mg/dL), and no need for external assistance, or an asymptomatic plasma glucose measurement <3.0 mmol/L (<54 mg/dL).
- Major (or severe) hypoglycaemic event, defined as a symptomatic event requiring external assistance due to severe impairment in consciousness or behaviour, with or without plasma glucose level <3.0 mmol/L (<54 mg/dL), and prompt recovery after glucose or glucagon administration. These events may be associated with sufficient neuroglycopenia to induce seizure or coma. Plasma glucose measurements may not be available during such an event, but neurological recovery attributable to the restoration of plasma glucose to normal is considered sufficient evidence that the event was induced by a low plasma glucose concentration.
- Mild or moderate hypoglycaemic events where plasma glucose measurement is not available will be considered suggestive of hypoglycaemia but will not be considered in the evaluation of the primary endpoint of the present study.

Plasma glucose values will be obtained from the central laboratory and when using the glucometers provided by AstraZeneca.

Data to be collected for each hypoglycaemic event:

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

- Intervention needed for recover, maximal intensity, action taken, causality and possible contributing factors
- Action taken with investigational products

All hypoglycaemic events reported by the patient in the Patient diary for hypoglycaemic events should be recorded in the Hypoglycaemic Adverse Event Module (HYPAE), regardless of measured glucose value.

The patient's diaries will be reviewed and data regarding hypoglycaemic events transcribed into the "Hypoglycaemic Adverse Event Module" in the eCRFs at each visit. New diaries for the next period will be handed over to the patient. If a major hypoglycaemic event occurs, or more than one mild or moderate since last visit, the patient should contact the investigator. For reporting of hypoglycaemic events/symptoms suggestive of hypoglycaemic events as AEs, see Section 6.4.3.10.

6.5 Patient reported outcomes (PRO)

6.5.1 Patient Diary for Glucose Measurement and Glucometers

The patients will be provided with a patient diary and a glucometer at Visit 2 to check and register their plasma glucose level at home. The measured value, capillary glucose, is recalculated by the glucometer to show the plasma value. During the lead-in period (Week –2 to Week 0) and titration period (Week 0 to Week 12), the plasma glucose level should be self-monitored at least every second day and the values registered into the patient diary. During the maintenance treatment period (Week 12 to Week 52), the plasma glucose should be monitored and registered into the patient diary at least once a week. The patients should receive instructions on the use of the glucometer, according to the manufacturer's manual.

The glucometer is equipped with a memory which should be reviewed by the study centre personnel at each visit. The patient diary will be collected at each visit and kept in the Investigator Study File, and a new patient diary for the next period will be handed over to the patient.

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

For measurements that are associated with hypoglycaemia events, see below.

6.5.2 Patient Diary for Hypoglycaemic Events

The patient will be asked always to self-monitor plasma glucose for symptoms suggestive of hypoglycaemia, for definition of hypoglycaemia see Section 6.4.9. If a hypoglycaemic event occurs, the following should be recorded in the patient diary: Date of start and stop, time of the day for start, plasma glucose values, and the presence of the following symptoms: sweating, shakiness, pounding heart, hunger, confusion, dizziness/lightheadness, drowsiness,

nausea, headache. If other symptoms occurs, these should also be recorded and specified. It should also be noted if assistance was needed to cope with the event. If a major hypoglycaemic event occurs, or more than one mild or moderate since last visit, the patient should contact the investigator. The patient diary will be collected at each visit and kept in the Investigator Study File, and a new patient diary for the next period will be handed over to the patient.

The study personnel will review the patient diary at each visit and enter data into the "Hypoglycaemic Adverse Events Module" in the eCRF, see Section 6.4.3.10.

6.5.3 Name of PRO questionnaires

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

The PRO questionnaires will be self-administered using paper versions. For further information, see Appendix D, E and F.

The following questionnaires will be administered:

- Diabetes Treatment Satisfaction Questionnaire, status and change versions (DTSQs and DTSQc) (Bradley et al 2002)
- Hypoglycaemia Fear Survey II (HFS-II) worry subscale (Cox et al 1987; Irvine et al 1994; Wild et al 2007)
- EuroQoL-5 Dimension (EQ-5D) (The EuroQoL Group 1990)

6.5.4 Method of assessment of PRO questionnaires

6.5.4.1 Diabetes Treatment Satisfaction Questionnaire (DTSQ)

The DTSQ has been developed to assess patient's satisfaction with treatment and perception of change in hyper- and hypoglycaemia. The DTSQ has two versions, the DTSQ status version (DTSQs) and the DTSQ change version (DTSQc). Both versions have eight items, and differ from each other only in Item 7. The DTSQc instructions and response options differ from those of the DTSQs, as the relative change in satisfaction will be assessed instead of a measure of absolute satisfaction.

The DTSQs will be self-administered and assessed at Visit 3. The DTSQc will be assessed at Visit 8 and Visit 11. The questionnaire will take approximately 5 minutes to answer.

6.5.4.2 Hypoglycaemia Fear Survey (HFS-II) Worry Subscale

The HFS-II worry subscale consists of 18 items, rated by patients using a 5-point Likert scale ranging from 0 (never) to 4 (almost always). Scores are obtained by the sum of all the responses on the worry scale and range from 0 to 72, with 0 representing least worry. Each of

the 18 items will be preceded by the statement 'Because my blood sugar could drop, I worried about …'. There are 18 categories of worry.

The HFS-II will take approximately 10 minutes to complete and will be completed at Visit 3, Visit 8 and Visit 11.

6.5.4.3 EuroQoL-5 Dimension (EQ-5D)

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

The questions (VAS and five dimensions) will take approximately 5 minutes to answer.

The EQ VAS and EQ-5D index will be filled-in at Visit 3, Visit 8 and Visit 11.

6.5.5 Administration of PRO questionnaires

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

6.6 Pharmacokinetics (Not applicable)

6.7 Pharmacodynamics (Not applicable)

6.8 Pharmacogenetics (Not applicable)

6.9 Health economics (Not applicable)

7. BIOLOGICAL SAMPLING PROCEDURES

7.1 Volume of blood

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

Table 4 Volume of blood to be drawn from each patient

Assessment		Sample volume (mL)	No. of samples	Total volume (mL)
Safety[a]	Clinical chemistry	8.5	4	34
Safety[b]	Haematology	4	8	32
Efficacy	FPG	4	9	36
Total				102

a includes the efficacy samples for lipids and insulin
b includes the efficacy samples for HbA_{1c}

7.1.1 Blood and urine samples

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

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

Sample labelling

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

Sample shipment

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

7.2 Handling, storage and destruction of biological samples

The samples will be disposed of after analyses.

7.3 Labelling and shipment of biohazard samples

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

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

7.4 Chain of custody of biological samples

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

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

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

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

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

7.5 Withdrawal of informed consent for donated biological samples

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

As collection of the biological samples is an integral part of the study, then the patient is withdrawn from further study participation.

The Principal investigator:

- Ensures patients` withdrawal of informed consent to the use of donated samples is notified immediately to AstraZeneca
- Ensures that biological samples from that patient, if stored at the study centre, are immediately identified, disposed of/destroyed, and the action documented

- Ensures the laboratory(ies) holding the samples is/are informed about the withdrawn consent immediately and that samples are disposed of/destroyed, the action documented and the signed document returned to the study centre
- Ensures that the patient and AstraZeneca are informed about the sample disposal

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

8. ETHICAL AND REGULATORY REQUIREMENTS

8.1 Ethical conduct of the study

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

8.2 Patient data protection

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

8.3 Ethics and regulatory review

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

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

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

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

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

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

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

AstraZeneca will provide Regulatory Authorities, Ethics Committees and Principal investigators with safety updates/reports according to local requirements.

8.4 Informed consent

The Principal investigator(s) at each study centre will:

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

8.5 Changes to the protocol and informed consent form

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

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

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

AstraZeneca will distribute any subsequent amendments and new versions of the protocol to each Principal investigator(s). For distribution to Ethics Committee see Section 8.3.

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

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

8.6 Audits and inspections

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

9. STUDY MANAGEMENT BY ASTRAZENECA

9.1 Pre-study activities

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

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

9.2 Training of study site personnel

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

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

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

9.3 Monitoring of the study

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

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

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

9.3.1 Source data

For location of source data, see Clinical Study Agreement.

9.4 Study agreements

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

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

9.4.1 Archiving of study documents

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

9.5 Study timetable and end of study

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

The study is expected to start in Q4 2009 and to end by Q3 2012.

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

10. DATA MANAGEMENT BY ASTRAZENECA

Data management will be performed by AstraZeneca personnel at the Swedish AstraZeneca Marketing Company.

Recording of data, see Section 6.1. 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 are tracked to provide an audit trail. When data has been entered, reviewed and edited and when Source Data Verification has been performed, the investigator will electronically sign the eCRF. The data will then be frozen to prevent further editing. After final validation has been performed and the study data has been locked, a copy of the eCRF will be provided to the study centre for archiving.

Patient Reported Outcomes questionnaires and data from patient diaries (glucose measurements and hypoglycaemic events) are collected on paper and will be entered into the WBDC system by study centre personnel.

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

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

The data will be verified and validated as defined in the Data Management Plan. Quality control procedures will be applied to each stage of data handling to ensure that all data are reliable and have been processed correctly.

AEs and medical/surgical history will be classified according to the terminology of the latest version of MedDRA. Medications will be classified according to the AstraZeneca Drug Dictionary (AZDD). All coding will be performed by personnel at the Swedish AstraZeneca Marketing Company.

Data verification and validation will be performed. Data queries will be raised in the WBDC system for inconsistent, impossible or missing data. The investigator should answer any queries raised by AstraZeneca in accordance with timelines specified in the Clinical Study Agreement, and query resolutions will be saved in the central database. All entries to the study database will be available in an audit trail. Prior to breaking the treatment codes, all decisions on the availability of the data from each individual patient must have been made and documented. When all data have been coded, validated, signed and locked, clean file will be declared. Any treatment revealing data may thereafter be added and the final database will be locked. The Study Delivery Team at AstraZeneca will document the date of clean file and database lock.

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

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.

11. EVALUATION AND CALCULATION OF VARIABLES BY ASTRAZENECA

11.1 Calculation or derivation of efficacy variable(s)

11.1.1 Baseline and change from baseline

Baseline is defined to be Visit 3 (randomisation). Change from baseline will be calculated as absolute difference between the value measured at or derived for a specific time point after baseline minus baseline value.

11.1.2 Homeostasis Model Assessment-β-cell function (HOMA-β)

HOMA-ß as the measurement of β-cell function will be calculated according to Wallace et al 2004.

11.1.3 Last Observation Carried Forward (LOCF)

The last observation carried forward approach will be applied to exploratory continuous endpoints only. This means that for a specific time-point post-baseline, analyses will be based on measurements available at that time-point or the last post-baseline measurement prior to the time-point, if no measurement is available at that time-point.

11.2 Calculation or derivation of safety variable(s)

11.2.1 Derivation or calculation of outcome variables

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

11.2.2 Other significant adverse events

During the evaluation of the AE data, an AstraZeneca medically qualified expert will review the list of AEs that were not reported as SAEs and DAEs (Discontinuation due to Adverse Event). Based on the expert's judgement, significant AEs of particular clinical importance may, after consultation with the Global Patient Safety Physician, be considered OAEs (Other significant Adverse Events) and reported as such in the CSR.

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

11.2.3 Definition of hypoglycaemic events

The hypoglycaemic event considered in the primary endpoint will be a composite endpoint of confirmed hypoglycaemia (any severity) as well as major (or severe) hypoglycaemias (with or without confirmed low glucose value) using the following definitions:

Confirmed hypoglycaemia: any events defined as either a symptomatic event with blood glucose level <3 mmol/L (<54 mg/dL) and no need for external assistance, or an asymptomatic blood glucose measurement <3 mmol/L (<54 mg/dL).

Major (or severe) hypoglycaemia: symptomatic events requiring external assistance due to severe impairment in consciousness or behaviour, with or without blood glucose level <3 mmol/L (<54 mg/dL), but with prompt recovery after glucose or glucagon administration. These events may be associated with sufficient neuroglycopenia to induce seizure or coma. Plasma glucose measurements may not be available during such an event, but neurological recovery, attributable to the restoration of plasma glucose to normal, is considered sufficient evidence that the event was induced by a low plasma glucose concentration.

N.B.: Mild or moderate hypoglycaemic events where blood glucose measurement is not available will be considered suggestive of hypoglycaemia but will not be considered in the primary endpoint. (Draft Guidance from FDA (February 2008), EMEA Diabetes Guidance document 2002))

11.2.4 Baseline and change from baseline

Baseline is defined to be Visit 1 for safety variables. Change from baseline will be calculated as absolute difference between the value measured at or derived for a specific time point after baseline minus baseline value.

11.3 Calculation or derivation of patient reported outcome variables

Method of assessment and purposes of patient reported outcomes (PRO) variables are presented in Section 6.5.4.

11.3.1 Diabetes Treatment Satisfaction Questionnaire (DTSQ)

In the DTSQs, the individual satisfaction with treatment items (1, 4, 5, 6, 7 and 8) are rated 6 (very satisfied, convenient, flexible etc) to 0 (very dissatisfied, inconvenient, inflexible etc) and added up to a Treatment Satisfaction score (range 0-36). The higher the score, the greater the satisfaction with treatment.

'Perceived frequency of hyperglycaemia' (Item 2) and 'Perceived frequency of hypoglycaemia' (Item 3) are rated 6 (most of the time) to 0 (none of the time). Lower scores indicate levels closer to the ideal and higher indicate problems.

These scores from the DTSQs, assessed at Visit 3, will be presented.

In the DTSQc, the individual satisfaction with treatment change items (1, 4, 5, 6, 7 and 8) are rated +3 (improvement) to –3 (deterioration) and added up to a Treatment Satisfaction (change) score (range +18 to –18). The higher (lower) the score, the greater the improvement (deterioration) in satisfaction with treatment. A score of 0 represents no change.

'Perceived frequency of hyperglycaemia' (Item 2) and 'Perceived frequency of hypoglycaemia' (Item 3) are rated +3 ('much more of the time now') to –3 ('much less of the time now'). Negative score indicate fewer problems with blood glucose levels. Positive scores indicate more problems than before.

These scores from the DTSQc assessed at Visit 8 and Visit 11 will be presented.

11.3.2 Hypoglycaemia Fear Survey-II (HFS-II) Worry Subscale

The HFS-II worry subscale consists of 18 items, rated by patients from 0 (never) to 4 (almost always). Scores are obtained by the sum of all the responses on the scale and range from 0 to 72, with 0 representing least worry. The score from HFS-II assessed at Visit 3, Visit 8 and Visit 11 will be presented.

11.3.3 EuroQoL-5 Dimension (EQ-5D)

The EQ-5D self-report questionnaire comprises two parts: the EQ VAS, which records an overall rating of health from 0-100 on a visual analogue scale (0=worst possible health to 100=best possible), and the EQ-5D self-classifier, which includes five dimensions (mobility, self-care, usual activity, pain/discomfort and anxiety/depression) with three levels each (no problems, some problems and severe problems). The EQ-5D index is constructed by applying utility weights to each of the levels within each dimension and adding these together. Utility weights are elicited from general population surveys that used one of the available direct utility assessment methods.

The EQ VAS and EQ-5D index will be presented at Visit 3, Visit 8 and Visit 11.

11.4 Calculation or derivation of pharmacokinetic variables (Not applicable)

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

11.6 Calculation or derivation of pharmacogenetic variables (Not applicable)

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

12. STATISTICAL METHODS AND SAMPLE SIZE DETERMINATION BY ASTRAZENECA

The primary objective of the study will be to show the superiority of saxagliptin compared to glimepiride in elderly patients (≥65 years) with type 2 diabetes in regard to the proportion of patients achieving the HbA_{1c} target of <7% without hypoglycaemia (confirmed or severe) after 52 weeks of treatment. Any patient who does not complete the 52-week treatment period will be considered as a non-responder, ie, as having not achieved the HbA_{1c} target without confirmed or severe hypoglycaemia. For definition of hypoglycaemic events, see Section 11.2.3.

The key secondary objective (safety analysis) will be to show the superiority of saxagliptin compared to glimepiride in regard to the proportion of patients having experienced at least one hypoglycaemic event (confirmed or severe) over the 52-week treatment period. A hierarchical testing procedure will be applied in order to control the type I error rate.

12.1 Description of analysis sets

Efficacy analyses for the primary endpoint will use the safety analysis set. The safety endpoints will be analysed from the safety analysis set.

A detailed description of analysis sets is given below. The decision to include or exclude patients from each analysis set will be performed in a blind data review prior to unblinding. A summary of the number of patients per analysis set will be given and reasons for exclusion of a patient from an analysis set will be listed.

12.1.1 Lead-in analysis set

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

12.1.2 Randomised analysis set

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

12.1.3 Full analysis set (FAS)

The full analysis set is defined for the analyses of exploratory efficacy endpoints as the subset of randomised analysis set including patients who took at least one randomised investigational product dose, have non-missing baseline and post-baseline efficacy data.

12.1.4 Per protocol (PP) analysis set

The PP analysis set is defined as a subset of the full analysis set including patients with no reason for exclusion. A PP analysis on the primary variable will only be performed if more than 10% of the patients in any regimen are found to significantly violate the terms and conditions of the protocol. Otherwise, analysis of the primary variable will be restricted to the safety analysis set.

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 products and significant deviations of study procedures. The exclusions from the PP analysis set will be explicitly defined in the Statistical Analysis Plan (SAP) before breaking the blind.

12.1.5 Safety analysis set

The safety analysis set is a subset of randomised analysis set including patients who took at least one investigational product dose.

12.1.6 Last Observation Carried Forward (LOCF)

The last observation carried forward approach will be applied to exploratory continuous endpoints only. This means that for a specific time-point post-baseline, analyses will be based on measurements available at that time-point or the last post-baseline measurement prior to the time-point, if no measurement is available at that time-point.

Furthermore, an observed cases analysis without any imputation of missing values will be conducted if a relevant number of missing values occurs. Details will be specified in the SAP before breaking the blind.

12.2 Methods of statistical analyses

12.2.1 Analyses of the primary and secondary endpoints

The proportion of patients reaching HbA_{1c} <7% after 52 weeks of treatment without confirmed or severe hypoglycaemia (for definition of hypoglycaemic events, see Section 11.2.3) will be analysed using the Cochran-Mantel-Haenszel (CMH) method for the odds ratio (OR), including a stratification variable for the age group (<75 versus ≥75 years).

The primary efficacy analysis will be performed on the safety analysis set using the above mentioned CMH approach providing statistical test results and 95% confidence intervals for the OR comparing treatments. There will be no re-assignment of treatments for this analysis, each patient will be analysed as randomised.

In order to assess the influence of including all drop-outs, irrespective of their reason, into the group of non-responders, a sensitivity analysis of the primary efficacy endpoint will be conducted for the subgroup of the safety analysis set, excluding all patients who terminated due to a reason not related to glycaemic control. Patients who discontinued due to glycaemic control reasons will continue to be counted as non-responders.

The key secondary objective (safety analysis), the proportion of patients having experienced at least one hypoglycaemic event (confirmed or severe) over the 52-week double-blinded treatment period, will be analysed using the same approach as in the analysis of the primary endpoint. Superiority of saxagliptin will be tested in the safety analysis set.

To preserve the type I error rate ≤0.05 (two-sided) across the primary and the key secondary endpoints, a hierarchical testing procedure will be used to interpret the statistical significance of these treatment comparisons. The primary endpoint will be tested first followed by the key secondary endpoint. Both comparisons will be tested at a two-sided significance level of α=0.05. However, a comparison of the key secondary objective will only be confirmed as statistically significant if the preceding primary comparison is statistically significant.

12.2.2 General analyses and exploratory endpoints

The time course of all continuous variables will be presented using standard descriptive summary statistics. Exploratory analyses of continuous endpoints will be performed using ANCOVA methods for the change from baseline. The ANCOVA model will use the factors treatment group and age (<75 versus ≥75 years) as a fixed effect and the respective baseline value as 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 measurement analysis by analogy with the ANCOVA model will be conducted, if appropriate.

Categorical variables will be summarized by counts, proportions, and if appropriate, corresponding 95% confidence intervals. Exploratory analyses of categorical endpoints will use the same approach as for the primary endpoint.

Due to the large number of centres and the expected low number of patients per centre, centre effects will not be included in the analysis. Tables by country will be provided in order to explore country effects. Country effects will be included in the statistical models in additional exploratory analyses, if appropriate. Any pooling of countries with few patients in geographical clusters will be specified in the SAP before breaking the blind.

12.3 Determination of sample size

Based on the available literature and previous trial results, we assume rates of patients reaching HbA_{1c} target without confirmed or severe hypoglycaemia of 57% for the saxagliptin group and of 45.5% for the glimepiride group, corresponding to a 1.59 times higher OR for saxagliptin compared to glimepiride (OR=1.59). As this trial carries a more conservative approach – the group of non-responders including all subjects dropping out due to reasons not related to glycaemic control – sample size calculations use accordingly lowered response rates and OR.

Assuming 10% of patients dropping out due to reasons not related to glycaemic control yields a reduced response rate of 51.3% for the saxagliptin group and of approximately 40.5% for the glimepiride group, based on a more conservative OR of 1.55. Sample size calculation based on the Cochran-Mantel-Haenszel method, using continuity correction and assuming equality of ORs across strata, yields a total of 698 patients, randomised and treated (349 patients in each treatment arm), needed to detect superiority with a two-sided significance level of α=0.05 and 80% power.

The selected sample size should result in a total number of 140 randomised and treated patients aged ≥75 years per treatment arm (40% of 349).

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

12.4 Data monitoring committee

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

12.4.1 Independent Adjudication Committee

An Independent Adjudication Committee, blinded to the treatment of the patient, will classify cardiovascular AEs, such as, but not limited to, 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.

13. IMPORTANT MEDICAL PROCEDURES TO BE FOLLOWED BY THE INVESTIGATOR

13.1 Medical emergencies and AstraZeneca/Bristol-Myers Squibb contacts

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

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

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

Name	Role in the study	Address & telephone number

13.2 Overdose

For the purposes of this study, before the randomisation 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 below, regardless of whether the overdose was associated with any symptom or not. All symptoms associated with the overdose should be reported as AEs.

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

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

13.3 Pregnancy (Not applicable)

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Clinical Study Protocol Appendix B

Drug Substance	Saxagliptin
Study Code	D1680L00002
Edition Number	1
Date	

Appendix B
Additional Safety Information

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

Life threatening

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

Hospitalisation

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 subject was enrolled in the study, provided that it did not deteriorate in an unexpected way during the study.

Important medical event or medical intervention

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

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

Examples of such events are:

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

The following factors should be considered when deciding if there is a "reasonable possibility" that an AE may have been caused by the drug.

- Time Course. Exposure to suspect drug. Has the subject actually received the suspect drug? Did the AE occur in a reasonable temporal relationship to the administration of the suspect drug?

- Consistency with known drug profile. Was the AE consistent with the previous knowledge of the suspect drug (pharmacology and toxicology) or drugs of the same pharmacological class? OR could the AE be anticipated from its pharmacological properties?

- Dechallenge experience. Did the AE resolve or improve on stopping or reducing the dose of the suspect drug?

- No alternative cause. The AE cannot be reasonably explained by another aetiology such as the underlying disease, other drugs, other host or environmental factors.

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

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

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

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

In difficult cases, other factors could be considered such as:

- Is this a recognised feature of overdose of the drug?

- Is there a known mechanism?

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

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Clinical Study Protocol Appendix C	
Drug Substance	Saxagliptin
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Appendix C
International Airline Transportation Association (IATA) 6.2 Guidance Document

LABELLING AND SHIPMENT OF BIOHAZARD SAMPLES

International Airline Transportation Association (IATA) classifies biohazardous agents into 3 categories **(http://www.iata.org/whatwedo/cargo/dangerous_goods/infectious_substances.htm).** For transport purposes the classification of infectious substances according to risk groups was removed from the Dangerous Goods Regulations (DGR) in the 46th edition (2005). Infectious substances are now classified either as Category A, Category B or Exempt. There is no direct relationship between Risk Groups and categories A and B.

Category A Infectious Substances are infectious substances in a form that, when exposure to it occurs, is capable of causing permanent disability, life-threatening or fatal disease in otherwise healthy humans or animals. Category A pathogens are eg, Ebola, Lassa fever virus:

- are to be packed and shipped in accordance with IATA Instruction 602.

Category B Infectious Substances are infectious Substances that do not meet the criteria for inclusion in Category A. Category B pathogens are eg, Hepatitis A, B, C, D, and E viruses, Human immunodeficiency virus (HIV) types 1 and 2. They are assigned the following UN number and proper shipping name:

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

Exempt - all other materials with minimal risk of containing pathogens

- Clinical trial samples will fall into Category B or exempt under IATA regulations
- Clinical trial samples will routinely be packed and transported at ambient temperature in IATA 650 compliant packaging **(http://www.iata.org/whatwedo/cargo/dangerous_goods/infectious_substances.htm)**
- **Biological samples transported in dry ice require additional dangerous goods specification for the dry-ice content**
- IATA compliant courier and packaging materials should be used for packing and transportation and packing should be done by an IATA certified person, as applicable
- Samples routinely transported by road or rail are subject to local regulations which require that they are also packed and transported in a safe and appropriate way to contain any risk of infection or contamination by using approved couriers and packaging / containment materials at all times. The IATA 650 biological sample containment standards are encouraged wherever possible when road or rail transport is used.

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Clinical Study Protocol Appendix D	
Drug Substance	Saxagliptin
Study Code	D1680L00002
Edition Number	1
Date	

Appendix D
Diabetes Treatment Statisfaction Questionnaire (DTSQs) and (DTSQc)

Diabetes Treatment Satisfaction Questionnaire: DTSQs

The following questions are concerned with the treatment for your diabetes (including insulin, tablets and/or diet) and your experience over the past few weeks. Please answer each question by circling a number on each of the scales.

1. How satisfied are you with your current treatment?

very satisfied	6	5	4	3	2	1	0	very dissatisfied

2. How often have you felt that your blood sugars have been unacceptably high recently?

most of the time	6	5	4	3	2	1	0	none of the time

3. How often have you felt that your blood sugars have been unacceptably low recently?

most of the time	6	5	4	3	2	1	0	none of the time

4. How convenient have you been finding your treatment to be recently?

very convenient	6	5	4	3	2	1	0	very inconvenient

5. How flexible have you been finding your treatment to be recently?

very flexible	6	5	4	3	2	1	0	very inflexible

6. How satisfied are you with your understanding of your diabetes?

very satisfied	6	5	4	3	2	1	0	very dissatisfied

7. Would you recommend this form of treatment to someone else with your kind of diabetes?

Yes, I would definitely recommend the treatment	6	5	4	3	2	1	0	No, I would definitely not recommend the treatment

8. How satisfied would you be to continue with your present form of treatment?

very satisfied	6	5	4	3	2	1	0	very dissatisfied

Please make sure that you have circled one number on each of the scales.

Health Psychology Research, Dept of Psychology, Royal Holloway, University of London, Egham, Surrey, TW20 0EX, UK.

Diabetes Treatment Satisfaction Questionnaire (change): DTSQc

For the past few weeks/months you have been taking part in a diabetes treatment study. At the start of the study you may have had a change of treatment. Today we would like to know how your experience of your current treatment (including medication and diet) has changed from your experience of treatment before the study began. Please answer each question by circling a number on each of the scales to indicate the extent to which you have experienced changes. If you have experienced no change, please circle '0'.

1. How satisfied are you with your current treatment?

much more satisfied now	3	2	1	0	-1	-2	-3	much less satisfied now

2. How often have you felt that your blood sugars have been unacceptably high recently?

much more of the time now	3	2	1	0	-1	-2	-3	much less of the time now

3. How often have you felt that your blood sugars have been unacceptably low recently?

much more of the time now	3	2	1	0	-1	-2	-3	much less of the time now

4. How convenient have you been finding your treatment to be recently?

much more convenient now	3	2	1	0	-1	-2	-3	much less convenient now

5. How flexible have you been finding your treatment to be recently?

much more flexible now	3	2	1	0	-1	-2	-3	much less flexible now

6. How satisfied are you with your understanding of your diabetes?

much more satisfied now	3	2	1	0	-1	-2	-3	much less satisfied now

7. How likely would you be to recommend your present treatment to someone else with your kind of diabetes?

much more likely to recommend the treatment now	3	2	1	0	-1	-2	-3	much less likely to recommend the treatment now

8. How satisfied would you be to continue with your present form of treatment?

much more satisfied now	3	2	1	0	-1	-2	-3	much less satisfied now

Please make sure that you have circled one number on each of the scales.

Health Psychology Research, Dept of Psychology, Royal Holloway, University of London, Egham, Surrey, TW20 0EX, UK.

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Clinical Study Protocol Appendix E	
Drug Substance	Saxagliptin
Study Code	D1680L00002
Edition Number	1
Date	

Appendix E
Hypoglycaemia Fear Survey-II (HFS-II) – worry subscale

Sample of Subject Questionnaire - HFS-II (Hypoglycaemia Fear Survey-II). - Worry subscale

Adult Low Blood Sugar Survey

II. Worry: Below is a list of concerns people with diabetes sometimes have about low blood sugar. Please read each item carefully (do not skip any). Circle one of the numbers to the right that best describes how often in the last 6 months you **WORRIED** about each item because of low blood sugar. (**Please do not skip any!**).

	Never	Rarely	Some-times	Often	Almost Always
Because my blood sugar levels could drop, I worried about					
1. Not realising that my blood sugar levels had dropped.	0	1	2	3	4
2. Not having food, fruit or juice available.	0	1	2	3	4
3. Passing out in public.	0	1	2	3	4
4. Embarrassing myself or my friends in a social situation.	0	1	2	3	4
5. Having a hypoglycemic episode while alone.	0	1	2	3	4
6. Appearing stupid or drunk.	0	1	2	3	4
7. Losing control.	0	1	2	3	4
8. No one being around to help me during a hypoglycemic episode.	0	1	2	3	4
9. Having a hypoglycemic episode while driving.	0	1	2	3	4
10. Making a mistake or having an accident.	0	1	2	3	4
11. Getting a bad evaluation or being criticised.	0	1	2	3	4
12. Difficulty thinking clearly when responsible for others.	0	1	2	3	4
13. Feeling lightheaded or dizzy.	0	1	2	3	4
14. Accidentally injuring myself or others.	0	1	2	3	4
15. Permanent injury or damage to my health or body.	0	1	2	3	4
16. Low blood sugar interfering with important things I was doing.	0	1	2	3	4
17. Becoming hypoglycemic during sleep.	0	1	2	3	4
18. Getting emotionally upset and being difficult to deal with.	0	1	2	3	4

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Clinical Study Protocol Appendix F	
Drug Substance	Saxagliptin
Study Code	D1680L00002
Edition Number	1
Date	

Appendix F
EuroQoL-5 Dimension (EQ-5D)

Health Questionnaire

English version for the UK
(validated for Ireland)

By placing a tick in one box in each group below, please indicate which statements best describe your own health state today.

Mobility

I have no problems in walking about ❑

I have some problems in walking about ❑

I am confined to bed ❑

Self-Care

I have no problems with self-care ❑

I have some problems washing or dressing myself ❑

I am unable to wash or dress myself ❑

Usual Activities (*e.g. work, study, housework, family or leisure activities)*

I have no problems with performing my usual activities ❑

I have some problems with performing my usual activities ❑

I am unable to perform my usual activities ❑

Pain/Discomfort

I have no pain or discomfort ❑

I have moderate pain or discomfort ❑

I have extreme pain or discomfort ❑

Anxiety/Depression

I am not anxious or depressed ❑

I am moderately anxious or depressed ❑

I am extremely anxious or depressed ❑

To help people say how good or bad a health state is, we have drawn a scale (rather like a thermometer) on which the best state you can imagine is marked 100 and the worst state you can imagine is marked 0.

We would like you to indicate on this scale how good or bad your own health is today, in your opinion. Please do this by drawing a line from the box below to whichever point on the scale indicates how good or bad your health state is today.

Your own health state today