Clinical Study Protocol

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A 24-Week National, Multi-centre, Randomized, Parallel-group, Double-blind, Placebo-controlled, Phase IIIb study in India to Evaluate the Efficacy and Safety of Saxagliptin in Adult Patients with Type 2 Diabetes who have Inadequate Glycaemic Control with Diet and Exercise.

License Holder:

Bristol Myers Squibb Company

Sponsor:

AstraZeneca AB, 151 85 Södertälje, Sweden

AstraZeneca Research and Development site representative

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

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

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

AstraZeneca

PROTOCOL SYNOPSIS

A 24-Week National, Multi-centre, Randomized, Parallel-group, Double-blind, Placebo-controlled, Phase IIIb study in India to Evaluate the Efficacy and Safety of Saxagliptin in Adult Patients with Type 2 Diabetes who have Inadequate Glycaemic Control with Diet and Exercise.

Investigator

The National coordinating investigators will be chosen for particular active contribution, active recruitment and for signing the clinical study report of this study.

Study centre(s) and number of patients planned

This national multi-centre study will be conducted at approximately 15 study centres in India. Approximately 206 patients will be randomized in the study.

Study period		**Phase of development**
Estimated date of first patient enrolled	Q2 2009	IIIb
Estimated date of last patient completed	Q3 2010	

Objectives

The primary efficacy objective of this study is to compare, after a 24-week oral administration of double-blind treatment, the absolute change from baseline in glycosylated haemoglobin A1c (HbA1c) achieved with saxagliptin versus placebo in treatment naïve patients with type 2 diabetes who have inadequate glycaemic control with diet and exercise alone.

Two secondary objectives will compare the effects of saxagliptin monotherapy versus placebo after a 24 week double-blind treatment for the following:

- The change from baseline in fasting plasma glucose (FPG)
- The proportion of patients achieving a therapeutic glycaemic response defined as HbA1c <7.0%

Other secondary objectives are:

Efficacy: To compare the effects of saxagliptin versus placebo given as monotherapy in a 24-week double-blind treatment period by evaluation of

- Change from baseline in β-cell function and insulin sensitivity (as measured by Homeostasis Model Assessment (HOMA-2)

- The change from baseline in fasting insulin

- The change from baseline in body mass index (BMI), waist circumference, and body weight

- The proportion of patients achieving a glycemic response for each category as defined below

- HbA1c ≤ 6.5%
- Reduction in HbA1c ≥ 0.5%
- Reduction in HbA1c ≥ 0.7%
- Fasting plasma glucose (FPG) < 110mg/dL (6.1 mmol/L)
- FPG < 126 mg/dL (7.0 mmol/L)

- Percent change from baseline in fasting lipids: Total cholesterol (TC), Low density lipoprotein-cholesterol (LDL-C), High density lipoprotein-cholesterol (HDL-C) and triglycerides (TG)

Safety: Safety and tolerability will be evaluated by assessment of Adverse Events (AEs) (including AE of special interest), hypoglycaemic events, laboratory values, electrocardiogram (ECG), pulse, blood pressure (BP), weight and physical examination.

Study design

This study is a 24-week, national, multi-centre, randomized, parallel-group, double-blind, placebo-controlled phase IIIb study to evaluate the efficacy and safety of saxagliptin in adult patients with type 2 diabetes who have inadequate glycaemic control with diet and exercise. The study comprises enrolment, a 4-week placebo lead-in period and a 24-week randomized treatment period.

Target patient population

Males and females with type 2 diabetes from 18 years of age, with inadequate glycaemic control defined as HbA1c $\geq$7.2 and ≤10.0% are eligible to enter the placebo lead-in period (Period B). Patients should be drug naïve prior to enrolment. Patients must have a fasting C-peptide level $\geq$ 0.33 nmol/L ($\geq$ 1ng/mL). Females must be postmenopausal or have undergone successful surgical sterilization or, if of childbearing potential, use adequate method of contraception.

After 4 weeks of placebo lead in period with diet and exercise, the patients with a HbA1c ≥7.0 and ≤10.0% are eligible for randomization (Period C).

Investigational product, dosage and mode of administration

Saxagliptin tablets 5 mg oral for the 24-week double-blind period.

Matching placebo tablets for saxagliptin 5 mg oral for the 4-week placebo lead-in period as well as the 24-week double-blind period.

Rescue medication, dosage and mode of administration

Open-label metformin 500 mg tablet oral at a daily dose of 500 mg-2500 mg, week 4 (visit 6 in period C) and throughout the study period.

Duration of treatment

Patients will have an enrolment (Period A) and lead-in period (Period B) of 4 weeks before day of randomization. The randomization treatment period (Period C) will be 24 weeks and will start on the first day of randomization. The total planned study duration is 28 weeks.

Outcome variables

Primary outcome variables:

Efficacy:

- The primary endpoint is change from baseline to Week 24 in HbA1c .

Secondary outcome variables:

Secondary outcome variables at Week 24 are:

- Change from baseline in fasting plasma glucose (FPG)
- Proportion of patients achieving a therapeutic glycaemic response defined as HbA1c <7.0%

Other outcome variables are:

- Change from baseline in β-cell function and insulin sensitivity (as measured by Homeostasis Model Assessment (HOMA-2)
- The change from baseline in fasting insulin
- Change from baseline in BMI, waist circumference and weight

Proportion of patients achieving a glycaemic response for each category defined below:

- HbA1c ≤6.5%

- Reduction in HbA1c ≥0.5%
- Reduction in HbA1c ≥0.7%
- FPG <110 mg/dL (6.1 mmol/L)
- FPG <126 mg/dL (7.0 mmol/L)

- Percent change from baseline in fasting lipids Total cholesterol (TC), Low density lipoprotein-cholesterol (LDL-C), High density lipoprotein-cholesterol (HDL-C) and triglycerides (TG)

Patient reported outcomes (PROs) – Not applicable

Health Economics – Not applicable

Pharmacokinetic– Not applicable

Pharmacodynamic – Not applicable

Genetics – Not applicable

Safety

- Adverse Events (AEs)
- Hypoglycaemic events
- Serious adverse events (SAEs)
- Laboratory values
- ECG
- Vital Signs (pulse and BP)
- Physical examination
- Weight

Statistical methods

The primary efficacy analysis is to compare saxagliptin treatment group with placebo treatment group on the absolute change from baseline in HbA1c to Week 24. The absolute change from baseline in HbA1c is to be analyzed on the full analysis set (FAS) using an analysis of covariance model (ANCOVA) with treatment group as an effect and baseline value as the covariate. Within the framework of the ANCOVA model, point estimates and the two-sided 95% confidence intervals for the mean change within each treatment group as well as

for the differences in mean change between the saxagliptin treatment arm and the placebo treatment arm will be presented.

With a total of 206 patients randomized and treated (or 103 per treatment group), there is 90% power to detect 0.5% difference between the two randomized treatment groups in absolute change from baseline to week 24 in HbA1c at the 5% level assuming standard deviation of change from baseline in HbA1c is 1.1%. A total of 218 patients will be randomized to account for 5% of patients being unevaluable for the primary endpoint analysis.

Two important secondary efficacy endpoints were identified for significance testing with the overall primary endpoints in a fixed-sequence testing procedure. The order of these secondary efficacy endpoints and the associated statistical methods for each are:

(1) Change from baseline to Week 24 in FPG; ANCOVA similar to the model used for the primary endpoint using FAS

(2) The treatment dependency of proportion of patients achieving a therapeutic glycaemic response defined as HbA1c <7.0% will be discriminated by two-sided Fisher's Exact test using FAS

Statistical inferences will start from the overall primary efficacy endpoint. If saxagliptin treatment group is superior in ΔHbA1c compared to the placebo group, then statistical inference will continue with the first secondary efficacy endpoint (1), else statistical inference of the overall efficacy endpoints will stop. The p-values that follow can not be considered as significant in this confirmatory analyses when the fixed sequence procedure is used to control the familywise type 1 error rate, even if the p-value is less than 0.05.

Similarly if saxagliptin treatment group is superior in ΔFPG than the placebo group, then statistical inference will continue with the second secondary efficacy endpoint (2), else statistical inference of the overall efficacy endpoints will stop.

The set of Other Secondary Efficacy endpoints will be analyzed by linear models using baseline value as a covariate similar to the method used for the primary variable. Within the framework of the ANCOVA model, point estimates and the two-sided 95% confidence intervals for the mean change within each treatment group as well as for the differences in mean change between the saxagliptin treatment arm and the placebo treatment arm will be presented.

Proportions of patients achieving glycaemic therapeutic response will be summarized by descriptive statistics for each category.

Analysis for safety and tolerability endpoints will be summarized by descriptive statistics or frequency tables and/or graphic method. There are no hypotheses proposed a priori to these safety endpoints.

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

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

Abbreviation or special term	Explanation
AE	Adverse Event (see definition in Section 4.7.1.1)
ANCOVA	Analysis of covariance model
Anti-HCV	Hepatitis C virus antibody
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
BMI	Body Mass Index
BUN	Blood urea nitrogen
CBC	Complete blood count
CD4	Cluster designation: cell surface marker expressed by lymphocytes
CD8	Cluster designation: cell surface marker expressed by lymphocytes
CK	Creatine kinase
CPMP	Committee for Proprietary Medicinal Products. CPMP has changed name to Committee for Medicinal Products for Human Use (CHMP).
CRO	Contract Research Organization
CSA	Clinical Study Agreement
CYP450 3A4	Cytochrome P450 3A4
DMC	Data Monitoring Committee
DPP-IV	Dipeptidyl peptidase IV
ECG	Electrocardiogram
E-code	Enrolment code
eCRF	electronic Case Report Form
Ethics Committee	Synonymous to Institutional Review Board and Independent Ethics Committee
FPG	Fasting plasma glucose
GCP	Good Clinical Practice
GIP	Glucose dependent insulinotropic peptide
GLP-1	Glucagon-like peptide-1
GMP	Good Manufacturing Practice
HbA1c	Glycosylated haemoglobin A1c

Abbreviation or special term	Explanation
HBsAg	Hepatitis B surface antigen
HCV PCR	Assay for Hepatitis C virus RNA
HDL-C	High-density lipoprotein-cholesterol
HIV	Human immunodeficiency virus
HOMA	Homeostasis model assessment
HRT	Hormone replacement therapy
ICH	International Conference on Harmonisation
IB	Investigator's Brochure
IP	Investigational product
Kg	Kilogram
LDL-C	Low-density lipoprotein-cholesterol
LOCF	Last observation carried forward
MedDRA	Medical Dictionary for Regulatory Activities
NYHA	New York Heart Association
PP	Per protocol
PRO	Patient reported outcomes
SAE	Serious Adverse Event (see definition in Section 4.7.1.1)
SAP	Statistical Analysis Plan
SDV	Source Data Verification
SU	Sulfonylurea
TG	Triglyceride
TC	Total cholesterol
TSH	Thyroid-stimulating hormone
TZD	Thiazolidinedione
WBDC	Web Based Data Capture
WOCBP	Women of Childbearing Potential

1. INTRODUCTION

1.1 Background

Type 2 diabetes is associated with long-term microvascular complications such as retinopathy, nephropathy, and neuropathy as well as cardiovascular events. Intensive treatment to reduce plasma glucose to within normal levels can minimize the risk of developing these complications. Current therapeutic agents have limited efficacy and are associated with side effects including hypoglycaemia, weight gain, oedema, and changes in the blood lipid profile. (DeFronzo 1999) Agents with new mechanisms of action for the treatment of type 2 diabetes are being explored. Inhibition of dipeptidyl peptidase IV (DPP-IV) 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 highly potent, selective, reversible, competitive inhibitor of human DPP-IV. DPP-IV is an enzyme that selectively cleaves dipeptides from the N-terminus of oligopeptides with proline or alanine in the penultimate position. DPP-IV 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-IV 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-IV inhibitors lead to enhanced glucose dependent insulin secretion, they are expected to present low risk of hypoglycaemia and may not lead to weight gain.

Several lines of evidence indicate that preservation of active GLP-1 by treatment with a DPP-IV inhibitor will improve the insulin secretion pattern from pancreatic β-cells, enhance postprandial glucose control, and result in long term improvements in both fasting and postprandial glycaemia and the diabetic state. Furthermore, experimental data suggest that DPP- IV 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.

The results from the eight clinical studies in the saxagliptin Phase 2b and 3 program in over 4600 subjects combined with the results from clinical pharmacology studies support the oral dose of saxagliptin 5 mg once daily as the usual clinical dose in a wide range of subjects with T2DM, as either monotherapy, add-on combination therapy with metformin, a thiazolidinedione (TZD), or a sulfonylurea (SU), or initial combination therapy with metformin.

In the Phase 2b dose-ranging study, administration of saxagliptin 5 mg was associated with significant inhibition of plasma DPP4 activity at the trough of the dosing interval as well as clinically meaningful decreases in A1C, fasting serum glucose and postprandial serum glucose. The results from the short-term periods of the Phase 3 studies confirmed clinically meaningful benefits of saxagliptin 5 mg on A1C, as well as FPG, postprandial glucose, insulin, C-peptide, and glucagon levels. A greater percentage of subjects treated with saxagliptin achieved target glycemic goals including A1C levels < 7% compared to subjects treated with placebo or active comparator. The saxagliptin 5 mg groups generally achieved greater reductions from baseline in A1C 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 up to 102 weeks, treatment with saxagliptin, at all doses tested, produced sustained reductions in A1C relative to control.

Saxagliptin treatment consistently demonstrated a beneficial antihyperglycemic effect across subgroups of demographic and baseline diabetes characteristics.

Once-daily, orally-administered saxagliptin was safe and well-tolerated at doses of up to 400 mg QD for 2 weeks, 100 mg QD for 6 weeks, 40 mg QD for 12 weeks, and at doses of 2.5, 5, and 10 mg QD for up to 102 weeks. In an extensive Phase 2b/3 program, the majority of reported adverse events were of mild intensity and did not require treatment discontinuation. The safety profile was generally consistent when saxagliptin was given as monotherapy, as add-on combination treatment to metformin, SU, or TZD, and as initial therapy in combination with metformin. Although the rate of certain AEs was higher in subjects who received saxagliptin 10 mg compared with those who received 2.5 and 5 mg, saxagliptin 10 mg was also safe and well tolerated, providing a safety margin for the saxagliptin 5 mg dose.

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

1.2 Rationale

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

In the regulatory guidelines for type 2 diabetes, glycosylated haemoglobin A1c (HbA1c) is the prescribed measure for determination of glycaemic control and is therefore chosen as the primary variable. Certain secondary variables have been selected for additional assessment because of their clinical relevance and importance. This study is being performed to evaluate the efficacy and safety of Saxagliptin in the Indian population.

This 24 week Phase III clinical study investigates the efficacy and safety of saxagliptin. The study is required to demonstrate that saxagliptin is effective in the treatment of type 2 diabetes as compared to the placebo in the Indian population.

2. STUDY OBJECTIVES

2.1 Primary objective

The primary efficacy objective of this study is to compare, after a 24-week oral administration of double-blind treatment, the absolute change from baseline in HbA1c achieved with saxagliptin versus placebo in treatment naïve patients with type 2 diabetes who have inadequate glycaemic control with diet and exercise alone.

2.2 Secondary objectives

Two secondary objectives will compare the effects of saxagliptin versus placebo after a 24 week double-blind treatment for the following:

- The change from baseline in fasting plasma glucose (FPG)
- The proportion of patients achieving a therapeutic glycaemic response defined as HbA1c <7.0%

Other secondary objectives are:

Efficacy: To compare the effects of saxagliptin versus placebo after a 24 week double-blind treatment for the following:

- Change from baseline in β-cell function and insulin sensitivity (as measured by Homeostasis Model Assessment (HOMA-2) (Wallace et al 2004)
- The change from baseline in fasting insulin
- The change from baseline in body mass index (BMI), waist circumference, and weight
- The proportion of patients achieving a glycemic response for each category as defined below:
  - HbA1c ≤ 6.5%
  - Reduction in HbA1c ≥ 0.5%
  - Reduction in HbA1c ≥ 0.7%
  - Fasting plasma glucose (FPG) < 110 mg/dL (6.1 mmol/L)
  - FPG < 126 mg/dL (7.0 mmol/L)
- Percent change from baseline in fasting lipids: Total cholesterol (TC), Low density lipoprotein-cholesterol (LDL-C), High density lipoprotein-cholesterol (HDL-C) and triglycerides (TG)

Safety: Safety and tolerability will be evaluated by assessment of Adverse Events (AEs) (including AE of special interest), hypoglycaemic events, laboratory values, electrocardiogram (ECG), pulse, blood pressure (BP), weight and physical examination.

3. STUDY PLAN AND PROCEDURES

3.1 Overall study design and flow chart

This Clinical Study Protocol has been subjected to a peer review according to AstraZeneca and Bristol-Myers Squibb standard procedures. The study will be a 24-week national, multi-centre, randomized, parallel-group, double-blind, placebo controlled, Phase IIIb study, which will be performed in India to evaluate the efficacy and safety of saxagliptin in adult patients with Type 2 Diabetes who have inadequate glycaemic control with diet and exercise.

Patients with type 2 diabetes from 18 years of age, with inadequate glycaemic control defined as HbA1c ≥7.2 and ≤10.0% are eligible to enter the 4-week placebo lead-in period (Period B). Period B is a 4 week single blinded dietary and exercise placebo lead-in period. After 4 weeks of placebo lead in, patients with a HbA1c ≥7.0 and ≤10.0% are eligible for the 24 week randomization treatment period (Period C). Patients will be randomized 1:1 to one of the following two treatment groups in the 24-week double-blind randomized period (Period C): saxagliptin 5mg or matching placebo. Patients must have a fasting C-peptide level ≥ 0.33 nmol/L (≥ 1ng/mL). Females must be postmenopausal or have undergone successful surgical sterilization or, if of childbearing potential, use adequate method of contraception. Males should also use adequate method of contraception.

This national multi-centre study will be conducted at approximately 15 study centres in India. Approximately 206 patients will be randomized in the study.

The study will consist of the following 3 periods.

The enrolment visit (Period A, visit 1):

Drug naïve patients with type 2 diabetes will be eligible to enrol in the study. Enrolment assessments as described in Table 1will be performed.

Lead-in period (Period B, visits 2-3):

Eligible patients with inadequate glycaemic control (HbA1c ≥7.2.% and ≤10.0%) will be given placebo in a single-blind fashion (blind to the patient) at Visit 2 (Visit 2 = 4 weeks prior to randomization). The patients will be counselled on dietary and life-style modifications according to usual clinical routine. A glucometer and a patient diary will be handed out and the patients will be instructed to monitor their blood glucose at least every second day. Information about hypoglycaemic events should be entered into the patient diary (see Section 4.7.4).

Visit 2 (week-4) should preferably be done at the clinic, but may be performed as a telephone visit if it is clear before the scheduled visit that the patient is not eligible due to the laboratory results from Visit 1.

Visit 3 should be done one week (± 3 days) before randomization. HbA1c, FPG and Safety laboratory measurements will be conducted to confirm the patient remains eligible for the study.

This placebo lead-in period will be 4 weeks.

Assessments as described in Table 1 will be performed

Randomized treatment period (Period C, visits 4-12):

Patients with (HbA1c ≥7.0% and ≤10.0%) and FPG<270 mg/dL (15 mmol/L) at visit 3 are eligible for randomization. The patients will be randomized, at Visit 4 (Week 0=baseline) and the double-blind treatment period will start. Either saxagliptin 5 mg or placebo will be dispensed. Dietary and life-style modification will be reinforced during the randomized treatment period. Patients will remain on saxagliptin 5mg or placebo from visit 4 through visit 12 (week 24).

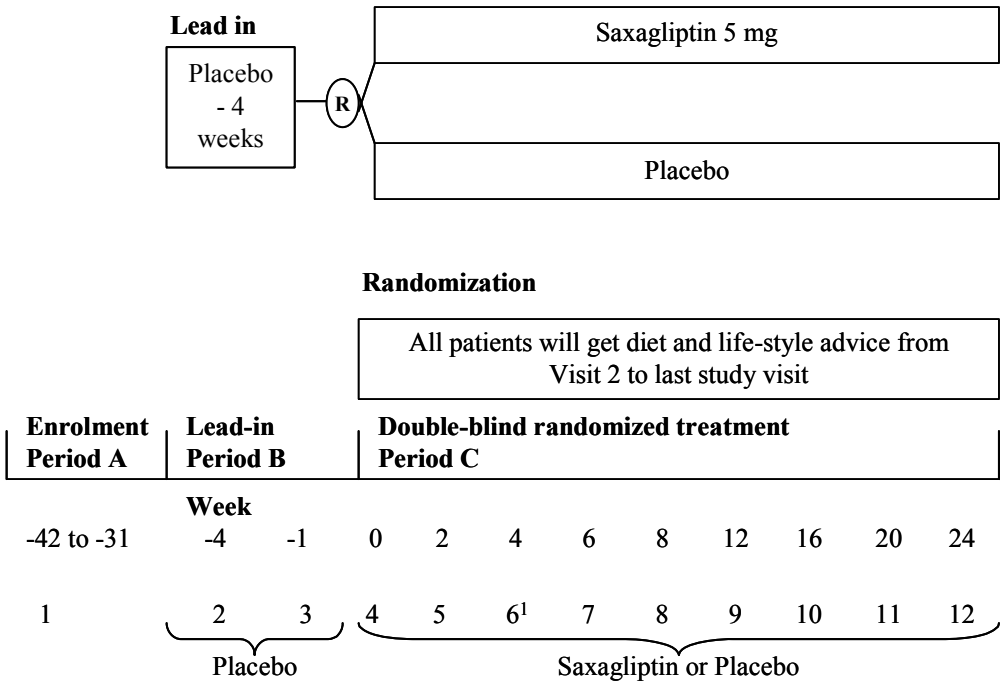
The patients will be instructed to monitor their blood glucose at least every second day. Hypoglycaemic events should be entered into the diary. Assessment of glycaemic parameters (based on results from central laboratory) will be done at each visit to determine if criteria for discontinuation/rescue are met during the period.

Rescue

Subjects with lack of adequate glucose control during period C may be eligible for the addition of open-label metformin as a rescue from continued hyperglycemia. Pre-specified glycemic parameters based upon FPG are established during the double-blind treatment phase (period C). See Section 3.3.5.1 for rescue criteria and procedures.

Patients in the Randomized treatment period who do not complete the entire study should complete the procedures described for Visit 12 (week24). End of study procedures will be completed per Table 1.

Figure 1 **Study flow chart for Enrolment, Lead-In and Double-blind Randomized Treatment period (Period A, B and C)**



1 For patients who meet the rescue criteria (see Section 3.3.5.1), open-label metformin (500 mg tablet oral at a daily dose of 500 mg-2500 mg) can be given from week 4 (visit 6 in period C) and throughout the study period. Metformin will be given added-onto, but not as replacement for, their current study medication regimen. For patients who meet criteria for rescue medication, additional visits may take place week 10, 14, 18 and 22.

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

	Enrolment (A)	Lead-in (B)		Treatment period (C)[a]								
Visit number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**
Study week	**-42 to 31 days**	**-4 w**	**-1 week**	**0w**	**2 w**	**4 w**	**6 w**	**8 w**	**12 w**	**16 w**	**20 w**	**24w**
Informed consent	X											
Randomization[a]				X								
Demography and Medical history	X											
Inclusion/exclusion criteria	X	X		X								
Physical examination	X			X			X		X			X
Brief physical examination					X	X		X		X	X	
Vital signs	X			X	X	X	X	X	X	X	X	X
Weight	X			X	X	X	X	X	X	X	X	X
Height				X								
Waist circumference				X								X
ECG	X			X								X
Concomitant medication	X	X	X	X	X	X	X	X	X	X	X	X
Laboratory assessments[b]	X		X	X	X	X	X	X	X	X	X	X
Pregnancy test[c]	X		X	X	X	X	X	X	X	X	X	X

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

	Enrolment (A)	Lead-in (B)		Treatment period (C)[a]								
Visit number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**
Study week	**-42 to 31 days**	**-4 w**	**-1 week**	**0w**	**2 w**	**4 w**	**6 w**	**8 w**	**12 w**	**16 w**	**20 w**	**24w**
AEs		X	X	X	X	X	X	X	X	X	X	X
Serious adverse events	X	X	X	X	X	X	X	X	X	X	X	X
Diet and life-style advice		X		X	X	X	X	X	X	X	X	X
Dispensation of investigational product (IP)		X		X		X		X	X	X	X	
Assessing glycemic rescue criteria (FPG)						X	X	X	X	X	X	
Dispensation of glucometer and/or supplies/provide instruction		X		X	X	X	X	X	X	X	X	X
Dispensation of patient diary (if applicable)		X		X	X	X	X	X	X	X	X	X
Patient diary review for hypoglycaemic events/check glucose values in glucometer				X	X	X	X	X	X	X	X	X

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

	Enrolment (A)	Lead-in (B)		Treatment period (C)[a]								
Visit number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**
Study week	**-42 to 31 days**	**-4 w**	**-1 week**	**0w**	**2 w**	**4 w**	**6 w**	**8 w**	**12 w**	**16 w**	**20 w**	**24w**
Drug accountability				X		X		X	X	X	X	X

[a] Randomized patients who do not complete the entire study should complete the procedures described for end of Period C (Visit 12)
[b] Specification of laboratory parameters is shown in Table 5 Efficacy laboratory variables Period A, B, C
[c] Pregnancy test will be done on all female patients who are not post menopausal or surgically sterile

Table 2 Visit design and visit windows

Visit ID	Visit description	Visit window
Visit 1	Enrolment (Period A)	-42 to -31 days
Visit 2	Lead-in (Period B)	-4 weeks (±3 days)
Visit 3	Labs to confirm eligibility for Visit 4	-1 week (±3 days)
Visit 4	Randomization (Period C)	0 weeks
Visit 5	Treatment (Period C)	2 weeks (±3 days)
Visit 6	Treatment (Period C)	4 weeks (±3 days)after Visit 4
Visit 7	Treatment (Period C)	6 weeks (±3 days) after Visit 4
Visit 8	Treatment (Period C)	8 weeks (±3 days)after Visit 4
Visit 9	Treatment (Period C)	12 weeks (±3 days) after Visit 4
Visit 10	Treatment (Period C)	16 weeks (±3 days)after Visit 4
Visit 11	Treatment (Period C)	20 weeks (±3 days) after Visit4
Visit 12	Treatment (Period C)	24 weeks (±3 days) after Visit 4

Any slippage in time must not accumulate. The randomized double-blind treatment period (Period C) must be at least 165 days and maximum 171 days.

For patients who meet criteria for rescue medication, additional visits may take place at week 10, 14, 18 and 22 (see Section 3.3.5.1).

3.2 Rationale and risk/benefit assessment

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

3.2.1.1 Study design and regulatory requirement

The purpose of the study is to investigate if treatment with saxagliptin is beneficial for patients with type 2 diabetes. A superiority comparison with placebo is designed in this randomized, double blind, placebo-controlled study. The study is done to support registration in India by providing a robust local clinical efficacy and safety experience as per recommendation of Indian health authorities.

3.2.1.2 Study doses and control groups

Many patients with type 2 diabetes do reach glycaemic control goals with monotherapy.

The current study is designed to demonstrate that saxagliptin is effective in the treatment of type 2 diabetes.

The dose of saxagliptin used in the study is 5 mg. This is the dose that was generally associated with maximal efficacy in a Phase II clinical study evaluating doses of saxagliptin in the range 2.5 mg to 40 mg as monotherapy in drug-naïve patients with type 2 diabetes. In this study, maximal decrease in both HbA1c as well as in FPG was seen with 5 mg of saxagliptin. Comparable decreases were seen with 5, 10, 20, and 40 mg saxagliptin. The saxagliptin 5 mg groups in phase III studies generally achieved greater reductions from baseline in A1C 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.

3.2.1.3 Choice of outcome variables

In the regulatory guidelines for type 2 diabetes, HbA1c is the prescribed measure for determination of glycaemic control and is therefore chosen as the primary variable. Certain secondary variables have been selected for additional assessment because of their clinical relevance and importance.

To better understand the mechanistic effects of saxagliptin the β-cell function will be measured by HOMA-2.

3.2.1.4 Choice of study population

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

The HbA1c criterion was selected to permit patients with a wide range of glycaemic control, thereby helping to broaden the potential applicability of the study. Although individual

guidelines (American Association of Clinical Endocrinologists 2007;American Diabetes Association 2008; International Diabetes Federation 2005; National Institute for Clinical Excellence 2002) recommend treatment to normal HbA1c levels, the risk of hypoglycaemia may limit the possibility to achieve this in clinical practice. Treatment with a compound with the mode of action as saxagliptin with low risk of hypoglycaemia may, however, offer the possibility to normalize blood glucose and achieve an optimal glycaemic control. The upper bound of this interval (i.e., 10%) is a commonly used and accepted value employed in studies of patients with diabetes.

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

3.2.2 Risk/benefit and ethical assessment

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

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

In this study, rescue medication (metformin) and a discontinuation plan will be used for subjects whose glycemia is not controlled based on the predefined hyperglycemic rescue/discontinuation criteria.

3.3 Selection of study population

3.3.1 Study selection record

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

3.3.2 Inclusion criteria

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

Inclusion Criteria at enrolment (Visit 1)

1. Provision of informed consent.

2. Diagnosed with type 2 diabetes.

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

4. Patients should be drug naïve. Drug naïve patients are defined as patients who have not received medical treatment for diabetes (insulin and/or oral hypoglycaemic agents) or have received medical treatment for diabetes for less than 6 months since original diagnosis. In addition patients should not have received any antihyperglycemic therapy for more than three consecutive days or a total of seven non-consecutive days during the 8 weeks (12 weeks for previous thiazolidinedione treatment) before screening. The exceptions are for women who have received treatment for gestational diabetes during their pregnancy and are no longer receiving therapy or patients who during a hospitalization received insulin treatment.

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

   Men participating in the study should also take precautions as described above to not father a baby while participating in the study and 4 weeks after the study.

   WOCBP include any female who has experienced menarche and who has not undergone successful surgical sterilization (hysterectomy, bilateral tubal ligation or bilateral oophorectomy) or is not postmenopausal (defined as amenorrhea ≥12 consecutive months; or women on hormone replacement therapy (HRT) with documented serum follicle stimulating hormone (FSH) level ≥35mIU/mL).

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

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

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

6. C-peptide level ≥0.33 nmol/L (≥1.0 ng/mL)

7. HbA1c ≥ 7.2% and ≤10.0% and FPG<270 mg/dL (15 mmol/L)

Inclusion criterion at randomization (Visit 4, laboratory values from Visit 3)

8. HbA1c ≥7.0% and ≤10.0% and FPG<270 mg/dL (15 mmol/L)

3.3.3 Exclusion criteria

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

Exclusion criteria at enrolment (Visit 1):

1. Pregnant or breastfeeding patients.

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

3. Previous treatment with any DPP-IV inhibitor.

4. Treatment with CYP450 3A4 inducers (carbamazepine, dexamethasone, phenobarbital, phenytoin, rifampin).

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

6. Human immunodeficiency virus (HIV) treatment/antiviral drugs (e.g., delavirdine, indinavir, nelfinavir, ritonavir, saquinavir).

7. Contraindications to therapy as outlined in the saxagliptin IB.

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

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

10. Symptoms of poorly controlled diabetes, including but not limited to marked polyuria and polydipsia with >10% weight loss during last 3 months prior to Visit 1 or other signs and symptoms.

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

12. Immunocompromised individuals such as patients that have undergone organ transplantation or patients diagnosed with HIV.

13. Gastrointestinal surgery that could impact the absorption of study drug (eg. gastroenterostomy or enterectomy).

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

15. History of unstable or rapidly progressing renal disease.

16. History of autoimmune skin disorder.

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

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

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

20. Participation in a clinical study during the last 90 days prior to visit 1.

21. Donation of blood, plasma or platelets within the past 90 days prior to visit 1.

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

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

24. Individuals at risk for protocol or medication non-compliance.

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

25. Serum creatinine ≥132.6 μmol/L (≥1.5 mg/dL) for men; ≥123.8μmol/L(≥1.4 mg/dL) for women

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

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

28. Creatine kinase (CK) ≥3xULN.

29. Patients that have an abnormal thyroid-stimulating hormone (TSH) value at visit 1 will be further evaluated by free T4. Patients with an abnormal free T4 will be excluded.

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

31. Patients that have lymphocytopenia or thrombocytopenia identified on laboratory tests, which in the judgement of the investigator would be of clinically significant abnormality.

Exclusion criteria at randomization (Visit 4, laboratory values from Visit 3):

32. Serum creatinine ≥132.6 µmol/L (≥1.5 mg/dL) for men; or Serum creatinine ≥123.8µmol/L(≥1.4 mg/dL) for women

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

34. Creatine kinase ≥3xULN.

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

36. Patients that have lymphocytopenia or thrombocytopenia identified on laboratory tests, which in the judgement of the investigator would be of clinically significant abnormality.

3.3.4 Restrictions

Due to the fasting laboratory assessments, all patients will visit the clinic on a fasting stomach in the morning, before 11:00 am. The patients will be instructed not to have ingested any food or beverages 8 hours before visiting the clinic (however, drinking water is allowed).

NB The patients will also be instructed not to take the IP in the morning before visiting the clinic. Allowed medications can be taken with water only.

If a patient arrives for a visit without having followed the instructions given above, then the patient should be re-scheduled for the entire visit (if possible within the allowed time-window).

The patients will be instructed to refrain from using traditional herbal medicine from visit 2 lead in period (Period B) through the final study assessments.

The patients should not donate blood, plasma or platelets during the study.

Restricted concomitant medications are listed in Section 3.7.2, 3.3.3 and 3.3.5.2, and fasting prior to laboratory assessments detailed in Section 4.7.2.1.

3.3.5 Rescue and/or Discontinuation

3.3.5.1 Open-label metformin rescue

During period C of this Clinical Study Protocol, subjects may be eligible for the addition of open-label metformin to their study medication regimen in order to treat ongoing hyperglycemia. If subjects meet the protocol specified glycemic criteria based on FPG (see below) they will be considered for "rescue" medication. Rescue medication means the addition of an approved oral antihyperglycemic agent, used according to conventional

standards of care, to treat hyperglycemia which may therefore allow the subject to remain in the trial. The rescue medication provided by the Sponsor will be metformin.

Subjects for whom metformin is not otherwise contraindicated may receive open-label metformin added-onto, but not as replacement for, their current study medication regimen. Open-label metformin (BMS) will be supplied from IPS Mölndal. As a guidance, metformin should be started as 500 mg daily in the morning given with breakfast. Titration can occur in increments of 500 mg at 2-week intervals up to a maximum of 2500 mg given in divided doses daily with meals (see prescribing practice and guidance in Appendix F).

When a subject is started on open-label metformin they should be scheduled for titration visits to titrate the metformin dose, as tolerated, up to a maximum of 2500 mg as indicated by their glycemic response. The Sponsor recommends that the subject be scheduled for 3 titration visits at 2-weeks intervals. At each visit the Sponsor recommends increasing the open-label metformin daily dose by 500 mg if the FPG is ≥ 126 mg/dL (7.0 mmol/L). Titration of open-label metformin as a rescue medication to control hyperglycemia should occur in accordance with the prescribing practice and guidance in Appendix F.

Rescue criteria:

During period C, pre-specified parameters based on FPG are established at weeks 4, 6, 8, 12, 16, and 20:

Table 3 Rescue and/or discontinuation criteria for lack of glycemic control for period C

Visit – Period C	Fasting Plasma Glucose (central lab)
6 and 7 (weeks 4 and 6)	FPG > 240 mg/dL (13.3 mmol/L)
8 (week 8)	FPG > 220 mg/dL (12.2 mmol/L)
9, 10 and 11 (weeks 12, 16, and 20)	FPG > 200 mg/dL (11.1 mmol/L)

Subject who meet the pre-defined rescue criteria, at the specified visit, will be scheduled for a follow-up visit (within 3-5 days) to obtain a second central lab FPG value. Their glycemic status should be reviewed (including review of their glucometer readings). If the second FPG value still meets the criteria, the subject can be rescued.

A subject who meets the rescue criteria in Period C must first complete a designated visit with procedures corresponding to those described for Visit 12 (end of Period C), before receiving open-label metformin. This will ensure that important trial endpoint measurements are collected and ensure the validity of the trial.

Dedicated rescue pages in the electronic Case Report Form (eCRF) should be completed for subjects who are rescued in period C, to properly document when the rescue occurred in the visit schedule. Subjects who meet the rescue criteria but do not wish to continue in the study

should be reported as early discontinuations for the reason of "lack of efficacy" and this should be clearly indicated on the Study Termination eCRF.

Rescued subjects will then continue period C according to their original visit schedule, although additional visits may take place at weeks 10, 14, 18 and 22.

Subjects who are rescued from period C and later discontinue due to lack of glycemic control should be reported as early discontinuations for the reason of "lack of efficacy". This should be clearly indicated on the Study Termination eCRF. Subjects whose glycemia is not controlled are defined as having:

- FPG > 200 mg/dL (11.1 mmol/L) after 3 months on a maximum tolerated dose of metformin

These patients will be discontinued from the study and referred for additional antihyperglycemic treatment.

3.3.5.2 Criteria for discontinuation

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

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

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

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

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

5. Patient lost to follow-up (as defined by, unable to reach the patient after 3 documented phone calls, fax, 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 patients medical records).

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

6. Lack of efficacy from study treatment, defined as use of (need for) any antihyperglycaemic medication other than IP or rescue medication, however insulin during hospitalisation is allowed.

7. Fasting plasma glucose >270 mg/dL (15 mmol/L) before Visit 6 (week 4) confirmed by central laboratory.

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

9. Severe and/or frequent hypoglycaemic events, defined as ≥ 1 major event or recurring minor events and the possibility if correcting contributing factors (eg, excessive physical activity) has been evaluated.

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

11. Pregnancy.

12. Subjects who enter the rescue and whose glycemia is not controlled (lack of efficacy from study treatment) defined as having: FPG > 200 mg/dL (11.1 mmol/L) after 3 months on a maximum tolerated dose of metformin.

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

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

15. Increase in serum creatinine to a level of ≥132.6µmol /L, ≥1.5 mg/dL for men, ≥123.8µmol/L, ≥1.4 mg/dL for women confirmed at a repeated measurement, see Section 3.3.5.3.

3.3.5.3 Procedures for discontinuation

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

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

Randomized patients in the Randomized treatment period (Period C) who do not complete the entire study should complete the procedures described for Visit 12 (end of Period C) .

3.3.5.4 Procedures for handling incorrectly enrolled patients

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

3.3.5.5 Criteria for entering the action plans

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

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

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

3.4 Treatments

3.4.1 Identity of investigational products and rescue medications

The IPs and additional drug presented in Table 4 will be supplied by Bristol-Myers Squibb Pharmaceutical Research Institute. The tablets may contain lactose, which may cause discomfort in lactose-intolerant individuals.

Table 4 Identity of investigational products and rescue medications

Treatment	Dosage form and strength	Manufacturer
IP:		
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
Rescue medication:		
Glucophage® (metformin hydrochloride)	Film coated, white to off-white round tablet, 500 mg	Bristol-Myers Squibb
Metformin	Tablet, 500 mg	Local sourcing

3.4.2 Doses and treatment regimens

The blinding is ensured by using double-blind, single dummy technique. The IPs saxagliptin or placebo will be taken orally. Saxagliptin or placebo should be taken once daily in the morning. The IP should be taken at approximately the same time of the day during the study period. Patients should be instructed to abstain from all food for 8 hours prior to each clinical visit; however, drinking water is allowed. For all visits, the patients should visit the study centre in the morning without taking the IP. In the morning prior to each visit, acceptable concomitant medications can be taken with water only.

Treatment during lead-in period (Period B):

During the lead-in period (Period B), each patient will receive 1 single-blind bottle containing 35 tablets of placebo to match saxagliptin 5 mg.

- One single-blind bottle containing 35 tablets of placebo to match saxagliptin 5 mg oral for the 4-week placebo lead-in period.

Treatment during double-blind randomized treatment period (C):

At each visit during the randomized treatment (Period C) with the exception of visit 5 and 7 each patient will receive 1 double-blind bottle containing 35 tablets of saxagliptin 5 mg or 1 bottle containing 35 tablets of matching placebo.

- Saxagliptin tablets 5 mg oral for the 24-week double-blind treatment period .
- Matching placebo tablets for saxagliptin 5 mg oral for the 24-week double-blind treatment period

Randomization Treatment Dose**:**

Saxagliptin 5 mg/placebo, 1 tablet as morning dose

Rescue medication

Open-label metformin will be provided by the Sponsor and dispensed as 500 mg tablets. As a guidance, metformin should be started as 500 mg daily in the morning given with breakfast. Titration can occur in increments of 500 mg at 2-week intervals up to a maximum of 2500 mg given in divided doses daily with meals (see Appendix F).

India will be supplied with metformin (BMS) from IPS Mölndal. These bottles will contain 100 tablets of metformin.

3.4.3 Labelling

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

All IPs will be packed in bottles. The saxagliptin/placebo bottles will contain 35 tablets. A tear-off label will be attached to the bottles. One part will be permanently affixed to the bottle and the other part will be a tear-off portion for insertion into the drug accountability section in the Investigator's Study File. The labels will fulfil GMP Annex 13 requirements and local regulatory guideline.

Meformin bottles for rescue medication to India will have a tear-off label attached to the bottles.

3.4.4 Storage

All IPs and rescue medication must be kept in a secure place under appropriate storage conditions. A description of the appropriate storage and shipment conditions are specified on the IP label, carton labels, and in the IB.

3.4.5 Accountability

It is the investigator and/or institution's responsibility to establish a system for handling study treatments, including investigational medicinal products, to ensure that:

- Deliveries of products from AstraZeneca are correctly received by the Investigator or their designee.
- Such deliveries are recorded on a drug log. The Investigator must maintain accurate records accounting for the receipt of the investigational materials (AstraZeneca or its designee will provide a copy of the Investigational Product Shipping Order/Delivery Note for this purpose) and for the disposition of the material. This record keeping will consist of a dispensing record including the identification of the person to whom the drug is dispensed, the quantity and the date of dispensing, and any unused drug returned to the Investigator. This record is in addition to any drug accountability information recorded on the eCRFs. At the completion of this study, it must be possible to reconcile delivery records with records of usage and returned stocks. Any discrepancies must be accounted for. Certificates of delivery and return must be signed, preferably by the Investigator or designated responsible person.
- Study treatments are handled and stored safely and properly (Section 0)
- Study treatments are only dispensed to study patients in accordance with this protocol.
- The investigational materials are to be prescribed only by the Investigator, sub investigator or their designee. Under no circumstances will the Investigator allow the investigational drug to be used other than as directed by the protocol without prior AstraZeneca approval.
- Any unused products are accounted for and returned to a designated facility or to AstraZeneca for destruction, or may be destroyed locally as per your local regulatory requirements.
- Patients must return all unused medication and empty containers to the Investigator. The number of tablets returned must be counted and checked against the number dispensed to determine subject compliance. This information must be captured on the appropriate eCRF page(s). The Investigator will retain all returned study medication along with any study treatments not dispensed. At the termination of the study or at the request of AstraZeneca or its' designee, the Investigator must

return any unused supplies to AstraZeneca. This return will be documented by using an Investigational Product Return Invoice (or an equivalent form) supplied by AstraZeneca or its' designee.

3.5 Method of assigning patients to treatment groups

After written informed consent has been obtained the patient will be assigned an enrolment code (E-code) (centre, and patient specific) by the investigator. The E-code will be used to identify the patient throughout study participation. Patient eligibility will be established before treatment randomization.

The randomization code will be assigned from a randomization list prepared by a computerized system at AstraZeneca. Patients within a centre will be randomized strictly sequentially as patients are eligible for randomization. The randomization will be done within blocks of consecutive randomization codes which are available at each study centre. Patients will be randomized balanced for the two possible treatment groups.

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

3.6 Blinding and procedures for unblinding the study

3.6.1 Methods for ensuring blinding

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

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

3.6.2 Methods for unblinding the study

Individual treatment codes, indicating the treatment randomization for each randomized patient, will be available to the investigator(s) or pharmacists at the study centre.

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

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

double blind treatment codes are broken should be discontinued from the study as soon as possible.

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

Treatment codes will not be broken for the planned analyses of data at Week 24 until all decisions on the evaluability of the data from each individual patient at the end of each period have been made and documented. However, the treatment code will be strictly kept within AstraZeneca and Bristol-Myers Squibb to safeguard the integrity of the double-blind treatment and hence to avoid possible bias in data handling to the greatest extent. Except for safety reasons, patients, investigators and study monitors in the field will have no access to the individual treatment code until after the finalisation of the Clinical Study Report.

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

3.7.1 General medication

Other medication than described in Exclusion Criteria Section 3.3.3 and Discontinuation Criteria Section 3.3.5.2, which is considered necessary for the patient's safety and well-being (e.g., to treat illnesses or complaints that occur during the study), may be given at the discretion of the Investigator(s). The administration of all medication (including IP or placebo must be recorded in the appropriate sections of the eCRF. The specific type of medication (trade or generic name), the indication for use, and the dates of usage should be reported.

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

Prohibited and restricted medications in this study are:

- Insulin therapy within one year of enrolment
- Previous treatment with any DPP-IV inhibitor
- Treatment with CYP450 3A4 inducers (carbamazepine, dexamethasone, phenobarbital, phenytoin, rifampin)
- Treatment with chronic systemic glucocorticoids other than replacement therapy. Inhaled, local injected and topical use of glucocorticoids is allowed. However, two temporary periods no longer than 7 days each are allowed
- Human immunodeficiency virus (HIV) treatment/antiviral drugs (e.g., delavirdine, indinavir, nelfinavir, ritonavir, saquinavir)
- Traditional herbal medicine should not be used from visit 2 lead in period (Period B) through the final study assessments.

This is also specified in the sections Exclusion Criteria Section 3.3.3, Restrictions Section 3.3.4 and Discontinuation Criteria Section 3.3.5.2.

3.7.3 Post-study treatment

After visit 12 (Last visit), the patients will be treated according to clinical practice at the discretion of the investigator.

3.8 Treatment compliance

Compliance will be discussed at each study visit and assessed based on returned tablet counts. Patients will be asked to return all unused IPs including empty packages to the clinic at each visit with the exception of visit 3, 5 and 7. Patients judged to be non-compliant (non-compliance is defined as patients taking less than 80% or more than 120% of their prescribed dose of IP), may continue in the study, but should be counselled on the importance of taking their study medication as prescribed.

4. MEASUREMENTS OF STUDY VARIABLES AND DEFINITIONS OF OUTCOME VARIABLES

4.1 Primary variable

The primary endpoint is change from baseline to Week 24 in HbA1c The HbA1c is used as the basis for the sample size calculation, see Section 6.5.

4.2 Screening and demographic measurements

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

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

- Prior and concomitant medication.

4.3 Patient-Reported Outcomes (PROs) - Not applicable

4.4 Health Economic measurements and variables - Not applicable

4.5 Pharmacokinetic measurements and variables - Not applicable

4.6 Efficacy and pharmacodynamic measurement and variables

The baseline is defined as the assessment at randomization visit (Visit 4). The laboratory parameters that will be measured to assess efficacy and at which visits are shown in Table 5. The results from baseline and onwards will not be reported to the investigator unless the values are meeting the defined rescue and/or discontinuation criteria in Section 3.3.5.1 and 3.3.5.2, except for total cholesterol (TC), High-density lipoprotein-cholesterol (HDL-C) , Low-density lipoprotein-cholesterol (LDL-C) and triglyceride (TG) which will be reported.

Table 5 Efficacy laboratory variables Period A, B and C

Visit number	1	2	3	4	5	6	7	8	9	10	11	12
Study week	**-42 -31 days**	**-4 w**	**-1w**	**0 w**	**2 w**	**4w**	**6 w**	**8 w**	**12 w**	**16 w**	**20 w**	**24 w**
HbA1c[a]	X		X	X		X		X	X	X	X	X
FPG[a]	X		X	X	X	X	X	X	X	X	X	X
Insulin[a]				X								X
C-peptide[a]	X											
TC[a]				X								X
LDL-C[a]				X								X
HDL-C[a]				X								X
TG[a]				X								X

[a] Fasting

4.6.1 Blood and urine samples

4.6.1.1 Methods of assessment

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

Sample collection

The central laboratory will provide the centres with all the appropriate materials for specimen collection and sample processing, packaging, and shipping. A laboratory manual for

investigators giving detailed instructions will be provided to each centre prior to the start of the Clinical Study. The investigator should follow the procedures defined in this manual.

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

Sample labelling

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

Sample shipment

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

4.7 Safety measurements and variables

The methods for collecting safety data by AstraZeneca and Bristol-Myers Squibb, per the Safety Data Exchange Agreement between these two companies, are described below.

4.7.1 Adverse events

4.7.1.1 Definitions

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

Adverse event

An AE is the development of an undesirable medical condition or the deterioration of a preexisting 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 (e.g., nausea, chest pain), signs (e.g., tachycardia, enlarged liver) or the abnormal results of an investigation (e.g., laboratory findings, ECG). In clinical studies, an AE can include an undesirable medical condition occurring at any time, including run-in, lead-in, or washout periods, even if no study treatment has been administered.

Serious adverse event

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

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

The causality of SAEs (i.e., their relationship to study treatment) will be assessed by the investigator(s), who in completing the relevant case report form must answer "yes" or "no" to the question "Do you consider that there is a reasonable possibility that the event may have been caused by any of the following – study medication – other medication?". For further guidance on the definition of an SAE and a guide to the interpretation of the causality question, see Appendix B to the Clinical Study Protocol.

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

AEs of special interest

Significant AEs of particular clinical importance, other than SAEs and those AEs leading to discontinuation of the patient from study treatment, include skin disorders, lymphocytopenia, thrombocytopenia, symptomatic edema of hands and feet and infections. Specific clinical details for AEs of special interest will be captured in the eCRF.

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

4.7.1.2 Recording of AEs

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

- mild (awareness of event but easily tolerated)
- moderate (discomfort enough to cause some interference with usual activity)
- severe (inability to carry out usual activity)

- very severe (debilitating, significantly incapacitates 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 4.7.1.1. An AE of severe intensity need not necessarily be considered serious. For example, nausea that persists for several hours may be considered severe nausea, but not an SAE. On the other hand, a stroke that results in only a limited degree of disability may be considered a mild stroke but would be an SAE.

Diagnosis

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

Causality

A causality assessment must be recorded for all SAEs and AEs. The eCRF asks the question, "In your medical judgment, is there a reasonable possibility that the event may have been caused by the investigational product?" If there is any valid reason, even if undetermined or untested, for suspecting a possible cause-and-effect relationship between the IP and the occurrence of the AE, then this should be answered "yes". Otherwise, if no valid reason exists for suggesting a possible relationship, then this should be answered "no". If more than one AE is identified, a causality assessment must be made for each AE. For SAEs the causality will also be assessed with regard to concomitant medication. For further guidance on the definition of an SAE and a guide to the interpretation of the causality question, see Appendix B to the Clinical Study Protocol.

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

Abnormal laboratory tests/ECGs/vital signs

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

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

- Any laboratory test result that meets the criteria for an SAE.
- Any laboratory abnormality that requires the patient to have IP discontinued or interrupted.

- Any laboratory abnormality that requires the patient to receive specific corrective therapy.

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

Follow-up of ongoing AEs

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

Adverse Events reported after end of treatment

All AEs will be collected up to and including the final visit. Only unsolicited SAEs will be collected for a period of up to 30 days after the last dose of IP. All SAEs and associated concomitant medications will be recorded in the appropriate sections of the eCRF and reported to the Bristol-Myers Squibb Pharmacovigilance as described in Section 4.7.1.3.

Hypoglycaemic events

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

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

Overdose

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

Pregnancy

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

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

4.7.1.3 Reporting of serious adverse events

Investigators and other centre personnel must inform appropriate AstraZeneca representatives via the web based data capture (WBDC) system of any SAE that occurs in the course of the study within 1 calendar day (ie, immediately but no later than the end of the next business day) of when he or she becomes aware of it. Follow-up information on SAEs must also be reported by the Investigator within the same time frame.

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

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

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

All SAEs have to be reported, whether or not considered causally related to the IP or to the study procedure(s). All SAEs will be recorded and reported to AstraZeneca in the eCRF as described in Section 4.7.1.2. AstraZeneca or the Investigator is responsible for informing the Ethics Committees of the SAE as per local requirements. Reporting of SAEs to Regulatory Authorities is the responsibility of AstraZeneca.

SAE handling using WBDC

SAE information will be entered and submitted into the WBDC system on the relevant eCRF modules. An automated e-mail alert will be sent to the designated AstraZeneca representative who will work with the Investigator to ensure that all the necessary information is available in the system within the required time frames. If the system is unavailable, the Investigator should fax a paper back-up SAE report to the AstraZeneca representative immediately, recognising that the same reporting time frames still apply. The Investigator is responsible for completing the eCRF as soon as the system becomes available again. The AstraZeneca representative will send a completed SAE report to the appropriate Bristol-Myers Squibb Pharmacovigilance representative via fax or e-mail.

4.7.2 Laboratory safety measurements and variables

4.7.2.1 Methods of assessment

Blood and urine specimens will be collected for laboratory analyses. The date and time of sampling will be recorded on the laboratory requisition form. The samples will be processed by a central laboratory and results will be reported back to the clinic within 72 hours.

Due to the fasting laboratory assessments, all patients will visit the clinic on a fasting stomach in the morning, before 11:00 AM. The patients will be instructed not to have ingested any food or beverages 8 hours before visiting the clinic (however, drinking water is allowed). Also, the patients will be instructed to not take the IP in the morning before visiting the clinic. Allowed medications can be taken with water only.

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

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

The complete list of safety laboratory tests is displayed in Table 6 and additional safety laboratory tests triggered by the action plans are listed in Table 7.

Table 6 Safety laboratory variables Period A, B and C

Visit number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**
Study week	**-42 to-31 days**	**-4 w**	**-1w**	**0 w**	**2 w**	**4 w**	**6w**	**8 w**	**12 w**	**16 w**	**20 w**	**24 w**
Haematology												
Haemoglobin	X		X	X		X		X	X	X	X	X
Haematocrit	X		X	X		X		X	X	X	X	X
Red blood cell count	X		X	X		X		X	X	X	X	X
White blood cell count and differential	X		X	X		X		X	X	X	X	X
Platelet count	X		X	X		X		X	X	X	X	X
Clinical chemistry												
AST	X		X	X		X		X	X	X	X	X
ALT	X		X	X		X		X	X	X	X	X
Alkaline Phosphatase	X		X	X		X		X	X	X	X	X
Creatine Kinase (CK)	X		X	X		X		X	X	X	X	X
Total Bilirubin	X		X	X		X		X	X	X	X	X
Blood Urea Nitrogen (BUN)	X		X	X		X		X	X	X	X	X
Electrolytes: - Sodium - Potassium - Chloride	X		X	X		X		X	X	X	X	X
Total Protein	X		X	X		X		X	X	X	X	X
Albumin	X		X	X		X		X	X	X	X	X
TSH[a]	X											

Visit number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**
Study week	**-42 to-31 days**	**-4 w**	**-1w**	**0 w**	**2 w**	**4 w**	**6w**	**8 w**	**12 w**	**16 w**	**20 w**	**24 w**
Serum Creatinine (SCr), calculated Creatinine Clearance [b]	X		X	X		X		X	X	X	X	X
Follicle Stimulating Hormone (FSH)[c]	X											
Hepatitis Screen Panel:	X											
- Hepatitis C virus antibody (anti-HCV)[d]												
- Hepatitis B Surface Antigen (HBsAg)												
Urinalyses												
pH	X		X	X		X		X	X	X	X	X
Protein [e]	X		X	X		X		X	X	X	X	X
Glucose	X		X	X		X		X	X	X	X	X
Leukocyte esterase[e]	X		X	X		X		X	X	X	X	X
Blood by dipstick [e]	X		X	X		X		X	X	X	X	X
Pregnancy test[f]	X		X	X	X	X	X	X	X	X	X	X
Albumin:creatinine ratio	X		X	X		X		X	X	X	X	X

a If abnormal, reflex to free T4
b Creatinine clearance will be estimated by the central lab by the method of Cockcroft -Gault
c For women on HRT
d If positive, reflex to Assay for Hepatitis C virus RNA (HCV PCR)
e Microscopy if dipstick positive for blood, leukocyte esterase or protein
f Urine HCG pregnancy test for WOCBP (HCG minimum sensitivity of 25 IU/L) (dipstick analysed at the study centre)

Table 7 Additional safety laboratory tests as potentially triggered by action plans

Visit number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**
Study week	**-42 to –31 days**	**-4 w**	**-1w**	**0 w**	**2 w**	**4 w**	**6w**	**8 w**	**12 w**	**16 w**	**20 w**	**24 w**
If elevated Serum Creatinine:												
- Serum Creatinine (SCr)	X			X		X		X	X	X	X	X
If lymphocytopenia[a]												
- Absolute lymphocyte count	X			X		X		X	X	X	X	X
- Complete Blood Count (CBC) with differential	X			X		X		X	X	X	X	X
- Lymphocyte subsets including: - CD4 + counts - CD8 + counts	X			X		X		X	X	X	X	X
If thrombocytopenia[b]												
- Thrombocyte count	X			X		X		X	X	X	X	X
- CBC with differential	X			X		X		X	X	X	X	X
- Peripheral blood smear	X			X		X		X	X	X	X	X
- Antiplatelet antibodies	X			X		X		X	X	X	X	X
- Test for fecal occult blood	X			X		X		X	X	X	X	X
- Optional bone marrow sample[c]					X[f]	X[f]	X[f]	X[f]	X[f]	X[f]	X[f]	X[f]

a See Appendix D
b See Appendix E
c Only done if a patient meet the criteria in Appendix E and investigator and hematologist consider that the patient needs to have bone marrow test done according to clinical judgment and patients also consent to do it. There is a separate informed consent for the bone marrow biopsy and it is not a mandatory part of the study.

Laboratory values outside the reference limits suspected to be of any clinical significance will be re-checked. Patients in whom the suspected clinical significance is confirmed at repeated sampling will either not be included or, if already included, will be followed until normalization or for as long as medically indicated.

At visit 1, all subjects will be tested for hepatitis B surface antigen, antibodies to hepatitis C virus, and antibodies to HIV. If a subject tests positive for HIV or hepatitis it will be reported according to local legislation and the subject will be excluded from entering, or continuing in, the study.

4.7.2.2 Derivation or calculation of outcome variables

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

4.7.3 Vital signs, ECG and physical examination

4.7.3.1 Methods of assessment

Pulse and blood pressure

One pulse measurement will be taken after the patient has been sitting and resting for at least 5 minutes and before blood samples are taken. The pulse measurement will be followed by three blood pressure measurements (at least 1 minute rest between each measurement), using a standardized cuff adapted to the size of the patient's arm.

ECG

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

Weight and height

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

Waist circumference

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

Physical examinations

The physical examination includes the following: General appearance including skin inspection, lymph nodes, thyroid, musculoskeletal/extremities, cardiovascular, lungs, abdomen, and reflexes. Baseline data is collected at Visit 4, and new findings at the following physical examinations are recorded as change from baseline.

Brief physical examinations

The brief physical examination includes the following: skin, extremities, cardiovascular, lungs, and abdomen. Baseline data is collected at Visit 4 during the full physical examination, and new findings at the following physical examinations are recorded as change from baseline.

4.7.3.2 Derivation or calculation of outcome variables

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

4.7.4 Other safety measurements and variables

4.7.4.1 Methods of assessment

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

Fasting plasma glucose concentrations

Fasting plasma glucose should be self-monitored at least every second day during the lead-in and the remaining treatment period. The patient diary will be collected from Visit 4 (and kept in the investigator study file and a new diary for the next period will be handed over to the patient, if needed.

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

Hypoglycaemic events

The patient will be asked to always 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. In the patient diary plasma glucose will be referred to as *blood glucose* in order not to confuse the patients.

A hypoglycaemic event can be either

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

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

Major hypoglycaemic events, defined as symptomatic events requiring external assistance due to severe impairment in consciousness or behaviour, with plasma glucose level <3.5 mmol/L, <63 mg/dL, and prompt recovery after glucose or glucagon administration.

Minor hypoglycaemic event, defined as either a symptomatic event with plasma glucose level <3.5 mmol/L, <63 mg/dL, and no need for external assistance, or an asymptomatic plasma glucose measurement <3.5 mmol/L, <63 mg/dL.

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

Plasma glucose values, not blood glucose values, will be obtained from the central laboratory and glucometers provided by AstraZeneca.

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

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

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

4.7.5 Independent Adjudication Committee

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

4.8 Volume of blood sampling and handling of biological samples

The total volume of blood that will be drawn from each patient in this study is shown in Table 8:

Table 8 Volume of Blood to be drawn from each Patient

Assessment		Total volume (mL)
Efficacy and safety	Clinical chemistry	100 (130)[a]
	Haematology	32 (45)[a]
	Possible additional samples for haematology which may be applicable for patients in the algorithm for thrombocytopenia and/or lymphocytopenia (depending on number of blood sample visits)	60
Rescue visits	Possible additional clinichal chemistry samples if the patient enters rescue (depending on number of rescue visits)	42
	Possible additional haematology samples if the patient enters rescue (depending on number of rescue visits)	12
Maximum total volume, no rescue visits		**192 (235)[a]**
Maximum total volume with 4 rescue visits		**246 (290)[a]**

[a] The blood volume stated within brackets may be applicable for patients with laboratory values outside the reference limits suspected to be of any clinical significance with need to be re-checked. Patients in whom a suspected clinical significance is confirmed at repeated sampling will be followed until normalization or for as long as medically indicated.

The maximum blood volume drawn at one visit will be less than 20 mL.

4.8.1 Analysis of biological samples

4.8.1.1 Clinical chemistry samples

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

If the contracted central clinical laboratory chooses to sub-contract the analytical work to another laboratory, the contracted central clinical laboratory must assure itself and provide

assurance to AstraZeneca that the other laboratory will apply defined stability limits to all analyses performed on behalf of AstraZeneca. Samples falling outside these limits must not be analysed or data reported. The other laboratory will inform AstraZeneca of the stability limits relevant to this study before the first patient gives informed consent to take part in the study.

5. DATA MANAGEMENT

Data will be entered in the WBDC system at the investigational centre within 2 business days after the scheduled visit (except for SAEs that should be entered within 1 calendar day). Trained study personnel will be responsible for entering data on the observations, tests and assessments specified in the protocol into the WBDC system and according to the eCRF Instructions. The eCRF Instructions will also provide the study site with data entry instructions. Data entered in the WBDC system will be immediately saved to a central database and changes tracked to provide an audit trail. When data have been entered reviewed, edited and Source Data Verification (SDV) performed the principal investigator will be notified to sign the eCRF electronically as per the agreed project process and data will be frozen to prevent further editing. A copy of the eCRF will be provided to the investigational centre after the study database has been locked for archiving at the investigational centre.

Data Management determines the format of the data to be received from external vendors and coordinates the flow of data to an external environment or clinical database (if applicable). Data Management will ensure that the data collection tool will be tested / validated as needed. External data reconciliation will be done with the clinical database as applicable.

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

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

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

Following database lock, required amendments to the database due to critical errors will only be allowed with the appropriate supporting documentation. Non-critical errors will not result in amendments to the database but will be captured via the appropriate documentation. An

electronic copy (disc or equivalent) of the eCRF will be made available to the Investigator centre after the study database has been locked.

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

Serious Adverse Event Reconciliation Reports are produced and reconciled with the BMS global pharmacovigilance database.

6. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

6.1 Statistical evaluation – general aspects

A comprehensive Statistical Analysis Plan (SAP) will be prepared before unblinding of the data, or in instances where the data are not blinded, database lock.

All statistical evaluation, as well as summaries and tabulations will be done by qualified personnel at AstraZeneca. Before breaking the treatment codes following clean file declaration, all decisions on the evaluability of the data from each individual patient will be made and documented and each patient will be assigned to the appropriate analysis data set.

6.2 Description of outcome variables in relation to objectives and hypotheses

The primary objective of this study is to assess whether saxagliptin is efficacious as compared to placebo (superior comparison) in improving glycaemic control in drug naïve patients with type 2 diabetes. The primary outcome variable is the absolute change from baseline to week 24 in HbA1c.

Secondary efficacy outcome variables are:

- Absolute change from baseline to week 24 in FPG for superior comparison between the treatment groups.

- Proportion of patients achieving a therapeutic glycaemic response defined as HbA1c <7.0% at end of the double blind treatment period for treatment dependency determination.

The other secondary efficacy endpoints are:

- Change from baseline to week 24 in β-cell function and insulin sensitivity (as measured by HOMA-2

- The change from baseline in fasting insulin

- Change from baseline in BMI, waist circumference and weight

- The proportion of patients achieving a glycaemic response for each category defined below:

- HbA1c ≤6.5%
- Reduction in HbA1c ≥0.5%
- Reduction in HbA1c ≥0.7%
- FPG <110 mg/dL (6.1 mmol/L)
- FPG <126 mg/dL (7.0 mmol/L)

- Percent change from baseline in fasting lipids TC, LDL-C, HDL-C and TG.

Safety: Safety and tolerability will be evaluated by assessment of AEs (including AE of special interest), hypoglycaemic events, laboratory values, electrocardiogram (ECG), pulse, blood pressure (BP), weight and physical examination.

6.3 Description of analysis sets

The primary outcome and secondary efficacy endpoints analyses will be performed on the full analysis sets (FAS) with last observation carried forward method to estimate the missing values at week 24. The safety endpoints will be analysed from the safety analysis set.

6.3.1 Lead-In analysis set

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

6.3.2 Randomized analysis set

For the summary of baseline characteristics, all patients with a randomization code who took at least one dose of double-blind treatment will be included in the analysis set.

6.3.3 Full analysis set (FAS)last observation carried forward (LOCF)

For the analysis of all Week 24 primary efficacy endpoint and all secondary efficacy endpoints, the Full Analysis set is a subset of randomized analysis set including patients who take at least one randomized IP dose, have non-missing baseline and post baseline efficacy data. Data recorded on or after rescue medication will be excluded from all analysis of efficacy data. The missing Week 24 efficacy endpoints will be replaced by last observed value prior to rescue medication after baseline. Missing baseline (Visit 4) data will be estimated by a single value assessed closest and prior to randomisation, if one exists. Statistical inference

on the primary endpoint will be drawn based on FAS result and augmented by the results from the PP analysis set.

6.3.4 Per protocol analysis set

The PP analysis set is a subset of Full Analysis set including patients who have no reasons for exclusions. The primary efficacy variable of change from baseline in HbA1c will only be analyzed using the PP analysis data set if more than 10% of the subjects in any regimen are found to significantly violate the terms and conditions of the protocol. Otherwise, analysis of the primary efficacy variable will be restricted to the FAS.

These exclusions from the PP analysis set will include but not be limited to the patients who took prohibited concomitant medications, non-compliance to IP and major deviations of study procedures. These exclusions for the PP analysis set will be explicitly defined in SAP prior to database locking.

6.3.5 Safety analysis set

The safety analysis set is a subset of randomized analysis set including patients who take at least one IP dose. Actual treatment will be re-assigned to patient who has taken IP dose other than what they were randomized to for the duration of the entire 24 weeks. Analysis will only use values that are actually measured. Safety data on or after rescue medication will be flagged.

6.4 Method of statistical analysis

6.4.1 Analysis of double-blind treatment period (week 0 – 24)

The primary efficacy analysis to establish superiority of saxagliptin treatment over placebo on the absolute change in HbA1c from baseline to Week 24 in drug naive patients with T2DM. Analysis of change from baseline in HbA1c will be performed on a Full analysis set using an analysis of covariance model (ANCOVA). The null and alternative hypotheses of interest are:

H_0: $\mu_s = \mu_p$ *VS* Ha: $\mu_s \neq \mu_p$,

Where μ_s and μ_p are adjusted mean change from baseline to week 24 in HbA1c for saxagliptin and placebo treatment groups, respectively.

The model will use treatment as an effect and baseline value as a covariate. Within the framework of the ANCOVA model, point estimates and the two-sided 95% confidence intervals for the mean change within each treatment group as well as for the differences in mean change between the saxagliptin treatment arm and the placebo treatment arm will be performed.

Analyses of the secondary efficacy endpoints for the following secondary efficacy endpoints and the associated statistical analysis methods to be used are:

(1) Change from baseline to Week 24 in FPG; ANCOVA similar to the model used for the primary endpoint using FAS;

(2) The treatment dependency of proportion of patients achieving a therapeutic glycaemic response defined as HbA1c <7.0% will be discriminated by two-sided Fisher's Exact test using FAS;

A fixed-sequence test method will be used for the overall primary efficacy endpoint and the three secondary efficacy endpoints described above to control type I error rate not to exceed the 0.05 level. The fixed-sequence test method will be applied to these endpoints in the sequential order as presented above.

Statistical inference will start from the overall primary efficacy endpoint, if saxagliptin treatment group is superior in ΔHbA1c than the placebo group, then statistical inference will continue with the first secondary efficacy endpoint (1), otherwise statistical inference of the overall efficacy endpoints will stop. The p-values that follow can not be considered as significant in this confirmatory analyses when the fixed-sequence procedure is used to control the familywise type 1 error rate, even if the p-value is less than 0.05.

Similarly if saxagliptin treatment group is superior in ΔFPG than the placebo group, then statistical inference will continue with the second secondary efficacy endpoint (2), otherwise statistical inference of the overall efficacy endpoints will stop.

The set of Other Secondary Efficacy endpoints will be analyzed by ANCOVA methods which will use treatment as an effect and baseline value as a covariate. Within the framework of the ANCOVA model, point estimates and the two-sided 95% confidence intervals for the mean change within each treatment group as well as for the differences in mean change between the two treatment groups will be reported. The proportion of patients achieving a glycaemic response will be summarized by frequency tables.

Other subgroup analysis, if warranted, will be specified in the SAP.

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

Analysis for safety and tolerability endpoints will be summarized by descriptive statistics or frequency tables and/or graphic method. There are no hypotheses proposed a priori to these safety endpoints.

6.5 Determination of sample size

With a total of 206 patients randomized and treated (or 103 per treatment group), there is 90% power to detect 0.5% difference between the two randomized treatment groups in absolute change from baseline to week 24 in HbA1c at the 5% level assuming standard deviation of change from baseline in HbA1c is 1.1%. A total of 218 patients will be randomized to account for 5% of patients being unevaluable for the primary endpoint analysis.

6.6 Interim analyses – Not applicable

6.7 Data monitoring committee

In this study, a Data Monitoring Committee will not be used.

7. STUDY MANAGEMENT

7.1 Monitoring

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

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

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

- Provide information and support to the investigator(s).
- Confirm that facilities remain acceptable.
- Confirm that the investigational team is adhering to the protocol that data are being accurately recorded in the eCRFs, and that IP accountability checks are being performed.
- Perform SDV (a comparison of the data in the eCRFs with the patient's medical records at the hospital or practice, and other records relevant to the study). This will require direct access to all original records for each patient (e.g., clinic charts).
- Perform source verification of the genetic consent of participating patients and ensure that the investigational team is adhering to the specific requirements of this genetic research.

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

7.2 Audits and inspections

Authorised representatives of AstraZeneca, a regulatory authority, or an Ethics Committee may visit the centre to perform audits or inspections, including SDV. The purpose of an AstraZeneca audit or inspection is to systematically and independently examine all study-

related activities and documents to determine whether these activities were conducted, and data were recorded, analysed, and accurately reported according to the protocol, Good Clinical Practice (GCP), guidelines of the International Conference on Harmonisation (ICH), and any applicable regulatory requirements. The investigator should contact AstraZeneca immediately if contacted by a regulatory agency about an inspection at his or her centre.

7.3 Training of staff

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

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

Before the first patient is entered into the study the investigational staff will have an opportunity to discuss the procedures associated with the collection of blood samples with AstraZeneca personnel. The ethical considerations and the importance of the informed consent process will be made clear. The requirements for the collections of the patients' samples will also be made clear.

7.4 Changes to the protocol

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

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

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

If a protocol amendment requires a change to a particular centre's Informed Consent Form, then AstraZeneca and the site's Ethics Committee must be notified. Approval of the revised Informed Consent Form by AstraZeneca and by the Ethics Committee is required before the revised form is used.

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

7.5 Study agreements

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

7.6 Study timetable and end of study

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

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

The planned overall timetable for the study is as follows:

First Patient In	Planned to Q2 2009
Last Patient In	Planned to Q1 2010
Last Patient Last Visit	Planned to Q3 2010
Data base lock	Planned to Q4 2010

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

8. ETHICS

8.1 Ethics review

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

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

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

Where there is a genetic research, approval must be obtained for this genetic research and the associated genetic informed consent from the Ethics Committee. It must be clearly stated in the approval that this genetic research is approved. The investigator must submit written approval to AstraZeneca before any patient participates in this genetic research.

8.2 Ethical conduct of the study

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

8.3 Informed consent

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

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

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

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

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

8.4 Patient data protection

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

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

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

9. PROCEDURES IN CASE OF EMERGENCY, OVERDOSE OR PREGNANCY

9.1 AstraZeneca emergency contact procedure

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

Role in the study	Name	Address & telephone number
Study Delivery Team Leader		
Study Delivery Team Physician		
The local AstraZeneca representative can be found in the 'Supplement 1 Study Delivery Team Contacts in the Event of Emergency'		

9.2 Procedures in case of medical emergency

The principal investigator(s) is responsible for ensuring that procedures and expertise are available to handle medical emergencies during the study. **A medical emergency usually constitutes an SAE and should be reported as such, see Section 4.7.1.1.**

The treatment code may not be broken unless in an emergency situation when the appropriate management of the patient necessitates knowledge of the treatment allocation. In such an emergency, the Investigator will, if time and circumstances permit, contact the local

AstraZeneca representative prior to breaking the treatment code. If the treatment code is broken, the date, time, and reason should be recorded and the Investigator should sign the record, see also Section 3.6.2.

9.3 Procedures in case of overdose

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

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

9.4 Procedures in case of pregnancy

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

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

10. REFERENCES

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Clinical Study Protocol Appendix A	
Drug Substance	Saxagliptin
Study Code	D1680C00008
Edition Number	1
Appendix Date	
Protocol Dated	

Appendix A
Signatures

ASTRAZENECA SIGNATURE(S)

A 24-Week National, Multi-centre, Randomized, Parallel-group, Double-blind, Placebo-controlled, Phase IIIb study in India to Evaluate the Efficacy and Safety of Saxagliptin in Adult Patients with Type 2 Diabetes who have Inadequate Glycaemic Control with Diet and Exercise.

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

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

AstraZeneca Research and Development site representative

ASTRAZENECA SIGNATURE(S)

A 24-Week National, Multi-centre, Randomized, Parallel-group, Double-blind, Placebo-controlled, Phase IIIb study in India to Evaluate the Efficacy and Safety of Saxagliptin in Adult Patients with Type 2 Diabetes who have Inadequate Glycaemic Control with Diet and Exercise.

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

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

Bristol Myers Squibb Research and Development site representative

ASTRAZENECA SIGNATURE(S)

A 24-Week National, Multi-centre, Randomized, Parallel-group, Double-blind, Placebo-controlled, Phase IIIb study in India to Evaluate the Efficacy and Safety of Saxagliptin in Adult Patients with Type 2 Diabetes who have Inadequate Glycaemic Control with Diet and Exercise.

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

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

Bristol Myers Squibb Research and Development site representative

Clinical Study Protocol: Appendix B

Drug Substance	Saxagliptin
Study Code	D1680C00008
Appendix Edition Number	1.0
Appendix Date	

Appendix B
Additional Safety Information

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

Life threatening

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

Hospitalization

Out-patient treatment in an emergency room is not in itself a serious AE, although the reasons for it may be (eg, bronchospasm, laryngeal oedema). Hospital admissions and/or surgical operations planned before or during a study are not considered AEs if the illness or disease existed before the patient was enrolled in the study, provided that it did not deteriorate in an unexpected way during the study.

Important medical event or medical intervention

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

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

Examples of such events are:

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

A GUIDE TO INTERPRETING THE CAUSALITY QUESTION

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

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

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

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

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

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

- Laboratory tests. Has a specific laboratory investigation (if performed) confirmed the relationship?

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

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

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

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

- Is there a known mechanism?

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

AstraZeneca

Clinical Study Protocol Appendix C	
Drug Substance	Saxagliptin
Study Code	D1680C00008
Appendix Edition Number	1.0
Appendix Date	

Appendix C
New York Heart Association (NYHA) Classification

1. NEW YORK HEART ASSOCIATION (NYHA) CLASSIFICATION

The NYHA classification will be based on the following definitions:

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

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

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

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

AstraZeneca

Clinical Study Protocol: Appendix D

Drug Substance	Saxagliptin
Study Code	D1680C00008
Appendix Edition Number	1.0
Appendix Date	

Appendix D
Algorithm for Lymphocytopenia

1. ALGORITHM FOR LYMPHOCYTOPENIA

1.1 Overview of procedures

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

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

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

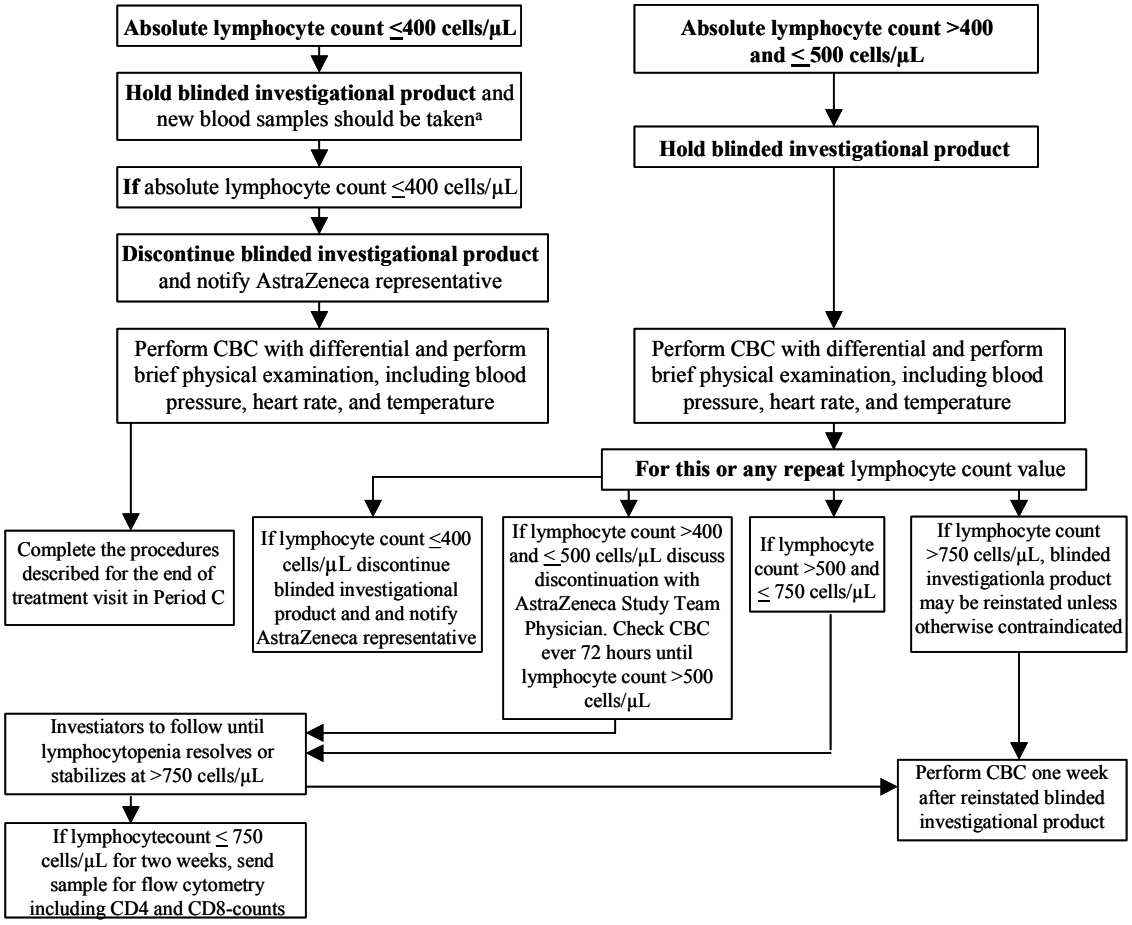
1.1.2 Patients who experience an absolute lymphocyte count ≤400 cells/µL during Period C

The Investigator and the Sponsor will be notified by the central laboratory when any patient experiences an absolute lymphocyte count ≤400 cells/µL. For patients with an absolute lymphocyte count ≤400 cells/µL at any time during Period C, investigational product should be held immediately and a new blood sample should be taken. If this second blood sample confirm an absolute lymphocyte ≤400 cells/µL the patient must discontinue from investigational product. The Investigator will notify AstraZeneca representative. Within 72 hours of the report of an absolute lymphocyte count ≤400 cells/µL, the patient will undergo brief physical examination including blood pressure, heart rate, and temperature determination, and a repeat CBC with differential will be collected. The Investigator will notify AstraZeneca representative of the repeat blood count values obtained. An end-of-study visit will be scheduled. At the end-of-study visit, all applicable procedures of a standard visit will be performed.

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

LYMPHOCYTOPENIA FLOWCHART

Double-blind treatment period C



[a] Lymphocyte count

AstraZeneca

Clinical Study Protocol Appendix E	
Drug Substance	Saxagliptin
Study Code	D1680C00008
Appendix Edition Number	1.0
Appendix Date	

Appendix E
Algorithm for Thrombocytopenia

1. ALGORITHM FOR THROMBOCYTOPENIA

1.1 Overview of procedures

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

The Investigator and the Sponsor will be notified by the central laboratory when any patient experiences a platelet count <75,000 cells/µL. The investigational product should be held immediately and a repeat blood sample should be taken. If the platelet count <75,000 cells/µL. is confirmed, the central laboratory will review the peripheral blood smear and notify the Investigator and the Sponsor as to whether the smear is compatible with the reported decrease in platelet count.

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

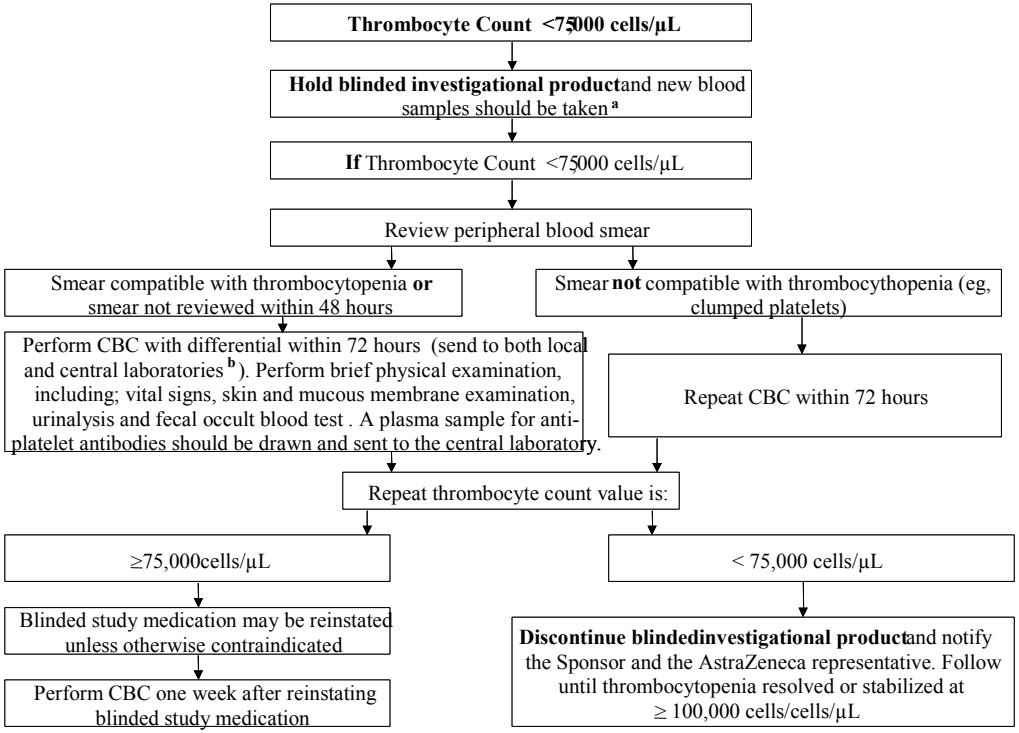
- If the peripheral blood smear **is compatible with** the reported decreased platelet count, or if the peripheral blood smear **is not reviewed within 48 hours** of the notification of the decreased platelet count, Within 72 hours, two CBCs with differential will be drawn and sent to local and central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

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

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

THROMBOCYTOPENIA FLOWCHART

Double-Blind Treatment Period C



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

Clinical Study Protocol Appendix F

Drug Substance	Saxagliptin
Study Code	D1680C00008
Appendix Edition Number	1.0
Appendix Date	

Appendix F
Metformin Prescribing Information

Bristol-Myers Squibb Company

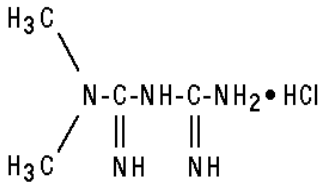
Rx only

GLUCOPHAGE®
(metformin hydrochloride tablets)

GLUCOPHAGE® XR
(metformin hydrochloride extended-release tablets)

DESCRIPTION

GLUCOPHAGE® (metformin hydrochloride tablets) and GLUCOPHAGE® XR (metformin hydrochloride extended-release tablets) are oral antihyperglycemic drugs used in the management of type 2 diabetes. Metformin hydrochloride (*N*,*N*-dimethylimidodicarbonimidic diamide hydrochloride) is not chemically or pharmacologically related to any other classes of oral antihyperglycemic agents. The structural formula is as shown:



Metformin hydrochloride is a white to off-white crystalline compound with a molecular formula of $C_4H_{11}N_5$ • HCl and a molecular weight of 165.63. Metformin hydrochloride is freely soluble in water and is practically insoluble in acetone, ether, and chloroform. The pK_a of metformin is 12.4. The pH of a 1% aqueous solution of metformin hydrochloride is 6.68.

GLUCOPHAGE tablets contain 500 mg, 850 mg, or 1000 mg of metformin hydrochloride. Each tablet contains the inactive ingredients povidone and magnesium stearate. In addition, the coating for the 500 mg and 850 mg tablets contains hypromellose and the coating for the 1000 mg tablet contains hypromellose and polyethylene glycol.

GLUCOPHAGE XR contains 500 mg or 750 mg of metformin hydrochloride as the active ingredient.

GLUCOPHAGE XR 500 mg tablets contain the inactive ingredients sodium carboxymethyl cellulose, hypromellose, microcrystalline cellulose, and magnesium stearate.

GLUCOPHAGE XR 750 mg tablets contain the inactive ingredients sodium carboxymethyl cellulose, hypromellose, and magnesium stearate.

System Components and Performance - GLUCOPHAGE XR comprises a dual hydrophilic polymer matrix system. Metformin hydrochloride is combined with a drug release controlling polymer to form an "inner" phase, which is then incorporated as discrete particles into an "external" phase of a second polymer. After administration, fluid from the gastrointestinal (GI) tract enters the tablet, causing the polymers to hydrate and swell. Drug is released slowly from the dosage form by a process of diffusion through the gel matrix that is essentially independent of pH. The hydrated polymer system is not rigid and is expected to be broken up by normal peristalsis in the GI tract. The biologically inert components of the tablet may occasionally remain intact during GI transit and will be eliminated in the feces as a soft, hydrated mass.

CLINICAL PHARMACOLOGY

Mechanism of Action

Metformin is an antihyperglycemic agent which improves glucose tolerance in patients with type 2 diabetes, lowering both basal and postprandial plasma glucose. Its pharmacologic mechanisms of action are different from other classes of oral antihyperglycemic agents. Metformin decreases hepatic glucose production, decreases intestinal absorption of glucose, and improves insulin sensitivity by increasing peripheral glucose uptake and utilization. Unlike sulfonylureas, metformin does not produce hypoglycemia in either patients with type 2 diabetes or normal subjects (except in special circumstances, see **PRECAUTIONS**) and does not cause hyperinsulinemia. With metformin therapy, insulin secretion remains unchanged while fasting insulin levels and day-long plasma insulin response may actually decrease.

Pharmacokinetics

Absorption and Bioavailability

The absolute bioavailability of a GLUCOPHAGE 500 mg tablet given under fasting conditions is approximately 50% to 60%. Studies using single oral doses of GLUCOPHAGE 500 mg to 1500 mg, and 850 mg to 2550 mg, indicate that there is a lack of dose proportionality with increasing doses, which is due to decreased absorption rather than an alteration in elimination. Food decreases the extent of and slightly delays the absorption of metformin, as shown by approximately a 40% lower mean peak plasma concentration (C_{max}), a 25% lower area under the plasma concentration versus time curve (AUC), and a 35-minute prolongation of time to peak plasma concentration (T_{max}) following administration of a single 850 mg tablet of metformin with food, compared to the same tablet strength administered fasting. The clinical relevance of these decreases is unknown.

Following a single oral dose of GLUCOPHAGE XR, C_{max} is achieved with a median value of 7 hours and a range of 4 hours to 8 hours. Peak plasma levels are approximately 20% lower compared to the same dose of GLUCOPHAGE, however, the extent of absorption (as measured by AUC) is similar to GLUCOPHAGE.

At steady state, the AUC and C_{max} are less than dose proportional for GLUCOPHAGE XR within the range of 500 mg to 2000 mg administered once daily. Peak plasma levels are approximately 0.6, 1.1, 1.4, and 1.8 μg/mL for 500, 1000, 1500, and 2000 mg once-daily doses, respectively. The extent of metformin absorption (as measured by AUC) from GLUCOPHAGE XR at a 2000 mg once-daily dose is similar to the same total daily dose administered as GLUCOPHAGE tablets 1000 mg twice daily. After repeated administration of GLUCOPHAGE XR, metformin did not accumulate in plasma.

Within-subject variability in C_{max} and AUC of metformin from GLUCOPHAGE XR is comparable to that with GLUCOPHAGE.

Although the extent of metformin absorption (as measured by AUC) from the GLUCOPHAGE XR tablet increased by approximately 50% when given with food, there was no effect of food on C_{max} and T_{max} of metformin. Both high and low fat meals had the same effect on the pharmacokinetics of GLUCOPHAGE XR.

Distribution

The apparent volume of distribution (V/F) of metformin following single oral doses of GLUCOPHAGE 850 mg averaged 654 ± 358 L. Metformin is negligibly bound to plasma proteins, in contrast to sulfonylureas, which are more than 90% protein bound. Metformin partitions into erythrocytes, most likely as a function of time. At usual clinical doses and dosing schedules of GLUCOPHAGE, steady state plasma concentrations of metformin are reached within 24 to 48 hours and are generally <1 μg/mL. During controlled clinical trials of GLUCOPHAGE, maximum metformin plasma levels did not exceed 5 μg/mL, even at maximum doses.

Metabolism and Elimination

Intravenous single-dose studies in normal subjects demonstrate that metformin is excreted unchanged in the urine and does not undergo hepatic metabolism (no metabolites have been identified in humans) nor biliary excretion. Renal clearance (see **Table 1**) is approximately 3.5 times greater than creatinine clearance, which indicates that tubular secretion is the major route of metformin elimination. Following oral administration, approximately 90% of the absorbed drug is eliminated via the renal route within the first 24 hours, with a plasma elimination half-life of approximately 6.2 hours. In blood, the elimination half-life is approximately 17.6 hours, suggesting that the erythrocyte mass may be a compartment of distribution.

Special Populations

Patients with Type 2 Diabetes

In the presence of normal renal function, there are no differences between single- or multiple-dose pharmacokinetics of metformin between patients with type 2 diabetes and normal subjects (see **Table 1**), nor is there any accumulation of metformin in either group at usual clinical doses.

The pharmacokinetics of GLUCOPHAGE XR in patients with type 2 diabetes are comparable to those in healthy normal adults.

Renal Insufficiency

In patients with decreased renal function (based on measured creatinine clearance), the plasma and blood half-life of metformin is prolonged and the renal clearance is decreased

in proportion to the decrease in creatinine clearance (see **Table 1**; also see **WARNINGS**).

Hepatic Insufficiency

No pharmacokinetic studies of metformin have been conducted in patients with hepatic insufficiency.

Geriatrics

Limited data from controlled pharmacokinetic studies of GLUCOPHAGE in healthy elderly subjects suggest that total plasma clearance of metformin is decreased, the half-life is prolonged, and C_{max} is increased, compared to healthy young subjects. From these data, it appears that the change in metformin pharmacokinetics with aging is primarily accounted for by a change in renal function (see **Table 1**). GLUCOPHAGE (metformin hydrochloride tablets) and GLUCOPHAGE XR (metformin hydrochloride extended-release tablets) treatment should not be initiated in patients ≥80 years of age unless measurement of creatinine clearance demonstrates that renal function is not reduced (see **WARNINGS** and **DOSAGE AND ADMINISTRATION**).

Table 1:	**Select Mean (±S.D.) Metformin Pharmacokinetic Parameters Following Single or Multiple Oral Doses of GLUCOPHAGE**		
Subject Groups: GLUCOPHAGE dose[a] (number of subjects)	**C_{max}[b] (μg/mL)**	**T_{max}[c] (hrs)**	**Renal Clearance (mL/min)**
Healthy, nondiabetic adults:			
500 mg single dose (24)	1.03 (±0.33)	2.75 (±0.81)	600 (±132)
850 mg single dose (74)[d]	1.60 (±0.38)	2.64 (±0.82)	552 (±139)
850 mg three times daily for 19 doses[e] (9)	2.01 (±0.42)	1.79 (±0.94)	642 (±173)
Adults with type 2 diabetes:			
850 mg single dose (23)	1.48 (±0.5)	3.32 (±1.08)	491 (±138)
850 mg three times daily for 19 doses[e] (9)	1.90 (±0.62)	2.01 (±1.22)	550 (±160)
Elderly[f], healthy nondiabetic adults:			
850 mg single dose (12)	2.45 (±0.70)	2.71 (±1.05)	412 (±98)
Renal-impaired adults:			
850 mg single dose			
Mild (CL_{cr}[g] 61-90 mL/min) (5)	1.86 (±0.52)	3.20 (±0.45)	384 (±122)
Moderate (CL_{cr} 31-60 mL/min) (4)	4.12 (±1.83)	3.75 (±0.50)	108 (±57)
Severe (CL_{cr} 10-30 mL/min) (6)	3.93 (±0.92)	4.01 (±1.10)	130 (±90)

[a] All doses given fasting except the first 18 doses of the multiple dose studies

[b] Peak plasma concentration

[c] Time to peak plasma concentration

[d] Combined results (average means) of five studies: mean age 32 years (range 23-59 years)

[e] Kinetic study done following dose 19, given fasting

[f] Elderly subjects, mean age 71 years (range 65-81 years)

[g] CL_{cr} = creatinine clearance normalized to body surface area of 1.73 m^2

Pediatrics

After administration of a single oral GLUCOPHAGE 500 mg tablet with food, geometric mean metformin C_{max} and AUC differed less than 5% between pediatric type 2 diabetic patients (12 to 16 years of age) and gender- and weight-matched healthy adults (20 to 45 years of age), all with normal renal function.

Gender

Metformin pharmacokinetic parameters did not differ significantly between normal subjects and patients with type 2 diabetes when analyzed according to gender (males = 19, females = 16). Similarly, in controlled clinical studies in patients with type 2 diabetes, the antihyperglycemic effect of GLUCOPHAGE was comparable in males and females.

Race

No studies of metformin pharmacokinetic parameters according to race have been performed. In controlled clinical studies of GLUCOPHAGE in patients with type 2 diabetes, the antihyperglycemic effect was comparable in whites (n=249), blacks (n=51), and Hispanics (n=24).

Clinical Studies

GLUCOPHAGE

In a double-blind, placebo-controlled, multicenter U.S. clinical trial involving obese patients with type 2 diabetes whose hyperglycemia was not adequately controlled with dietary management alone (baseline fasting plasma glucose [FPG] of approximately 240 mg/dL), treatment with GLUCOPHAGE (up to 2550 mg/day) for 29 weeks resulted in significant mean net reductions in fasting and postprandial plasma glucose (PPG) and hemoglobin A_{1c} (HbA_{1c}) of 59 mg/dL, 83 mg/dL, and 1.8%, respectively, compared to the placebo group (see **Table 2**).

Table 2:	**GLUCOPHAGE vs Placebo Summary of Mean Changes from Baseline* in Fasting Plasma Glucose, HbA_{1c}, and Body Weight, at Final Visit (29-week study)**		
	GLUCOPHAGE (n=141)	**Placebo (n=145)**	**p–Value**
FPG (mg/dL)			
Baseline	241.5	237.7	NS**
Change at FINAL VISIT	-53.0	6.3	0.001
Hemoglobin A_{1c} (%)			
Baseline	8.4	8.2	NS**
Change at FINAL VISIT	-1.4	0.4	0.001
Body Weight (lbs)			
Baseline	201.0	206.0	NS**
Change at FINAL VISIT	-1.4	-2.4	NS**

*All patients on diet therapy at Baseline **Not statistically significant

A 29-week, double-blind, placebo-controlled study of GLUCOPHAGE and glyburide, alone and in combination, was conducted in obese patients with type 2 diabetes who had failed to achieve adequate glycemic control while on maximum doses of glyburide (baseline FPG of approximately 250 mg/dL) (see **Table 3**). Patients randomized to the combination arm started therapy with GLUCOPHAGE 500 mg and glyburide 20 mg. At the end of each week of the first four weeks of the trial, these patients had their dosages of GLUCOPHAGE increased by 500 mg if they had failed to reach target fasting plasma glucose. After week four, such dosage adjustments were made monthly, although no patient was allowed to exceed GLUCOPHAGE 2500 mg. Patients in the GLUCOPHAGE only arm (metformin plus placebo) followed the same titration schedule. At the end of the trial, approximately 70% of the patients in the combination group were taking GLUCOPHAGE 2000 mg/glyburide 20 mg or GLUCOPHAGE 2500 mg/glyburide 20 mg. Patients randomized to continue on glyburide experienced worsening of glycemic control, with mean increases in FPG, PPG, and HbA_{1c} of 14 mg/dL, 3 mg/dL, and 0.2%, respectively. In contrast, those randomized to GLUCOPHAGE (up to 2500 mg/day) experienced a slight improvement, with mean reductions in FPG, PPG, and HbA_{1c} of 1 mg/dL, 6 mg/dL, and 0.4%, respectively. The combination of GLUCOPHAGE and glyburide was effective in reducing FPG, PPG, and HbA_{1c} levels by 63 mg/dL, 65 mg/dL, and 1.7%, respectively. Compared to results of glyburide treatment alone, the

net differences with combination treatment were -77 mg/dL, -68 mg/dL, and -1.9%, respectively (see **Table 3**).

Table 3: Combined GLUCOPHAGE/Glyburide (Comb) vs Glyburide (Glyb) or GLUCOPHAGE (GLU) Monotherapy: Summary of Mean Changes from Baseline* in Fasting Plasma Glucose, HbA_{1c}, and Body Weight, at Final Visit (29-week study)

	Comb (n=213)	Glyb (n=209)	GLU (n=210)	p-values		
				Glyb vs Comb	GLU vs Comb	GLU vs Glyb
Fasting Plasma Glucose (mg/dL)						
Baseline	250.5	247.5	253.9	NS**	NS**	NS**
Change at FINAL VISIT	-63.5	13.7	-0.9	0.001	0.001	0.025
Hemoglobin A_{1c} (%)						
Baseline	8.8	8.5	8.9	NS**	NS**	0.007
Change at FINAL VISIT	-1.7	0.2	-0.4	0.001	0.001	0.001
Body Weight (lbs)						
Baseline	202.2	203.0	204.0	NS**	NS**	NS**
Change at FINAL VISIT	0.9	-0.7	-8.4	0.011	0.001	0.001

*All patients on glyburide, 20 mg/day, at Baseline **Not statistically significant

The magnitude of the decline in fasting blood glucose concentration following the institution of GLUCOPHAGE (metformin hydrochloride tablets) therapy was proportional to the level of fasting hyperglycemia. Patients with type 2 diabetes with higher fasting glucose concentrations experienced greater declines in plasma glucose and glycosylated hemoglobin.

In clinical studies, GLUCOPHAGE, alone or in combination with a sulfonylurea, lowered mean fasting serum triglycerides, total cholesterol, and LDL cholesterol levels and had no adverse effects on other lipid levels (see **Table 4**).

Table 4:	**Summary of Mean Percent Change From Baseline of Major Serum Lipid Variables at Final Visit (29-week studies)**				
	GLUCOPHAGE vs Placebo		**Combined GLUCOPHAGE/Glyburide vs Monotherapy**		
	GLUCOPHAGE (n=141)	**Placebo (n=145)**	**GLUCOPHAGE (n=210)**	**GLUCOPHAGE/ Glyburide (n=213)**	**Glyburide (n=209)**
Total Cholesterol (mg/dL)					
Baseline	211.0	212.3	213.1	215.6	219.6
Mean % Change at FINAL VISIT	-5%	1%	-2%	-4%	1%
Total Triglycerides (mg/dL)					
Baseline	236.1	203.5	242.5	215.0	266.1
Mean % Change at FINAL VISIT	-16%	1%	-3%	-8%	4%
LDL-Cholesterol (mg/dL)					
Baseline	135.4	138.5	134.3	136.0	137.5
Mean % Change at FINAL VISIT	-8%	1%	-4%	-6%	3%
HDL-Cholesterol (mg/dL)					
Baseline	39.0	40.5	37.2	39.0	37.0
Mean % Change at FINAL VISIT	2%	-1%	5%	3%	1%

In contrast to sulfonylureas, body weight of individuals on GLUCOPHAGE tended to remain stable or even decrease somewhat (see **Tables 2** and **3**).

A 24-week, double-blind, placebo-controlled study of GLUCOPHAGE plus insulin versus insulin plus placebo was conducted in patients with type 2 diabetes who failed to achieve adequate glycemic control on insulin alone (see **Table 5**). Patients randomized to receive GLUCOPHAGE plus insulin achieved a reduction in HbA_{1c} of 2.10%, compared to a 1.56% reduction in HbA_{1c} achieved by insulin plus placebo. The improvement in glycemic control was achieved at the final study visit with 16% less insulin, 93.0 U/day vs 110.6 U/day, GLUCOPHAGE plus insulin versus insulin plus placebo, respectively, p=0.04.

Table 5:	**Combined GLUCOPHAGE/Insulin vs Placebo/Insulin Summary of Mean Changes from Baseline in HbA_{1c} and Daily Insulin Dose**		
	GLUCOPHAGE/ Insulin (n=26)	**Placebo/ Insulin (n=28)**	**Treatment Difference Mean ± SE**
Hemoglobin A_{1c} (%)			
Baseline	8.95	9.32	
Change at FINAL VISIT	-2.10	-1.56	-0.54 ± 0.43[a]
Insulin Dose (U/day)			
Baseline	93.12	94.64	
Change at FINAL VISIT	-0.15	15.93	-16.08 ± 7.77[b]

[a] Statistically significant using analysis of covariance with baseline as covariate (p=0.04)
Not significant using analysis of variance (values shown in table)

[b] Statistically significant for insulin (p=0.04)

A second double-blind, placebo-controlled study (n=51), with 16 weeks of randomized treatment, demonstrated that in patients with type 2 diabetes controlled on insulin for 8 weeks with an average HbA_{1c} of 7.46 ± 0.97%, the addition of GLUCOPHAGE maintained similar glycemic control (HbA_{1c} 7.15 ± 0.61 versus 6.97 ± 0.62 for GLUCOPHAGE plus insulin and placebo plus insulin, respectively) with 19% less insulin versus baseline (reduction of 23.68 ± 30.22 versus an increase of 0.43 ± 25.20 units for GLUCOPHAGE plus insulin and placebo plus insulin, $p<0.01$). In addition, this study demonstrated that the combination of GLUCOPHAGE plus insulin resulted in reduction in body weight of 3.11 ± 4.30 lbs, compared to an increase of 1.30 ± 6.08 lbs for placebo plus insulin, p=0.01.

GLUCOPHAGE XR

A 24-week, double-blind, placebo-controlled study of GLUCOPHAGE XR, taken once daily with the evening meal, was conducted in patients with type 2 diabetes who had failed to achieve glycemic control with diet and exercise (HbA_{1c} 7.0-10.0%, FPG 126-270 mg/dL). Patients entering the study had a mean baseline HbA_{1c} of 8.0% and a mean baseline FPG of 176 mg/dL. After 12 weeks treatment, mean HbA_{1c} had increased from baseline by 0.1% and mean FPG decreased from baseline by 2 mg/dL in the placebo group, compared with a decrease in mean HbA_{1c} of 0.6% and a decrease in mean FPG of

23 mg/dL in patients treated with GLUCOPHAGE XR 1000 mg once daily. Subsequently, the treatment dose was increased to 1500 mg once daily if HbA_{1c} was ≥7.0% but <8.0% (patients with HbA_{1c} ≥8.0% were discontinued from the study). At the final visit (24-week), mean HbA_{1c} had increased 0.2% from baseline in placebo patients and decreased 0.6% with GLUCOPHAGE XR.

A 16-week, double-blind, placebo-controlled, dose-response study of GLUCOPHAGE XR, taken once daily with the evening meal or twice daily with meals, was conducted in patients with type 2 diabetes who had failed to achieve glycemic control with diet and exercise (HbA_{1c} 7.0-11.0%, FPG 126-280 mg/dL). Changes in glycemic control and body weight are shown in **Table 6**.

Table 6: Summary of Mean Changes from Baseline* in HbA_{1c}, Fasting Plasma Glucose, and Body Weight at Final Visit (16-week study)

	GLUCOPHAGE XR					Placebo
	500 mg Once Daily	1000 mg Once Daily	1500 mg Once Daily	2000 mg Once Daily	1000 mg Twice Daily	
Hemoglobin A_{1c} (%)	**(n=115)**	**(n=115)**	**(n=111)**	**(n=125)**	**(n=112)**	**(n=111)**
Baseline	8.2	8.4	8.3	8.4	8.4	8.4
Change at FINAL VISIT	-0.4	-0.6	-0.9	-0.8	-1.1	0.1
p-value[a]	<0.001	<0.001	<0.001	<0.001	<0.001	-
FPG (mg/dL)	**(n=126)**	**(n=118)**	**(n=120)**	**(n=132)**	**(n=122)**	**(n=113)**
Baseline	182.7	183.7	178.9	181.0	181.6	179.6
Change at FINAL VISIT	-15.2	-19.3	-28.5	-29.9	-33.6	7.6
p-value[a]	<0.001	<0.001	<0.001	<0.001	<0.001	-
Body Weight (lbs)	**(n=125)**	**(n=119)**	**(n=117)**	**(n=131)**	**(n=119)**	**(n=113)**
Baseline	192.9	191.8	188.3	195.4	192.5	194.3
Change at FINAL VISIT	-1.3	-1.3	-0.7	-1.5	-2.2	-1.8
p-value[a]	NS**	NS**	NS**	NS**	NS**	-

* All patients on diet therapy at Baseline

a All comparisons versus Placebo

** Not statistically significant

Compared with placebo, improvement in glycemic control was seen at all dose levels of GLUCOPHAGE XR (metformin hydrochloride extended-release tablets) and treatment was not associated with any significant change in weight (see **DOSAGE AND ADMINISTRATION** for dosing recommendations for GLUCOPHAGE and GLUCOPHAGE XR).

A 24-week, double-blind, randomized study of GLUCOPHAGE XR, taken once daily with the evening meal, and GLUCOPHAGE (metformin hydrochloride tablets), taken twice daily (with breakfast and evening meal), was conducted in patients with type 2 diabetes who had been treated with GLUCOPHAGE 500 mg twice daily for at least 8 weeks prior to study entry. The GLUCOPHAGE dose had not necessarily been titrated to achieve a specific level of glycemic control prior to study entry. Patients qualified for the study if HbA_{1c} was ≤8.5% and FPG was ≤200 mg/dL. Changes in glycemic control and body weight are shown in **Table 7**.

Table 7:	**Summary of Mean Changes from Baseline* in HbA_{1c}, Fasting Plasma Glucose, and Body Weight at Week 12 and at Final Visit (24-week study)**		
	GLUCOPHAGE 500 mg Twice Daily	**GLUCOPHAGE XR**	
		1000 mg Once Daily	**1500 mg Once Daily**
Hemoglobin A_{1c} (%)	**(n=67)**	**(n=72)**	**(n=66)**
Baseline	7.06	6.99	7.02
Change at 12 Weeks	0.14	0.23	0.04
(95% CI)	(-0.03, 0.31)	(0.10, 0.36)	(-0.08, 0.15)
Change at FINAL VISIT	0.14[a]	0.27	0.13
(95% CI)	(-0.04, 0.31)	(0.11, 0.43)	(-0.02, 0.28)
FPG (mg/dL)	**(n=69)**	**(n=72)**	**(n=70)**
Baseline	127.2	131.0	131.4
Change at 12 Weeks	12.9	9.5	3.7
(95% CI)	(6.5, 19.4)	(4.4, 14.6)	(-0.4, 7.8)
Change at FINAL VISIT	14.0	11.5	7.6
(95% CI)	(7.0, 21.0)	(4.4, 18.6)	(1.0, 14.2)
Body Weight (lbs)	**(n=71)**	**(n=74)**	**(n=71)**
Baseline	210.3	202.8	192.7
Change at 12 Weeks	0.4	0.9	0.7
(95% CI)	(-0.4, 1.5)	(0.0, 2.0)	(-0.4, 1.8)
Change at FINAL VISIT	0.9	1.1	0.9
(95% CI)	(-0.4, 2.2)	(-0.2, 2.4)	(-0.4, 2.0)

* All patients on GLUCOPHAGE 500 mg twice daily at Baseline

[a] n=68

After 12 weeks of treatment, there was an increase in mean HbA_{1c} in all groups; in the GLUCOPHAGE XR 1000 mg group, the increase from baseline of 0.23% was statistically significant (see **DOSAGE AND ADMINISTRATION**).

Changes in lipid parameters in the previously described placebo-controlled dose-response study of GLUCOPHAGE XR are shown in **Table 8**.

Table 8:	**Summary of Mean Percent Changes from Baseline* in Major Lipid Variables at Final Visit (16-week study)**					
	GLUCOPHAGE XR					**Placebo**
	500 mg Once Daily	**1000 mg Once Daily**	**1500 mg Once Daily**	**2000 mg Once Daily**	**1000 mg Twice Daily**	
Total Cholesterol (mg/dL)	**(n=120)**	**(n=113)**	**(n=110)**	**(n=126)**	**(n=117)**	**(n=110)**
Baseline	210.3	218.1	214.6	204.4	208.2	208.6
Mean % Change at FINAL VISIT	1.0%	1.7%	0.7%	-1.6%	-2.6%	2.6%
Total Triglycerides (mg/dL)	**(n=120)**	**(n=113)**	**(n=110)**	**(n=126)**	**(n=117)**	**(n=110)**
Baseline	220.2	211.9	198.0	194.2	179.0	211.7
Mean % Change at FINAL VISIT	14.5%	9.4%	15.1%	14.9%	9.4%	10.9%
LDL-Cholesterol (mg/dL)	**(n=119)**	**(n=113)**	**(n=109)**	**(n=126)**	**(n=117)**	**(n=107)**
Baseline	131.0	134.9	135.8	125.8	131.4	131.9
Mean % Change at FINAL VISIT	-1.4%	-1.6%	-3.5%	-3.3%	-5.5%	3.2%
HDL-Cholesterol (mg/dL)	**(n=120)**	**(n=108)**	**(n=108)**	**(n=125)**	**(n=117)**	**(n=108)**
Baseline	40.8	41.6	40.6	40.2	42.4	39.4
Mean % Change at FINAL VISIT	6.2%	8.6%	5.5%	6.1%	7.1%	5.8%

*All patients on diet therapy at Baseline

Changes in lipid parameters in the previously described study of GLUCOPHAGE and GLUCOPHAGE XR are shown in **Table 9**.

Table 9:	**Summary of Mean Percent Changes from Baseline* in Major Lipid Variables at Final Visit (24-week study)**		
	GLUCOPHAGE 500 mg Twice Daily	**GLUCOPHAGE XR**	
		1000 mg Once Daily	**1500 mg Once Daily**
Total Cholesterol (mg/dL)	**(n=68)**	**(n=70)**	**(n=66)**
Baseline	199.0	201.9	201.6
Mean % Change at FINAL VISIT	0.1%	1.3%	0.1%
Total Triglycerides (mg/dL)	**(n=68)**	**(n=70)**	**(n=66)**
Baseline	178.0	169.2	206.8
Mean % Change at FINAL VISIT	6.3%	25.3%	33.4%
LDL-Cholesterol (mg/dL)	**(n=68)**	**(n=70)**	**(n=66)**
Baseline	122.1	126.2	115.7
Mean % Change at FINAL VISIT	-1.3%	-3.3%	-3.7%
HDL-Cholesterol (mg/dL)	**(n=68)**	**(n=70)**	**(n=65)**
Baseline	41.9	41.7	44.6
Mean % Change at FINAL VISIT	4.8%	1.0%	-2.1%

*All patients on GLUCOPHAGE 500 mg twice daily at Baseline

Pediatric Clinical Studies

In a double-blind, placebo-controlled study in pediatric patients aged 10 to 16 years with type 2 diabetes (mean FPG 182.2 mg/dL), treatment with GLUCOPHAGE (up to 2000 mg/day) for up to 16 weeks (mean duration of treatment 11 weeks) resulted in a significant mean net reduction in FPG of 64.3 mg/dL, compared with placebo (see **Table 10**).

Table 10:	**GLUCOPHAGE vs Placebo (Pediatrics[a]) Summary of Mean Changes from Baseline* in Plasma Glucose and Body Weight at Final Visit**		
	GLUCOPHAGE	**Placebo**	**p-Value**
FPG (mg/dL)	**(n=37)**	**(n=36)**	
Baseline	162.4	192.3	
Change at FINAL VISIT	-42.9	21.4	<0.001
Body Weight (lbs)	**(n=39)**	**(n=38)**	
Baseline	205.3	189.0	
Change at FINAL VISIT	-3.3	-2.0	NS**

[a] Pediatric patients mean age 13.8 years (range 10-16 years)
* All patients on diet therapy at Baseline
** Not statistically significant

INDICATIONS AND USAGE

GLUCOPHAGE (metformin hydrochloride tablets) and GLUCOPHAGE XR (metformin hydrochloride extended-release tablets), as monotherapy, are indicated as an adjunct to diet and exercise to improve glycemic control in patients with type 2 diabetes. GLUCOPHAGE is indicated in patients 10 years of age and older, and GLUCOPHAGE XR is indicated in patients 17 years of age and older.

GLUCOPHAGE or GLUCOPHAGE XR may be used concomitantly with a sulfonylurea or insulin to improve glycemic control in adults (17 years of age and older).

CONTRAINDICATIONS

GLUCOPHAGE and GLUCOPHAGE XR are contraindicated in patients with:

1. Renal disease or renal dysfunction (e.g., as suggested by serum creatinine levels ≥1.5 mg/dL [males], ≥1.4 mg/dL [females] or abnormal creatinine clearance) which may also result from conditions such as cardiovascular collapse (shock), acute myocardial infarction, and septicemia (see **WARNINGS** and **PRECAUTIONS**).

2. Known hypersensitivity to metformin hydrochloride.

3. Acute or chronic metabolic acidosis, including diabetic ketoacidosis, with or without coma. Diabetic ketoacidosis should be treated with insulin.

GLUCOPHAGE and GLUCOPHAGE XR should be temporarily discontinued in patients undergoing radiologic studies involving intravascular administration of iodinated contrast materials, because use of such products may result in acute alteration of renal function. (See also **PRECAUTIONS**.)

WARNINGS

Lactic Acidosis:

Lactic acidosis is a rare, but serious, metabolic complication that can occur due to metformin accumulation during treatment with GLUCOPHAGE or GLUCOPHAGE XR; when it occurs, it is fatal in approximately 50% of cases. Lactic acidosis may also occur in association with a number of pathophysiologic conditions, including diabetes mellitus, and whenever there is significant tissue hypoperfusion and hypoxemia. Lactic acidosis is characterized by elevated blood lactate levels (>5 mmol/L), decreased blood pH, electrolyte disturbances with an increased anion gap, and an increased lactate/pyruvate ratio. When metformin is implicated as the cause of lactic acidosis, metformin plasma levels >5 μg/mL are generally found.

The reported incidence of lactic acidosis in patients receiving metformin hydrochloride is very low (approximately 0.03 cases/1000 patient-years, with approximately 0.015 fatal cases/1000 patient-years). In more than 20,000 patient-years exposure to metformin in clinical trials, there were no reports of lactic acidosis. Reported cases have occurred primarily in diabetic patients with significant renal insufficiency, including both intrinsic renal disease and renal hypoperfusion, often in the setting of multiple concomitant medical/surgical problems and multiple concomitant medications. Patients with congestive heart failure requiring pharmacologic management, in particular those with unstable or acute congestive heart failure who are at risk of hypoperfusion and hypoxemia, are at increased risk of lactic acidosis. The risk of lactic acidosis increases with the degree of renal dysfunction and the patient's age. The risk of lactic acidosis may, therefore, be significantly decreased by regular monitoring of renal function in patients taking GLUCOPHAGE or GLUCOPHAGE XR and by use of the minimum effective dose of GLUCOPHAGE or GLUCOPHAGE XR. In particular, treatment of the elderly should be accompanied by careful monitoring of renal function. GLUCOPHAGE or GLUCOPHAGE XR treatment should not be initiated in patients ≥80 years of age unless measurement of creatinine clearance demonstrates that renal function is not reduced, as these patients are more

susceptible to developing lactic acidosis. In addition, GLUCOPHAGE and GLUCOPHAGE XR should be promptly withheld in the presence of any condition associated with hypoxemia, dehydration, or sepsis. Because impaired hepatic function may significantly limit the ability to clear lactate, GLUCOPHAGE and GLUCOPHAGE XR should generally be avoided in patients with clinical or laboratory evidence of hepatic disease. Patients should be cautioned against excessive alcohol intake, either acute or chronic, when taking GLUCOPHAGE or GLUCOPHAGE XR, since alcohol potentiates the effects of metformin hydrochloride on lactate metabolism. In addition, GLUCOPHAGE and GLUCOPHAGE XR should be temporarily discontinued prior to any intravascular radiocontrast study and for any surgical procedure (see also PRECAUTIONS).

The onset of lactic acidosis often is subtle, and accompanied only by nonspecific symptoms such as malaise, myalgias, respiratory distress, increasing somnolence, and nonspecific abdominal distress. There may be associated hypothermia, hypotension, and resistant bradyarrhythmias with more marked acidosis. The patient and the patient's physician must be aware of the possible importance of such symptoms and the patient should be instructed to notify the physician immediately if they occur (see also PRECAUTIONS). GLUCOPHAGE and GLUCOPHAGE XR should be withdrawn until the situation is clarified. Serum electrolytes, ketones, blood glucose, and if indicated, blood pH, lactate levels, and even blood metformin levels may be useful. Once a patient is stabilized on any dose level of GLUCOPHAGE or GLUCOPHAGE XR, gastrointestinal symptoms, which are common during initiation of therapy, are unlikely to be drug related. Later occurrence of gastrointestinal symptoms could be due to lactic acidosis or other serious disease.

Levels of fasting venous plasma lactate above the upper limit of normal but less than 5 mmol/L in patients taking GLUCOPHAGE or GLUCOPHAGE XR do not necessarily indicate impending lactic acidosis and may be explainable by other mechanisms, such as poorly controlled diabetes or obesity, vigorous physical activity, or technical problems in sample handling. (See also PRECAUTIONS.)

Lactic acidosis should be suspected in any diabetic patient with metabolic acidosis lacking evidence of ketoacidosis (ketonuria and ketonemia).

Lactic acidosis is a medical emergency that must be treated in a hospital setting. In a patient with lactic acidosis who is taking GLUCOPHAGE or GLUCOPHAGE XR,

the drug should be discontinued immediately and general supportive measures promptly instituted. Because metformin hydrochloride is dialyzable (with a clearance of up to 170 mL/min under good hemodynamic conditions), prompt hemodialysis is recommended to correct the acidosis and remove the accumulated metformin. Such management often results in prompt reversal of symptoms and recovery. (See also CONTRAINDICATIONS and PRECAUTIONS.)

PRECAUTIONS

General

Monitoring of renal function—Metformin is known to be substantially excreted by the kidney, and the risk of metformin accumulation and lactic acidosis increases with the degree of impairment of renal function. Thus, patients with serum creatinine levels above the upper limit of normal for their age should not receive GLUCOPHAGE or GLUCOPHAGE XR. In patients with advanced age, GLUCOPHAGE and GLUCOPHAGE XR should be carefully titrated to establish the minimum dose for adequate glycemic effect, because aging is associated with reduced renal function. In elderly patients, particularly those ≥80 years of age, renal function should be monitored regularly and, generally, GLUCOPHAGE and GLUCOPHAGE XR should not be titrated to the maximum dose (see **WARNINGS** and **DOSAGE AND ADMINISTRATION**).

Before initiation of GLUCOPHAGE or GLUCOPHAGE XR therapy and at least annually thereafter, renal function should be assessed and verified as normal. In patients in whom development of renal dysfunction is anticipated, renal function should be assessed more frequently and GLUCOPHAGE or GLUCOPHAGE XR discontinued if evidence of renal impairment is present.

Use of concomitant medications that may affect renal function or metformin disposition—Concomitant medication(s) that may affect renal function or result in significant hemodynamic change or may interfere with the disposition of metformin, such as cationic drugs that are eliminated by renal tubular secretion (see **PRECAUTIONS: Drug Interactions**), should be used with caution.

Radiologic studies involving the use of intravascular iodinated contrast materials (for example, intravenous urogram, intravenous cholangiography, angiography, and computed tomography (CT) scans with intravascular contrast materials)—Intravascular contrast studies with iodinated materials can lead to acute alteration of renal function and

have been associated with lactic acidosis in patients receiving metformin (see **CONTRAINDICATIONS**). Therefore, in patients in whom any such study is planned, GLUCOPHAGE or GLUCOPHAGE XR should be temporarily discontinued at the time of or prior to the procedure, and withheld for 48 hours subsequent to the procedure and reinstituted only after renal function has been re-evaluated and found to be normal.

Hypoxic states—Cardiovascular collapse (shock) from whatever cause, acute congestive heart failure, acute myocardial infarction and other conditions characterized by hypoxemia have been associated with lactic acidosis and may also cause prerenal azotemia. When such events occur in patients on GLUCOPHAGE or GLUCOPHAGE XR therapy, the drug should be promptly discontinued.

Surgical procedures—GLUCOPHAGE or GLUCOPHAGE XR therapy should be temporarily suspended for any surgical procedure (except minor procedures not associated with restricted intake of food and fluids) and should not be restarted until the patient's oral intake has resumed and renal function has been evaluated as normal.

Alcohol intake—Alcohol is known to potentiate the effect of metformin on lactate metabolism. Patients, therefore, should be warned against excessive alcohol intake, acute or chronic, while receiving GLUCOPHAGE or GLUCOPHAGE XR.

Impaired hepatic function—Since impaired hepatic function has been associated with some cases of lactic acidosis, GLUCOPHAGE and GLUCOPHAGE XR should generally be avoided in patients with clinical or laboratory evidence of hepatic disease.

Vitamin B_{12} levels—In controlled clinical trials of GLUCOPHAGE of 29 weeks duration, a decrease to subnormal levels of previously normal serum vitamin B_{12} levels, without clinical manifestations, was observed in approximately 7% of patients. Such decrease, possibly due to interference with B_{12} absorption from the B_{12}-intrinsic factor complex, is, however, very rarely associated with anemia and appears to be rapidly reversible with discontinuation of GLUCOPHAGE or vitamin B_{12} supplementation. Measurement of hematologic parameters on an annual basis is advised in patients on GLUCOPHAGE or GLUCOPHAGE XR and any apparent abnormalities should be appropriately investigated and managed (see **PRECAUTIONS: Laboratory Tests**).

Certain individuals (those with inadequate vitamin B_{12} or calcium intake or absorption) appear to be predisposed to developing subnormal vitamin B_{12} levels. In these patients, routine serum vitamin B_{12} measurements at two- to three-year intervals may be useful.

Change in clinical status of patients with previously controlled type 2 diabetes—A patient with type 2 diabetes previously well controlled on GLUCOPHAGE or GLUCOPHAGE XR who develops laboratory abnormalities or clinical illness (especially vague and poorly defined illness) should be evaluated promptly for evidence of ketoacidosis or lactic acidosis. Evaluation should include serum electrolytes and ketones, blood glucose and, if indicated, blood pH, lactate, pyruvate, and metformin levels. If acidosis of either form occurs, GLUCOPHAGE or GLUCOPHAGE XR must be stopped immediately and other appropriate corrective measures initiated (see also **WARNINGS**).

Hypoglycemia—Hypoglycemia does not occur in patients receiving GLUCOPHAGE or GLUCOPHAGE XR alone under usual circumstances of use, but could occur when caloric intake is deficient, when strenuous exercise is not compensated by caloric supplementation, or during concomitant use with other glucose-lowering agents (such as sulfonylureas and insulin) or ethanol.

Elderly, debilitated, or malnourished patients, and those with adrenal or pituitary insufficiency or alcohol intoxication are particularly susceptible to hypoglycemic effects. Hypoglycemia may be difficult to recognize in the elderly, and in people who are taking beta-adrenergic blocking drugs.

Loss of control of blood glucose—When a patient stabilized on any diabetic regimen is exposed to stress such as fever, trauma, infection, or surgery, a temporary loss of glycemic control may occur. At such times, it may be necessary to withhold GLUCOPHAGE or GLUCOPHAGE XR and temporarily administer insulin. GLUCOPHAGE or GLUCOPHAGE XR may be reinstituted after the acute episode is resolved.

The effectiveness of oral antidiabetic drugs in lowering blood glucose to a targeted level decreases in many patients over a period of time. This phenomenon, which may be due to progression of the underlying disease or to diminished responsiveness to the drug, is known as secondary failure, to distinguish it from primary failure in which the drug is ineffective during initial therapy. Should secondary failure occur with either GLUCOPHAGE or GLUCOPHAGE XR or sulfonylurea monotherapy, combined therapy with GLUCOPHAGE or GLUCOPHAGE XR and sulfonylurea may result in a response. Should secondary failure occur with combined GLUCOPHAGE/sulfonylurea therapy or GLUCOPHAGE XR/sulfonylurea therapy, it may be necessary to consider therapeutic alternatives including initiation of insulin therapy.

Information for Patients

Patients should be informed of the potential risks and benefits of GLUCOPHAGE or GLUCOPHAGE XR and of alternative modes of therapy. They should also be informed about the importance of adherence to dietary instructions, of a regular exercise program, and of regular testing of blood glucose, glycosylated hemoglobin, renal function, and hematologic parameters.

The risks of lactic acidosis, its symptoms, and conditions that predispose to its development, as noted in the **WARNINGS** and **PRECAUTIONS** sections, should be explained to patients. Patients should be advised to discontinue GLUCOPHAGE or GLUCOPHAGE XR immediately and to promptly notify their health practitioner if unexplained hyperventilation, myalgia, malaise, unusual somnolence, or other nonspecific symptoms occur. Once a patient is stabilized on any dose level of GLUCOPHAGE or GLUCOPHAGE XR, gastrointestinal symptoms, which are common during initiation of metformin therapy, are unlikely to be drug related. Later occurrence of gastrointestinal symptoms could be due to lactic acidosis or other serious disease.

Patients should be counselled against excessive alcohol intake, either acute or chronic, while receiving GLUCOPHAGE or GLUCOPHAGE XR.

GLUCOPHAGE or GLUCOPHAGE XR alone does not usually cause hypoglycemia, although it may occur when GLUCOPHAGE or GLUCOPHAGE XR is used in conjunction with oral sulfonylureas and insulin. When initiating combination therapy, the risks of hypoglycemia, its symptoms and treatment, and conditions that predispose to its development should be explained to patients and responsible family members. (See **Patient Information** printed below.)

Patients should be informed that GLUCOPHAGE XR must be swallowed whole and not crushed or chewed, and that the inactive ingredients may occasionally be eliminated in the feces as a soft mass that may resemble the original tablet.

Laboratory Tests

Response to all diabetic therapies should be monitored by periodic measurements of fasting blood glucose and glycosylated hemoglobin levels, with a goal of decreasing these levels toward the normal range. During initial dose titration, fasting glucose can be used to determine the therapeutic response. Thereafter, both glucose and glycosylated hemoglobin should be monitored. Measurements of glycosylated hemoglobin may be

especially useful for evaluating long-term control (see also **DOSAGE AND ADMINISTRATION**).

Initial and periodic monitoring of hematologic parameters (e.g., hemoglobin/hematocrit and red blood cell indices) and renal function (serum creatinine) should be performed, at least on an annual basis. While megaloblastic anemia has rarely been seen with GLUCOPHAGE therapy, if this is suspected, vitamin B_{12} deficiency should be excluded.

Drug Interactions (Clinical Evaluation of Drug Interactions Conducted with GLUCOPHAGE)

Glyburide—In a single-dose interaction study in type 2 diabetes patients, coadministration of metformin and glyburide did not result in any changes in either metformin pharmacokinetics or pharmacodynamics. Decreases in glyburide AUC and C_{max} were observed, but were highly variable. The single-dose nature of this study and the lack of correlation between glyburide blood levels and pharmacodynamic effects, makes the clinical significance of this interaction uncertain (see **DOSAGE AND ADMINISTRATION: Concomitant GLUCOPHAGE or GLUCOPHAGE XR and Oral Sulfonylurea Therapy in Adult Patients**).

Furosemide—A single-dose, metformin-furosemide drug interaction study in healthy subjects demonstrated that pharmacokinetic parameters of both compounds were affected by coadministration. Furosemide increased the metformin plasma and blood C_{max} by 22% and blood AUC by 15%, without any significant change in metformin renal clearance. When administered with metformin, the C_{max} and AUC of furosemide were 31% and 12% smaller, respectively, than when administered alone, and the terminal half-life was decreased by 32%, without any significant change in furosemide renal clearance. No information is available about the interaction of metformin and furosemide when coadministered chronically.

Nifedipine—A single-dose, metformin-nifedipine drug interaction study in normal healthy volunteers demonstrated that coadministration of nifedipine increased plasma metformin C_{max} and AUC by 20% and 9%, respectively, and increased the amount excreted in the urine. T_{max} and half-life were unaffected. Nifedipine appears to enhance the absorption of metformin. Metformin had minimal effects on nifedipine.

Cationic drugs—Cationic drugs (e.g., amiloride, digoxin, morphine, procainamide, quinidine, quinine, ranitidine, triamterene, trimethoprim, or vancomycin) that are

eliminated by renal tubular secretion theoretically have the potential for interaction with metformin by competing for common renal tubular transport systems. Such interaction between metformin and oral cimetidine has been observed in normal healthy volunteers in both single- and multiple-dose, metformin-cimetidine drug interaction studies, with a 60% increase in peak metformin plasma and whole blood concentrations and a 40% increase in plasma and whole blood metformin AUC. There was no change in elimination half-life in the single-dose study. Metformin had no effect on cimetidine pharmacokinetics. Although such interactions remain theoretical (except for cimetidine), careful patient monitoring and dose adjustment of GLUCOPHAGE or GLUCOPHAGE XR and/or the interfering drug is recommended in patients who are taking cationic medications that are excreted via the proximal renal tubular secretory system.

Other—Certain drugs tend to produce hyperglycemia and may lead to loss of glycemic control. These drugs include the thiazides and other diuretics, corticosteroids, phenothiazines, thyroid products, estrogens, oral contraceptives, phenytoin, nicotinic acid, sympathomimetics, calcium channel blocking drugs, and isoniazid. When such drugs are administered to a patient receiving GLUCOPHAGE or GLUCOPHAGE XR, the patient should be closely observed for loss of blood glucose control. When such drugs are withdrawn from a patient receiving GLUCOPHAGE or GLUCOPHAGE XR, the patient should be observed closely for hypoglycemia.

In healthy volunteers, the pharmacokinetics of metformin and propranolol, and metformin and ibuprofen were not affected when coadministered in single-dose interaction studies.

Metformin is negligibly bound to plasma proteins and is, therefore, less likely to interact with highly protein-bound drugs such as salicylates, sulfonamides, chloramphenicol, and probenecid, as compared to the sulfonylureas, which are extensively bound to serum proteins.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term carcinogenicity studies have been performed in rats (dosing duration of 104 weeks) and mice (dosing duration of 91 weeks) at doses up to and including 900 mg/kg/day and 1500 mg/kg/day, respectively. These doses are both approximately four times the maximum recommended human daily dose of 2000 mg based on body surface area comparisons. No evidence of carcinogenicity with metformin was found in either male or female mice. Similarly, there was no tumorigenic potential observed with

metformin in male rats. There was, however, an increased incidence of benign stromal uterine polyps in female rats treated with 900 mg/kg/day.

There was no evidence of a mutagenic potential of metformin in the following *in vitro* tests: Ames test (*S. typhimurium*), gene mutation test (mouse lymphoma cells), or chromosomal aberrations test (human lymphocytes). Results in the *in vivo* mouse micronucleus test were also negative.

Fertility of male or female rats was unaffected by metformin when administered at doses as high as 600 mg/kg/day, which is approximately three times the maximum recommended human daily dose based on body surface area comparisons.

Pregnancy

Teratogenic Effects: Pregnancy Category B

Recent information strongly suggests that abnormal blood glucose levels during pregnancy are associated with a higher incidence of congenital abnormalities. Most experts recommend that insulin be used during pregnancy to maintain blood glucose levels as close to normal as possible. Because animal reproduction studies are not always predictive of human response, GLUCOPHAGE and GLUCOPHAGE XR should not be used during pregnancy unless clearly needed.

There are no adequate and well-controlled studies in pregnant women with GLUCOPHAGE or GLUCOPHAGE XR. Metformin was not teratogenic in rats and rabbits at doses up to 600 mg/kg/day. This represents an exposure of about two and six times the maximum recommended human daily dose of 2000 mg based on body surface area comparisons for rats and rabbits, respectively. Determination of fetal concentrations demonstrated a partial placental barrier to metformin.

Nursing Mothers

Studies in lactating rats show that metformin is excreted into milk and reaches levels comparable to those in plasma. Similar studies have not been conducted in nursing mothers. Because the potential for hypoglycemia in nursing infants may exist, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother. If GLUCOPHAGE or GLUCOPHAGE XR is discontinued, and if diet alone is inadequate for controlling blood glucose, insulin therapy should be considered.

Pediatric Use

The safety and effectiveness of GLUCOPHAGE for the treatment of type 2 diabetes have been established in pediatric patients ages 10 to 16 years (studies have not been conducted in pediatric patients below the age of 10 years). Use of GLUCOPHAGE in this age group is supported by evidence from adequate and well-controlled studies of GLUCOPHAGE in adults with additional data from a controlled clinical study in pediatric patients ages 10 to 16 years with type 2 diabetes, which demonstrated a similar response in glycemic control to that seen in adults. (See **CLINICAL PHARMACOLOGY: Pediatric Clinical Studies**.) In this study, adverse effects were similar to those described in adults. (See **ADVERSE REACTIONS: Pediatric Patients**.) A maximum daily dose of 2000 mg is recommended. (See **DOSAGE AND ADMINISTRATION: Recommended Dosing Schedule: Pediatrics**.)

Safety and effectiveness of GLUCOPHAGE XR in pediatric patients have not been established.

Geriatric Use

Controlled clinical studies of GLUCOPHAGE and GLUCOPHAGE XR did not include sufficient numbers of elderly patients to determine whether they respond differently from younger patients, although other reported clinical experience has not identified differences in responses between the elderly and younger patients. Metformin is known to be substantially excreted by the kidney and because the risk of serious adverse reactions to the drug is greater in patients with impaired renal function, GLUCOPHAGE and GLUCOPHAGE XR should only be used in patients with normal renal function (see **CONTRAINDICATIONS, WARNINGS,** and **CLINICAL PHARMACOLOGY: Pharmacokinetics**). Because aging is associated with reduced renal function, GLUCOPHAGE or GLUCOPHAGE XR should be used with caution as age increases. Care should be taken in dose selection and should be based on careful and regular monitoring of renal function. Generally, elderly patients should not be titrated to the maximum dose of GLUCOPHAGE or GLUCOPHAGE XR (see also **WARNINGS** and **DOSAGE AND ADMINISTRATION**).

ADVERSE REACTIONS

In a US double-blind clinical study of GLUCOPHAGE in patients with type 2 diabetes, a total of 141 patients received GLUCOPHAGE therapy (up to 2550 mg per day) and 145 patients received placebo. Adverse reactions reported in greater than 5% of the GLUCOPHAGE patients, and that were more common in GLUCOPHAGE- than placebo-treated patients, are listed in **Table 11**.

Table 11: Most Common Adverse Reactions (>5.0 Percent) in a Placebo-Controlled Clinical Study of GLUCOPHAGE Monotherapy*

Adverse Reaction	GLUCOPHAGE Monotherapy (n=141)	Placebo (n=145)
	% of Patients	
Diarrhea	53.2	11.7
Nausea/Vomiting	25.5	8.3
Flatulence	12.1	5.5
Asthenia	9.2	5.5
Indigestion	7.1	4.1
Abdominal Discomfort	6.4	4.8
Headache	5.7	4.8

* Reactions that were more common in GLUCOPHAGE- than placebo-treated patients.

Diarrhea led to discontinuation of study medication in 6% of patients treated with GLUCOPHAGE. Additionally, the following adverse reactions were reported in ≥1.0 - ≤5.0% of GLUCOPHAGE patients and were more commonly reported with GLUCOPHAGE than placebo: abnormal stools, hypoglycemia, myalgia, lightheaded, dyspnea, nail disorder, rash, sweating increased, taste disorder, chest discomfort, chills, flu syndrome, flushing, palpitation.

In worldwide clinical trials over 900 patients with type 2 diabetes have been treated with GLUCOPHAGE XR in placebo- and active-controlled studies. In placebo-controlled trials, 781 patients were administered GLUCOPHAGE XR and 195 patients received placebo. Adverse reactions reported in greater than 5% of the GLUCOPHAGE XR patients, and that were more common in GLUCOPHAGE XR- than placebo-treated patients, are listed in **Table 12**.

Table 12:	**Most Common Adverse Reactions (>5.0 Percent) in Placebo-Controlled Studies of GLUCOPHAGE XR***	
	GLUCOPHAGE XR (n=781)	**Placebo (n=195)**
Adverse Reaction	**% of Patients**	
Diarrhea	9.6	2.6
Nausea/Vomiting	6.5	1.5

* Reactions that were more common in GLUCOPHAGE XR- than placebo-treated patients.

Diarrhea led to discontinuation of study medication in 0.6% of patients treated with GLUCOPHAGE XR. Additionally, the following adverse reactions were reported in ≥1.0% - ≤5.0% of GLUCOPHAGE XR patients and were more commonly reported with GLUCOPHAGE XR than placebo: abdominal pain, constipation, distention abdomen, dyspepsia/heartburn, flatulence, dizziness, headache, upper respiratory infection, taste disturbance.

Pediatric Patients

In clinical trials with GLUCOPHAGE in pediatric patients with type 2 diabetes, the profile of adverse reactions was similar to that observed in adults.

OVERDOSAGE

Overdose of metformin hydrochloride has occurred, including ingestion of amounts greater than 50 grams. Hypoglycemia was reported in approximately 10% of cases, but no causal association with metformin hydrochloride has been established. Lactic acidosis has been reported in approximately 32% of metformin overdose cases (see **WARNINGS**). Metformin is dialyzable with a clearance of up to 170 mL/min under good hemodynamic conditions. Therefore, hemodialysis may be useful for removal of accumulated drug from patients in whom metformin overdosage is suspected.

DOSAGE AND ADMINISTRATION

There is no fixed dosage regimen for the management of hyperglycemia in patients with type 2 diabetes with GLUCOPHAGE or GLUCOPHAGE XR or any other pharmacologic agent. Dosage of GLUCOPHAGE or GLUCOPHAGE XR must be individualized on the basis of both effectiveness and tolerance, while not exceeding the maximum recommended daily doses. The maximum recommended daily dose of

GLUCOPHAGE is 2550 mg in adults and 2000 mg in pediatric patients (10-16 years of age); the maximum recommended daily dose of GLUCOPHAGE XR in adults is 2000 mg.

GLUCOPHAGE should be given in divided doses with meals while GLUCOPHAGE XR should generally be given once daily with the evening meal. GLUCOPHAGE or GLUCOPHAGE XR should be started at a low dose, with gradual dose escalation, both to reduce gastrointestinal side effects and to permit identification of the minimum dose required for adequate glycemic control of the patient.

During treatment initiation and dose titration (see **Recommended Dosing Schedule**), fasting plasma glucose should be used to determine the therapeutic response to GLUCOPHAGE or GLUCOPHAGE XR and identify the minimum effective dose for the patient. Thereafter, glycosylated hemoglobin should be measured at intervals of approximately three months. **The therapeutic goal should be to decrease both fasting plasma glucose and glycosylated hemoglobin levels to normal or near normal by using the lowest effective dose of GLUCOPHAGE or GLUCOPHAGE XR, either when used as monotherapy or in combination with sulfonylurea or insulin.**

Monitoring of blood glucose and glycosylated hemoglobin will also permit detection of primary failure, i.e., inadequate lowering of blood glucose at the maximum recommended dose of medication, and secondary failure, i.e., loss of an adequate blood glucose lowering response after an initial period of effectiveness.

Short-term administration of GLUCOPHAGE or GLUCOPHAGE XR may be sufficient during periods of transient loss of control in patients usually well-controlled on diet alone.

GLUCOPHAGE XR tablets must be swallowed whole and never crushed or chewed. Occasionally, the inactive ingredients of GLUCOPHAGE XR will be eliminated in the feces as a soft, hydrated mass. (See **Patient Information** printed below.)

Recommended Dosing Schedule

Adults - In general, clinically significant responses are not seen at doses below 1500 mg per day. However, a lower recommended starting dose and gradually increased dosage is advised to minimize gastrointestinal symptoms.

The usual starting dose of GLUCOPHAGE (metformin hydrochloride tablets) is 500 mg twice a day or 850 mg once a day, given with meals. Dosage increases should be made in

increments of 500 mg weekly or 850 mg every 2 weeks, up to a total of 2000 mg per day, given in divided doses. Patients can also be titrated from 500 mg twice a day to 850 mg twice a day after 2 weeks. For those patients requiring additional glycemic control, GLUCOPHAGE may be given to a maximum daily dose of 2550 mg per day. Doses above 2000 mg may be better tolerated given three times a day with meals.

The usual starting dose of GLUCOPHAGE XR (metformin hydrochloride extended-release tablets) is 500 mg once daily with the evening meal. Dosage increases should be made in increments of 500 mg weekly, up to a maximum of 2000 mg once daily with the evening meal. If glycemic control is not achieved on GLUCOPHAGE XR 2000 mg once daily, a trial of GLUCOPHAGE XR 1000 mg twice daily should be considered. If higher doses of metformin are required, GLUCOPHAGE should be used at total daily doses up to 2550 mg administered in divided daily doses, as described above. (See **CLINICAL PHARMACOLOGY: Clinical Studies**.)

In a randomized trial, patients currently treated with GLUCOPHAGE were switched to GLUCOPHAGE XR. Results of this trial suggest that patients receiving GLUCOPHAGE treatment may be safely switched to GLUCOPHAGE XR once daily at the same total daily dose, up to 2000 mg once daily. Following a switch from GLUCOPHAGE to GLUCOPHAGE XR, glycemic control should be closely monitored and dosage adjustments made accordingly (see **CLINICAL PHARMACOLOGY: Clinical Studies**).

Pediatrics - The usual starting dose of GLUCOPHAGE is 500 mg twice a day, given with meals. Dosage increases should be made in increments of 500 mg weekly up to a maximum of 2000 mg per day, given in divided doses. Safety and effectiveness of GLUCOPHAGE XR in pediatric patients have not been established.

Transfer From Other Antidiabetic Therapy

When transferring patients from standard oral hypoglycemic agents other than chlorpropamide to GLUCOPHAGE or GLUCOPHAGE XR, no transition period generally is necessary. When transferring patients from chlorpropamide, care should be exercised during the first two weeks because of the prolonged retention of chlorpropamide in the body, leading to overlapping drug effects and possible hypoglycemia.

Concomitant GLUCOPHAGE or GLUCOPHAGE XR and Oral Sulfonylurea Therapy in Adult Patients

If patients have not responded to four weeks of the maximum dose of GLUCOPHAGE or GLUCOPHAGE XR monotherapy, consideration should be given to gradual addition of an oral sulfonylurea while continuing GLUCOPHAGE or GLUCOPHAGE XR at the maximum dose, even if prior primary or secondary failure to a sulfonylurea has occurred. Clinical and pharmacokinetic drug-drug interaction data are currently available only for metformin plus glyburide (glibenclamide).

With concomitant GLUCOPHAGE or GLUCOPHAGE XR and sulfonylurea therapy, the desired control of blood glucose may be obtained by adjusting the dose of each drug. In a clinical trial of patients with type 2 diabetes and prior failure on glyburide, patients started on GLUCOPHAGE 500 mg and glyburide 20 mg were titrated to 1000/20 mg, 1500/20 mg, 2000/20 mg or 2500/20 mg of GLUCOPHAGE and glyburide, respectively, to reach the goal of glycemic control as measured by FPG, HbA_{1c} and plasma glucose response (see **CLINICAL PHARMACOLOGY: Clinical Studies**). However, attempts should be made to identify the minimum effective dose of each drug to achieve this goal. With concomitant GLUCOPHAGE or GLUCOPHAGE XR and sulfonylurea therapy, the risk of hypoglycemia associated with sulfonylurea therapy continues and may be increased. Appropriate precautions should be taken. (See Package Insert of the respective sulfonylurea.)

If patients have not satisfactorily responded to one to three months of concomitant therapy with the maximum dose of GLUCOPHAGE or GLUCOPHAGE XR and the maximum dose of an oral sulfonylurea, consider therapeutic alternatives including switching to insulin with or without GLUCOPHAGE or GLUCOPHAGE XR.

Concomitant GLUCOPHAGE or GLUCOPHAGE XR and Insulin Therapy in Adult Patients

The current insulin dose should be continued upon initiation of GLUCOPHAGE or GLUCOPHAGE XR therapy. GLUCOPHAGE or GLUCOPHAGE XR therapy should be initiated at 500 mg once daily in patients on insulin therapy. For patients not responding adequately, the dose of GLUCOPHAGE or GLUCOPHAGE XR should be increased by 500 mg after approximately 1 week and by 500 mg every week thereafter until adequate glycemic control is achieved. The maximum recommended daily dose is 2500 mg for GLUCOPHAGE and 2000 mg for GLUCOPHAGE XR. It is recommended that the insulin dose be decreased by 10% to 25% when fasting plasma glucose

concentrations decrease to less than 120 mg/dL in patients receiving concomitant insulin and GLUCOPHAGE or GLUCOPHAGE XR. Further adjustment should be individualized based on glucose-lowering response.

Specific Patient Populations

GLUCOPHAGE or GLUCOPHAGE XR are not recommended for use in pregnancy. GLUCOPHAGE is not recommended in patients below the age of 10 years. GLUCOPHAGE XR is not recommended in pediatric patients (below the age of 17 years).

The initial and maintenance dosing of GLUCOPHAGE or GLUCOPHAGE XR should be conservative in patients with advanced age, due to the potential for decreased renal function in this population. Any dosage adjustment should be based on a careful assessment of renal function. Generally, elderly, debilitated, and malnourished patients should not be titrated to the maximum dose of GLUCOPHAGE or GLUCOPHAGE XR.

Monitoring of renal function is necessary to aid in prevention of lactic acidosis, particularly in the elderly. (See **WARNINGS**.)

HOW SUPPLIED

GLUCOPHAGE® (metformin hydrochloride tablets)

500 mg	Bottles of 100	NDC 0087-6060-05
500 mg	Bottles of 500	NDC 0087-6060-10
850 mg	Bottles of 100	NDC 0087-6070-05
1000 mg	Bottles of 100	NDC 0087-6071-11

GLUCOPHAGE 500 mg tablets are round, white to off-white, film coated tablets debossed with “BMS 6060” around the periphery of the tablet on one side and “500” debossed across the face of the other side.

GLUCOPHAGE 850 mg tablets are round, white to off-white, film coated tablets debossed with “BMS 6070” around the periphery of the tablet on one side and “850” debossed across the face of the other side.

GLUCOPHAGE 1000 mg tablets are white, oval, biconvex, film coated tablets with “BMS 6071” debossed on one side and “1000” debossed on the opposite side and with a bisect line on both sides.

GLUCOPHAGE® XR (metformin hydrochloride extended-release tablets)

500 mg	Bottles of 100	NDC 0087-6063-13
750 mg	Bottles of 100	NDC 0087-6064-13

GLUCOPHAGE XR 500 mg tablets are white to off-white, capsule shaped, biconvex tablets, with "BMS 6063" debossed on one side and "500" debossed across the face of the other side.

GLUCOPHAGE XR 750 mg tablets are capsule shaped, biconvex tablets, with "BMS 6064" debossed on one side and "750" debossed on the other side. The tablets are pale red and may have a mottled appearance.

Storage

Store at 20°–25° C (68°–77° F); excursions permitted to 15°–30° C (59°–86° F). [See USP Controlled Room Temperature.]

Dispense in light-resistant containers.

GLUCOPHAGE® is a registered trademark of Merck Santé S.A.S., an associate of Merck KGaA of Darmstadt, Germany. Licensed to Bristol-Myers Squibb Company.

Distributed by:
Bristol-Myers Squibb Company
Princeton, NJ 08543 USA

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Bristol-Myers Squibb Company

Rx only

Patient Information

GLUCOPHAGE®
(metformin hydrochloride tablets)
and
GLUCOPHAGE® XR
(metformin hydrochloride extended-release tablets)

Read this information carefully before you start taking this medicine and each time you refill your prescription. There may be new information. This information does not take the place of your doctor's advice. Ask your doctor or pharmacist if you do not understand some of this information or if you want to know more about this medicine.

What are GLUCOPHAGE and GLUCOPHAGE XR?

GLUCOPHAGE and GLUCOPHAGE XR are used to treat type 2 diabetes. This is also known as non-insulin-dependent diabetes mellitus. People with type 2 diabetes are not able to make enough insulin or respond normally to the insulin their bodies make. When this happens, sugar (glucose) builds up in the blood. This can lead to serious medical problems including kidney damage, amputations, and blindness. Diabetes is also closely linked to heart disease. The main goal of treating diabetes is to lower your blood sugar to a normal level.

High blood sugar can be lowered by diet and exercise, by a number of medicines taken by mouth, and by insulin shots. Before you take GLUCOPHAGE or GLUCOPHAGE XR, try to control your diabetes by exercise and weight loss. While you take your diabetes medicine, continue to exercise and follow the diet advised for your diabetes. No matter what your recommended diabetes management plan is, studies have shown that maintaining good blood sugar control can prevent or delay complications of diabetes, such as blindness.

GLUCOPHAGE and GLUCOPHAGE XR have the same active ingredient. However, GLUCOPHAGE XR works longer in your body. Both of these medicines help control your blood sugar in a number of ways. These include helping your body respond better to the insulin it makes naturally, decreasing the amount of sugar your liver makes, and decreasing the amount of sugar your intestines absorb. GLUCOPHAGE and

GLUCOPHAGE XR do not cause your body to make more insulin. Because of this, when taken alone, they rarely cause hypoglycemia (low blood sugar), and usually do not cause weight gain. However, when they are taken with a sulfonylurea or with insulin, hypoglycemia is more likely to occur, as is weight gain.

WARNING: A small number of people who have taken GLUCOPHAGE have developed a serious condition called lactic acidosis. Lactic acidosis is caused by a buildup of lactic acid in the blood. This happens more often in people with kidney problems. Most people with kidney problems should not take GLUCOPHAGE or GLUCOPHAGE XR. (See "What are the side effects of GLUCOPHAGE and GLUCOPHAGE XR?")

Who should not take GLUCOPHAGE or GLUCOPHAGE XR?

Some conditions increase your chance of getting lactic acidosis, or cause other problems if you take either of these medicines. Most of the conditions listed below can increase your chance of getting lactic acidosis.

Do not take GLUCOPHAGE or GLUCOPHAGE XR if you:

- have kidney problems
- have liver problems
- have heart failure that is treated with medicines, such as Lanoxin® (digoxin) or Lasix® (furosemide)
- drink a lot of alcohol. This means you binge drink for short periods or drink all the time
- are seriously dehydrated (have lost a lot of water from your body)
- are going to have an x-ray procedure with injection of dyes (contrast agents)
- are going to have surgery
- develop a serious condition, such as heart attack, severe infection, or a stroke
- are 80 years or older and you have NOT had your kidney function tested

Tell your doctor if you are pregnant or plan to become pregnant. GLUCOPHAGE and GLUCOPHAGE XR may not be right for you. Talk with your doctor about your choices. You should also discuss your choices with your doctor if you are nursing a child.

Can GLUCOPHAGE or GLUCOPHAGE XR be used in children?

GLUCOPHAGE has been shown to effectively lower glucose levels in children (ages 10 to 16 years) with type 2 diabetes. GLUCOPHAGE has not been studied in children younger than 10 years old. GLUCOPHAGE has not been studied in combination with other oral glucose-control medicines or insulin in children. If you have any questions about the use of GLUCOPHAGE in children, talk with your doctor or other healthcare provider.

GLUCOPHAGE XR has not been studied in children.

How should I take GLUCOPHAGE or GLUCOPHAGE XR?

Your doctor will tell you how much medicine to take and when to take it. You will probably start out with a low dose of the medicine. Your doctor may slowly increase your dose until your blood sugar is better controlled. You should take GLUCOPHAGE or GLUCOPHAGE XR with meals.

Your doctor may have you take other medicines along with GLUCOPHAGE or GLUCOPHAGE XR to control your blood sugar. These medicines may include insulin shots. Taking GLUCOPHAGE or GLUCOPHAGE XR with insulin may help you better control your blood sugar while reducing the insulin dose.

Continue your exercise and diet program and test your blood sugar regularly while taking GLUCOPHAGE or GLUCOPHAGE XR. Your doctor will monitor your diabetes and may perform blood tests on you from time to time to make sure your kidneys and your liver are functioning normally. There is no evidence that GLUCOPHAGE or GLUCOPHAGE XR causes harm to the liver or kidneys.

Tell your doctor if you:

- have an illness that causes severe vomiting, diarrhea or fever, or if you drink a much lower amount of liquid than normal. These conditions can lead to severe dehydration (loss of water in your body). You may need to stop taking GLUCOPHAGE or GLUCOPHAGE XR for a short time.
- plan to have surgery or an x-ray procedure with injection of dye (contrast agent). You may need to stop taking GLUCOPHAGE or GLUCOPHAGE XR for a short time.
- start to take other medicines or change how you take a medicine. GLUCOPHAGE and GLUCOPHAGE XR can affect how well other drugs work, and some drugs can affect how well GLUCOPHAGE and GLUCOPHAGE XR work. Some medicines may cause high blood sugar.

GLUCOPHAGE XR must be swallowed whole and never crushed or chewed. Occasionally, the inactive ingredients of GLUCOPHAGE XR may be eliminated as a soft mass in your stool that may look like the original tablet; this is not harmful and will not affect the way GLUCOPHAGE XR works to control your diabetes.

What should I avoid while taking GLUCOPHAGE or GLUCOPHAGE XR?

Do not drink a lot of alcoholic drinks while taking GLUCOPHAGE or GLUCOPHAGE XR. This means you should not binge drink for short periods, and you should not drink a lot of alcohol on a regular basis. Alcohol can increase the chance of getting lactic acidosis.

What are the side effects of GLUCOPHAGE and GLUCOPHAGE XR?

Lactic Acidosis. **In rare cases, GLUCOPHAGE and GLUCOPHAGE XR can cause a serious side effect called lactic acidosis. This is caused by a buildup of lactic acid in your blood. This buildup can cause serious damage.** Lactic acidosis caused by GLUCOPHAGE and GLUCOPHAGE XR is rare and has occurred mostly in people whose kidneys were not working normally. Lactic acidosis has been reported in about one in 33,000 patients taking GLUCOPHAGE over the course of a year. Although rare, if lactic acidosis does occur, it can be fatal in up to half the people who develop it.

It is also important for your liver to be working normally when you take GLUCOPHAGE or GLUCOPHAGE XR. Your liver helps remove lactic acid from your blood.

Make sure you tell your doctor before you use GLUCOPHAGE or GLUCOPHAGE XR if you have kidney or liver problems. You should also **stop using GLUCOPHAGE or GLUCOPHAGE XR and call your doctor right away if you have signs of lactic acidosis. Lactic acidosis is a medical emergency that must be treated in a hospital**.

Signs of lactic acidosis are:

- feeling very weak, tired, or uncomfortable
- unusual muscle pain
- trouble breathing
- unusual or unexpected stomach discomfort

- feeling cold
- feeling dizzy or lightheaded
- suddenly developing a slow or irregular heartbeat

If your medical condition suddenly changes, stop taking GLUCOPHAGE or GLUCOPHAGE XR and call your doctor right away. This may be a sign of lactic acidosis or another serious side effect.

Other Side Effects. Common side effects of GLUCOPHAGE and GLUCOPHAGE XR include diarrhea, nausea, and upset stomach. These side effects generally go away after you take the medicine for a while. Taking your medicine with meals can help reduce these side effects. Tell your doctor if the side effects bother you a lot, last for more than a few weeks, come back after they've gone away, or start later in therapy. You may need a lower dose or need to stop taking the medicine for a short period or for good.

About 3 out of every 100 people who take GLUCOPHAGE or GLUCOPHAGE XR have an unpleasant metallic taste when they start taking the medicine. It lasts for a short time.

GLUCOPHAGE and GLUCOPHAGE XR rarely cause hypoglycemia (low blood sugar) by themselves. However, hypoglycemia can happen if you do not eat enough, if you drink alcohol, or if you take other medicines to lower blood sugar.

General advice about prescription medicines

If you have questions or problems, talk with your doctor or other healthcare provider. You can ask your doctor or pharmacist for the information about GLUCOPHAGE and GLUCOPHAGE XR that is written for healthcare professionals. Medicines are sometimes prescribed for purposes other than those listed in a patient information leaflet. Do not use GLUCOPHAGE or GLUCOPHAGE XR for a condition for which it was not prescribed. Do not share your medicine with other people.

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