Name of Sponsor/Company: Bristol-Myers Squibb	Individual Study Table Referring to the Dossier	*(For National Authority Use Only)*
Name of Finished Product:		
Name of Active Ingredient: Saxagliptin		

SYNOPSIS

Final Short-Term Clinical Study Report for Study CV181039

TITLE OF STUDY: A Multicenter, Randomized, Double-Blind, Active-Controlled, Phase 3 Trial to Evaluate the Efficacy and Safety of Saxagliptin in Combination with Metformin IR as Initial Therapy Compared to Saxagliptin Monotherapy and to Metformin IR Monotherapy in Subjects with Type 2 Diabetes Who Have Inadequate Glycemic Control

INVESTIGATORS/STUDY CENTERS: 196 investigators at 196 sites (46 in Russian Federation, 44 in the United States, 19 in Argentina, 13 in India, 13 in Mexico, 12 in Germany, 10 in the Ukraine, 8 in Brazil, 8 in Poland, 8 in the Philippines, 6 in Puerto Rico, 5 in Hungary, and 4 in Italy)

PUBLICATIONS: None

STUDY PERIOD: Study Initiation Date: 30-May-2006 **CLINICAL PHASE:** 3
Study Completion Date: 27-Nov-2007

OBJECTIVES:

Primary Efficacy Objective - To compare, after 24 weeks of oral administration of double-blind treatment, the change from baseline in hemoglobin A1C (A1C) achieved with each dose of saxagliptin + metformin immediate release (IR) compared to saxagliptin + placebo and to metformin IR + placebo in subjects with type 2 diabetes who have inadequate glycemic control defined as A1C $\geq$ 8% but $\leq$ 12%.

Secondary Efficacy Objectives - To compare each dose of saxagliptin + metformin IR versus saxagliptin + placebo and metformin IR + placebo after 24 weeks of oral administration of double-blind therapy for the following: 1) change from baseline in fasting plasma glucose (FPG), 2) proportion of subjects achieving a therapeutic glycemic response defined as A1C < 7.0%, 3) change from baseline in the AUC from 0 to 180 minutes for postprandial glucose (PPG) response to an oral glucose tolerance test (OGTT), 4) proportion of subjects achieving a therapeutic glycemic response defined as A1C $\leq$ 6.5%, and 5) proportion of subjects requiring rescue for failing to achieve pre-specified glycemic targets or discontinuing for lack of efficacy within the 24 week, short-term, double-blind treatment period.

Other Efficacy Objectives - To compare/assess each dose of saxagliptin + metformin IR versus saxagliptin + placebo and metformin IR + placebo for the following: 1) differences in the change from baseline to Week 12 in FPG, 2) differences in the change from baseline to Week 24 for the following: a) AUC from 0 to 180 minutes for postprandial insulin, postprandial glucagon and postprandial C-peptide response to an OGTT, b) beta cell function (as measured by Homeostasis Model Assessment, HOMA-2B), c) insulin resistance (as measured by HOMA-2 IR), d) fasting glucagon, fasting insulin and fasting C-peptide, e) glucose, C-peptide, insulin, and glucagon concentrations at 0-, 30- 60, 120- and 180 minutes during an OGTT, f) excursion profiles for glucose, C-peptide, insulin, and glucagon concentrations (defined as the difference between 0 minutes and 30, 60, 120 and 180 minute postprandial values) after an OGTT, g) insulin sensitivity and β-cell function derived from measurements of insulin, C-peptide and

glucose during the OGTT, h) body mass index (BMI), waist circumference, and total body weight, i) the proportion of subjects achieving a glycemic response for each of the following categories: A1C ≤ 8.0%, reduction in A1C ≥ 0.5%, reduction in A1C ≥ 0.7%, FPG < 110 mg/dL (6.1 mmol/L), FPG < 126 mg/dL (7.0 mmol/L), 120-minute PPG < 140 mg/dL (7.8 mmol/L), 120-minute PPG < 200 mg/dL (11.1 mmol/L), (j) percent change from baseline in fasting lipids: total cholesterol (total-C), low density lipoprotein cholesterol (LDL-C), high density lipoprotein cholesterol (HDL-C), triglycerides (TG), and free fatty acids (FFA), (k) change from baseline in metabolic surrogate markers (hs-CRP, PAI-1, and fibrinogen) and interleukin-6 (IL-6) and (l) proportion of subjects requiring rescue for failing to achieve pre-specified glycemic targets or discontinuing for lack of efficacy at Weeks 4, 6, 8, 12, 16, 20 and 24.

Safety Objective - To assess the safety and tolerability of each dose of saxagliptin + metformin IR, saxagliptin + placebo and metformin IR + placebo when administered for up to 24 weeks of short-term double-blind therapy.

METHODOLOGY: This was a Phase 3, randomized, 4-arm, parallel group, double-blind, active-controlled, multi-center study in drug naïve subjects with inadequate glycemic control (A1C ≥8.0% and ≤12.0%). Following screening evaluations, subjects who met eligibility criteria were enrolled in a 1-week, single-blind, dietary and exercise placebo lead-in period. Subjects meeting the randomization criteria were randomized (1:1:1:1) in a double-blind fashion to either saxagliptin 10 mg plus metformin IR 500 mg (Saxa 10mg + Met), saxagliptin 5 mg plus metformin IR 500 mg (Saxa 5mg+Met), saxagliptin 10 mg plus placebo (Saxa 10mg), or metformin IR 500 mg plus placebo (Met). At Week 1, subjects receiving metformin as monotherapy or in combination with saxagliptin were to be titrated, as tolerated, from metformin 500 mg/d to 1000 mg/d in divided doses. At Weeks 2, 3, 4, and 5, subjects were to be titrated, as tolerated, in increments of 500 mg up to a maximum of 2000 mg/d in divided doses if mean fasting plasma glucose (MFPG) > 110 mg/dL (6.1 mmol/L) or mean fasting whole blood glucose (MFWBG) > 104 mg/dL (5.8 mmol/L). Subjects who met glycemic rescue criteria during the 24-week, short-term period were eligible to enter the long-term (12 months) period where they received open-label pioglitazone added to their blinded study medication. Subjects who completed all visits during the 24-week, short-term period and did not meet glycemic rescue criteria were eligible to enter the long-term period where they received the same treatment as they received during the short-term period. The long-term extension period is ongoing.

NUMBER OF SUBJECTS (Planned and Analyzed): Planned (enrolled) 1470; Enrolled (signed study specific informed consent) 2936; Entered lead-in period 1394; Randomized 1309; Treated 1306; Total treated with saxagliptin 978. A total of 991 subjects completed the short-term period. Of the 315 subjects who did not complete short-term treatment, 137 were rescued and went into the long-term phase of the study.

DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION:

- Subjects with a diagnosis of type 2 diabetes mellitus
- A1C ≥ 8% but ≤ 12% obtained at the screening visit
- Fasting C-peptide concentration ≥ 1.0 ng/ml
- Subjects were to be drug naïve. Drug naïve subjects were defined as subjects who have never received medical treatment for diabetes (insulin and/or oral hypoglycemic agents) or have received medical treatment for diabetes for less than a total of 1 month since original diagnosis. In addition, subjects should not have received any antihyperglycemic therapy for more than 3 consecutive days or a total of 7 non-consecutive days during the 8 weeks prior to screening. The exceptions were for women who have received treatment for gestational diabetes during their pregnancy and were no longer receiving therapy or subjects who during a hospitalization received a short course of insulin treatment.
- BMI ≤ 40 kg/m^2

TEST PRODUCT, DOSE AND MODE OF ADMINISTRATION, DURATION OF TREATMENT, BATCH NUMBERS: Saxagliptin (BMS-477118) tablets used during the 24-week, double-blind, short-term period are shown in the table below. Subjects were instructed to take 1 tablet daily prior to the morning meal.

Product	Potency	Appearance	Batch Numbers
Saxagliptin	5 mg as the free base	Plain, yellow, biconvex, round, film coated tablet	6H17796, 6C15675, 6B19549
Saxagliptin	10 mg as the free base	Plain, yellow, biconvex, round, film coated tablet	5L08927, 6C15678, 6E12062

REFERENCE THERAPY, DOSE AND MODE OF ADMINISTRATION, DURATION OF TREATMENT, BATCH NUMBERS: Matching placebo tablets for saxagliptin and open-label metformin tablets used during the 24-week, double-blind, short-term period are shown in the following table. Subjects in the Met group were instructed to take 1 tablet of saxagliptin placebo daily prior to the morning meal. Subjects in the Saxa 10mg group were instructed to take 1 tablet of metformin placebo daily prior to the morning meal. If at the Week 1, 2, 3, 4 or 5 visit, a subject in the Saxa 5mg + Met, Saxa 10mg + Met and Met groups met the criteria to initiate blinded metformin titration, titration was to occur as follows. Note that subjects in the 3 groups who received metformin had to titrate in a blinded fashion. Subjects in the Saxa 10 mg group received dummy titration.

Initial titration: **0** tablet(s) daily with the morning meal, **1** tablet daily with the evening meal.

Second titration: **1** tablet daily with the morning meal, **1** tablet daily with the evening meal.

Third titration: **1** tablet daily with the morning meal, **2** tablets daily with the evening meal.

Product	Potency	Appearance	Batch Numbers
Saxagliptin Placebo	N/A	Plain, yellow, biconvex, round, film coated tablet	6B13898, 6B13899, 6H17797
Metformin Hydrochloride	500 mg	White to off-white, round, film-coated tablet	6A17279, 6D16956, 6D17286, 6H16141
Metformin Placebo	N/A	White to off-white, round, film-coated tablet	6B12609, 6J21037

Subjects meeting the criteria for rescue during the 24-week, short-term period were eligible to enter the long-term (12 months) period where they received open-label pioglitazone added to their blinded study medication. Subjects were instructed to take pioglitazone daily prior to the morning meal.

Product	Potency	Appearance	Batch Numbers
Pioglitazone HCl (US sourced product)	15 mg	White to off-white, round, flat, non-scored tablet	7D26486, 7G22196
Pioglitazone HCl (UK sourced product)	15 mg	White to off-white, round, flat tablet	9210022A

CRITERIA FOR EVALUATION:

Primary Efficacy Endpoint: The change in A1C from baseline to Week 24 or the last post-baseline measurement prior to Week 24 and before rescue, if no Week 24 assessment was available.

Secondary Efficacy Endpoints: The secondary efficacy endpoints assessed at Week 24 were:1) change from baseline in FPG, 2) proportion of subjects achieving A1C < 7.0%, 3) change from baseline in AUC from 0 to 180 minutes for PPG response to an OGTT, 4) proportion of subjects achieving A1C ≤ 6.5%, and 5) proportion of subjects requiring rescue for failing to achieve pre-specified glycemic targets or discontinuing for lack of efficacy within the 24 week, short-term, double-blind treatment period. For each secondary efficacy endpoint, if no Week 24 measurement was available, then the last post-baseline measurement before Week 24 and before rescue (if any) was used.

Other Efficacy Endpoints: Other efficacy endpoints were: 1) changes from baseline to Week 12 in FPG, 2) changes from baseline to Week 24 in AUCs from 0 to 180 minutes for postprandial insulin, glucagon, and C-peptide response to an OGTT, 3) change from baseline to Week 24 in β-cell function (as measured by HOMA-2B), 4) change from baseline to Week 24 in insulin resistance (as measured by HOMA-2 IR), 5) changes from baseline to Week 24 in fasting glucagon, insulin and C-peptide, 6) changes from baseline to Week 24 in glucose, C-peptide, insulin, and glucagon concentrations at 0, 30, 60, 120, and 180 minutes in response to an OGTT, 7) changes from baseline to Week 24 in the respective excursion profiles for glucose, C-peptide, insulin, and glucagon concentrations, 8) changes from baseline to Week 24 in the insulin sensitivity and β-cell function derived from measurements of insulin, C-peptide and glucose during an OGTT, 9) changes from baseline to Week 24 in BMI, waist circumference, and body weight, 10) proportion of subjects achieving a glycemic response at Week 24 based on predefined categories for A1C and glucose, 11) percent changes from baseline to Week 24 in total-C, LDL-C, HDL-C, TG, and FFA, 12) changes from baseline to Week 24 in hs-CRP, PAI-1, fibrinogen, and IL-6, and (13) proportion of subjects requiring rescue for failing to achieve pre-specified glycemic targets or discontinuing for lack of efficacy at Weeks 4, 6, 8, 12, 16, 20 and 24.

Safety: Safety endpoints included the frequency of clinical adverse events (AEs), serious adverse events (SAEs), and discontinuations due to AEs, as well as results for electrocardiograms (ECGs), vital signs and clinical laboratory tests.

STATISTICAL CONSIDERATIONS:

The primary endpoint was the change in A1C from baseline to Week 24 of the short-term treatment period. The primary efficacy analysis was performed using an analysis of covariance (ANCOVA) with treatment group as an effect and baseline value as the covariate. Within the framework of the ANCOVA model, point estimates and 95% confidence intervals were calculated for the mean changes within each treatment group as well as for the differences in mean changes between the following treatment groups:

- Saxa 5mg + Met relative to the Saxa 10mg group and relative to the Met group
- Saxa 10mg + Met group relative to Saxa 10mg group and relative to the Met group.

Each combination treatment group was compared with each individual component (ie, Saxa 10mg and Met); each comparison was performed at the 0.027 alpha level from Dunnett's adjustment so that the overall (familywise) Type I error rate was controlled at the 0.05 significance level. Sequential testing methodology was utilized for secondary efficacy endpoints. At each step in the testing sequence, only the combination treatment group significantly superior to both controls was tested at the subsequent step.

SUMMARY OF RESULTS:

Demographics and Other Pertinent Baseline Characteristics: Demographic and baseline characteristics were generally balanced across all treatment groups. Of the 1306 treated subjects, 49% were men and 76% were white. The mean age was 52 years (range 19 to 77 years), and 13% of subjects were ≥ 65 years of age. The median duration of type 2 diabetes was 0.4 years, and the mean baseline A1C was 9.5%.

Extent of Exposure: The mean duration of exposure to double-blind study medication was 151 days with Saxa 5mg − Met, 151 days with Saxa 10mg + Met, 137 days with Saxa 10mg and 144 days with Met.

EFFICACY RESULTS: Primary and secondary efficacy findings at Week 24 are shown in the following table.

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