Clinical Study Report Synopsis

Drug Substance	Saxagliptin
Study Code	D1680C00006
Edition Number	1
Date	24 March 2010

A 24-Week International, Multi-centre, Randomized, Parallel-group, Double-blind, Placebo-controlled, Phase III Study to Evaluate the Efficacy and Safety of Saxagliptin in Combination with Metformin in Adult Patients with Type 2 Diabetes who have Inadequate Glycaemic Control on Metformin Therapy in Addition to Diet and Exercise

Study dates: First subject enrolled: 12 June 2008
Last subject last visit: 23 September 2009

Phase of development: Therapeutic confirmatory (III)

This study was performed in compliance with Good Clinical Practice, including the archiving of essential documents.

Study centers

This study was conducted at 40 centers in the following countries: China (21 sites), India (7 sites), and South Korea (12 sites).

Publications

None at the time of writing this report.

Objectives

The primary efficacy objective of this study was to compare, after a 24-week oral administration of double-blind treatment, the absolute change from baseline in glycosylated hemoglobin (HbA1c) achieved with saxagliptin plus metformin versus placebo plus metformin in patients with type 2 diabetes who have inadequate glycemic control on 1500 mg or higher doses of metformin in addition to diet and exercise.

Three key secondary objectives were to compare the effects of saxagliptin versus placebo both given as add-on therapy to metformin after a 24-week double-blind treatment for the following:

- The change from baseline in fasting plasma glucose (FPG)
- The change from baseline in the area under the curve (AUC) from 0 to 180 minutes for postprandial glucose (PPG) during a mixed meal (instant noodles) tolerance test (MMTT) on a subset of approximately 100 patients
- The proportion of patients achieving a therapeutic glycemic response defined as HbA1c <7.0%

Other efficacy objectives were to compare the effects of saxagliptin versus placebo given as add-on therapy to metformin after a 24-week double-blind treatment for the following:

- The change from baseline in the incremental AUC from 0 to 180 minutes for PPG during an MMTT on a subset of approximately 100 patients*
- Change from baseline in mixed meal insulin sensitivity model (MMIS) on a subset of approximately 100 patients **
- 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, C-peptide, glucagon, proinsulin, and proinsulin/insulin ratio

- The change from baseline in AUC from 0 to 180 minutes for postprandial insulin, C-peptide, and glucagon during an MMTT on a subset of approximately 100 patients

- 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%

  - FPG <6.1 mmol/L (110 mg/dL)

  - FPG <7.0 mmol/L (126 mg/dL)

  - 120-minute PPG <7.8 mmol/L (140 mg/dL)

  - 120-minute PPG <11.1 mmol/L (200 mg/dL)

- 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)

- Change from baseline in 120-minute PPG during an MMTT**

- Change from baseline in glucose excursion during an MMTT**

*Incremental AUC for PPG (0 to 180 minutes) was the baseline-subtracted net increase in AUC PPG for this time interval.

**As changes from the protocol to the planned analyses, the Matsuda index (for insulin sensitivity) and insulinogenic index (for early insulin secretion) were added as variables in place of the MMIS for the subset of subjects for whom an MMTT was conducted. The change from baseline in insulin sensitivity was deleted (only change from baseline β-cell function was to be calculated), and variables for glucose excursion and 120-minute PPG during an MMTT were added.

Safety and tolerability were evaluated by assessment of adverse events (AEs) (including AEs of special interest), hypoglycemic events, laboratory values, electrocardiograms (ECGs), pulse, blood pressure (BP), weight, and physical examination.

Study design

This study was a 24-week, international, multicenter, randomized, parallel-group, double-blind, placebo-controlled Phase 3 study to evaluate the efficacy and safety of saxagliptin in combination with metformin in adult subjects with type 2 diabetes who have inadequate glycemic control on metformin therapy in addition to diet and exercise. The study comprised an enrollment period, a 2-week placebo lead-in period, and a 24-week randomized treatment period. This multinational study was performed to evaluate the efficacy and safety of saxagliptin in combination with metformin in the Asian population in the Asian Pacific region, in particular, China. The results of the analysis of the China cohort of this multinational study are presented in a separate clinical study report (hereafter referred to as the "China supplement").

Target population and sample size

Men or women who were ≥18 years of age diagnosed with type 2 diabetes with inadequate glycemic control (HbA1c ≥7.2% and ≤10.0%) while on treatment with metformin alone at stable doses of 1500 mg or higher per day for at least 8 weeks prior to enrollment.

With a total of 530 subjects randomized and treated (or 265 per treatment group), there would be 98% power to detect a 0.5% difference between the two randomized treatment groups in absolute change from baseline to Week 24 in HbA1c at the 5% level, assuming a standard deviation (SD) of change from baseline in HbA1c of 1.2%.

For the China cohort, a total of 308 subjects were expected to be randomized (approximately 154 per treatment group). The sample size for the China cohort also assumed about a 20% dropout rate. The sample size of 308 subjects would be sufficient for a 90% power to detect a 0.5% difference between the two randomized treatment groups in absolute change from baseline to Week 24 in HbA1c, assuming a SD of change from baseline in HbA1c of 1.2%. The remaining 222 subjects were to be allocated to approximately 133 from India and approximately 89 from Korea.

Investigational product and comparator(s): dosage, mode of administration, and batch numbers´

Saxagliptin 5 mg tablets (batch number H 2024-01-01-01) for oral administration once daily in the morning, and open-label metformin 500 mg immediate-release tablets (batch number H 1605-04-01-01) for oral administration once or twice daily depending on the dose directed by the investigator (1500 mg to 2500 mg) in accordance with the manufacturer's recommendations and clinical practice, and placebo tablets matching saxagliptin 5 mg (batch number H 2014-01-01-01, H 2014-01-01-02, H 2014-01-01-03) for oral administration once daily in the morning.

Duration of treatment

The total duration of treatment with study drug was 24 weeks. Subjects were treated with open-label metformin treatment for a 2-week placebo lead-in period, followed by the 24-

week, double-blind treatment period, in which subjects received saxagliptin 5 mg and metformin or placebo and metformin for comparator. All subjects received open-label metformin throughout the 2-week lead-in and 24-week, double-blind periods.

Criteria for evaluation - efficacy (main variables)

The primary variable for the study was the change from baseline to Week 24 in HbA1c.

The key secondary variables were:

- Change from baseline to Week 24 in FPG
- Change from baseline to Week 24 in PPG AUC (0 to 180 minutes) during MMTT
- Proportion of patients achieving a therapeutic glycemic response defined as HbA1c <7.0% at Week 24

Other secondary efficacy variables were:

- Change from baseline in incremental PPG AUC (0 to 180 minutes) during MMTT
- Change from baseline in Matsuda index and insulinogenic index
- Change from baseline in β-cell function (as measured by HOMA-2)
- Change from baseline in fasting insulin, C-peptide, glucagon, proinsulin, and proinsulin/insulin ratio
- Change from baseline in AUC for insulin, C-peptide, and glucagon as well as change from baseline in 120-minute PPG and in glucose excursion following an MMTT
- Change from baseline in BMI, waist circumference, and body weight
- Proportion of subjects achieving a therapeutic glycemic response defined as: HbA1c ≤6.5%; reduction in HbA1c ≥0.5%; reduction in HbA1c ≥0.7%; FPG <6.1 mmol/L (110 mg/dL); FPG <7.0 mmol/L (126 mg/dL); 120-minute PPG <7.8 mmol/L (140 mg/dL); and 120-minute PPG <11.1 mmol/L (200 mg/dL)
- Change from baseline in TC, LDL-C, HDL-C and TG

Criteria for evaluation - safety (main variables)

Safety and tolerability were evaluated by assessment of AEs (including AEs of special interest), hypoglycemic events, laboratory values, ECGs, pulse, BP, weight, and physical examination.

Statistical methods

The primary analysis for efficacy variables was based on the Full analysis set, which included subjects who took at least 1 dose of investigational product (IP) and had both baseline and post-baseline efficacy data. A sensitivity analysis was to be performed based on the Per Protocol (PP) analysis set (subjects in the Full analysis set who had no reasons for exclusion), only if more than 10% of the subjects in any treatment group were found to deviate significantly from the terms and conditions of the protocol. Otherwise, analysis of and inference to the primary efficacy variable, demographics, and baseline diabetes-related characteristics were restricted to the Full analysis set. If PP analysis was deemed necessary, then the analysis was to be performed on the primary variable (change from baseline in HbA1c at Week 24), demographics, and baseline diabetes-related characteristics only. The analysis of MMTT included participants in that test only. (Note: All MMTT participants were subjects enrolled in China.)

All statistical analyses were performed using Version 8 (or higher) of SAS®.

The primary efficacy analysis was to establish superiority of saxagliptin plus metformin over placebo plus metformin for the absolute change from baseline in HbA1c to Week 24, analyzed on the Full analysis set using an analysis of covariance (ANCOVA) model. The model used absolute change from baseline as a dependent variable, treatment and country as fixed main effects, and baseline HbA1c as a covariate. Within the framework of the ANCOVA model, point estimates and the 2-sided 95% confidence intervals (CIs) for the mean change within each treatment group, as well as for the differences in mean change between the saxagliptin + metformin treatment arm and the placebo + metformin treatment arm, were presented.

To assess the robustness of the primary efficacy analysis, the modelling of the primary analysis was repeated utilizing repeated measures analysis (using mixed model). This model contained terms for treatment group, baseline measurement, country, time, and time by treatment group. Subgroup analyses for the primary efficacy variable included country, gender (male, female); age (<65 years, ≥65 years, and ≥75 years); baseline (Week 0) HbA1c (<8.0%, ≥8.0% to <9.0%, and ≥9.0%); duration of type 2 diabetes since diagnosis (≤1.5 years, ≤3 years, >3 years to <5 years, ≥5 years, and ≥10 years); and baseline BMI (<30 kg/m^2 and ≥30 kg/m^2).

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

1. Change from baseline to Week 24 in FPG; ANCOVA similar to the model used for the primary endpoint using the Full analysis set

2. Change from baseline to Week 24 in AUC (0 to 180 minutes) in PPG during MMTT; ANCOVA similar to the model used for the primary endpoint using the Full analysis set on a subset of approximately 100 subjects

3. The treatment dependency of proportion of subjects achieving a therapeutic glycemic response defined as HbA1c <7.0%, discriminated by 2-sided Fisher's Exact test using the Full analysis set

Statistical inferences started from the overall primary efficacy endpoint. If saxagliptin plus metformin was superior in change from baseline in HbA1c compared to placebo plus metformin, then statistical inference continued with the first secondary efficacy endpoint (1); otherwise, statistical inference of the overall efficacy endpoints was to stop. The p-values that followed could not be considered as significant in this confirmatory analysis when the fixed sequence procedure was used to control the overall type 1 error rate, even if the p-value was less than 0.05. Similarly, if saxagliptin plus metformin was superior in change from baseline in FPG compared to placebo plus metformin, then statistical inference continued with the second secondary efficacy endpoint (2); otherwise, statistical inference of the overall efficacy endpoints was to stop. Similar statistical inference was followed with the prescribed order (1) to (3) with the same decision rule until all 3 secondary endpoints were analyzed or interrupted at any non-significant finding. These same secondary efficacy endpoints were analyzed by country using the same method as described. Point estimates and 2-sided 95% CIs were presented for each endpoint by country.

The other efficacy variables were analyzed similarly.

All comparisons were 2-sided at the 5% significance level.

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

All efficacy analyses and safety summaries described above were also repeated for the China cohort only and are reported separately.

Subject population

A total of 570 subjects were randomized and treated (at least 1 dose) with either saxagliptin + metformin (n=283) or placebo + metformin (n=287). The proportions of subjects who completed the 24-week, double-blind, randomized treatment period were high (88%) and were similar between the 2 treatment groups (90% in the saxagliptin + metformin group and 86% in the placebo + metformin group). The most common reasons for discontinuation in both treatment groups were withdrawal of consent (n=36, 4.6% in the saxagliptin + metformin group and 8.0% in the placebo + metformin group), study-specific discontinuation criteria (n=15, 1.4% in the saxagliptin + metformin group and 3.8% in the placebo + metformin group), and AEs (n=9; 1.8% in the saxagliptin + metformin group and 1.4% in the placebo + metformin group).

Of the 570 randomized and treated subjects, 51.8% were female and the mean age was 54 years (range: 20 to 80 years). A total of 101 (17.7%) subjects were ≥ 65 years of age and 5 (0.9%) were ≥75 years of age. Mean body weight was 68.94 kg (range: 42.00 kg to

123.00 kg). Approximately 12% of the study population had a mean BMI ≥30.0 kg/m^2. Baseline demographic and disease characteristics were well balanced across the 2 treatment groups in the Randomized, Full, and MMTT analysis sets and were representative of subjects with type 2 diabetes with inadequate glycemic control on metformin therapy in addition to diet and exercise. Mean HbA1c at baseline was 7.9% in the Randomized analysis set in both treatment groups. The observed levels of compliance were similar among the 2 treatment groups and therefore were unlikely to have any effect on the results of the study. The majority of subjects in the study achieved ≥80% and ≤120% treatment compliance for IP (saxagliptin [97.5%] or placebo [96.9%]).

Summary of efficacy results

Table S1 summarizes the change in HbA1c from baseline to Week 24 of randomized treatment for the Full analysis set (last observation carried forward [LOCF]) (the primary analysis).

Mean baseline HbA1c values were similar in the 2 treatment groups. Adjusted mean changes from baseline to Week 24 were -0.78% for the saxagliptin + metformin group and -0.37% for the placebo + metformin group. Based on the difference in adjusted mean changes from baseline, treatment with saxagliptin 5 mg added to metformin significantly decreased HbA1c compared with placebo added to metformin (difference vs placebo -0.42%, 95% CI -0.55% to -0.29%; $p<0.0001$).

Similar results were obtained in the Full analysis set using observed values and in the repeated measures analysis.

Table S1 Change in HbA1c from baseline to Week 24 (LOCF) (Full analysis set)

	Saxa + Met (N=278)	Placebo + Met (N=281)
n	275	279
Units: %		
Baseline mean (SE)	7.90 (0.049)	7.94 (0.050)
Week 24 mean (SE)	7.10 (0.056)	7.55 (0.062)
Mean change from baseline (SE)	-0.80 (0.051)	-0.39 (0.048)
Adjusted change from baseline		
Mean (SE)	-0.78 (0.051)	-0.37 (0.050)
2-sided 95% CI	-0.88, -0.68	-0.46, -0.27
Difference vs placebo + metformin		
Mean (SE)[a]	-0.42 (0.067)	NA
2-sided 95% CI	-0.55, -0.29	NA
P-value	<0.0001	

Baseline is defined as the last assessment within 42 days before the first dose of double-blind study drug, and before or including the first Day 1 assessment.
ANCOVA model: post – pre = pre + treatment + country.
[a] Estimate=adjusted mean change for (saxa + met) – adjusted mean change for (placebo + met).
ANCOVA Analysis of covariance; CI Confidence interval; HbA1c Glycosylated hemoglobin; LOCF Last observation carried forward; Met Metformin; NA Not applicable; Saxa Saxagliptin; SE Standard error.

Key secondary efficacy findings included:

- Saxagliptin added to metformin resulted in a significant reduction in FPG compared with placebo added to metformin at Week 24 (adjusted mean difference of -0.56 mmol/L (-10.10 mg/dL) (2-sided 95% CI -0.85 to -0.26 mmol/L [-15.37 to -4.83 mg/dL], p=0.0002).

- Saxagliptin added to metformin resulted in a significant reduction in PPG AUC compared with placebo added to metformin following an MMTT at Week 24 (adjusted mean difference of -155 mmol•min/L [-2802 mg•min/dL]; 2-sided 95% CI -264 to -47 mmol•min/L [-4753 to -852 mg•min/dL]; p=0.0052).

- Saxagliptin added to metformin resulted in a significantly greater proportion of subjects achieving therapeutic glycemic response defined by HbA1c <7% at Week 24 compared with placebo added to metformin (46.5% and 30.5%, respectively; adjusted mean difference of 16.1%; 2-sided 95% CI 8.0% to 24.0%; p=0.0001).

Other secondary efficacy findings included:

- Saxagliptin added to metformin resulted in numerically greater reductions compared with placebo added to metformin in:
  - incremental PPG AUC (0 to 180 minutes) during MMTT (adjusted mean difference of -133 mmol/L•min/L [-2408 mg•min/dL]; 2-sided 95% CI -201 to -65 mmol•min/L [-3629 to -1187 mg•min/dL])
  - 120-minute PPG during MMTT (adjusted mean difference of -1.05 mmol/L [-18.96 mg/dL]; 2-sided 95% CI -1.79 to -0.31 mmol/L [-32.34 to -5.58 mg/dL])
  - insulin AUC (0 to 180 minutes) during MMTT (adjusted mean difference of -973.7 pmol•min/L [-140.6 µU•min/mL]; 2-sided 95% CI -5777.5 to 3830.1 pmol•min/L [-832.3 to 551.1 µU•min/mL])
  - glucagon AUC (0 to 180 minutes) during MMTT (adjusted mean difference of -395 pmol•min/L [-1363 pg•min/mL]; 2-sided 95% CI -615 to -175 pmol•min/L [-2125 to -601 pg•min/mL])
  - fasting proinsulin (adjusted mean difference of -2.5 pmol/L; 95% CI -6.1 to 1.1 pmol/L), and fasting proinsulin/insulin % ratio (adjusted mean difference of -2.9%; 2-sided 95% CI -7.0% to 1.3%)
- There were no apparent differences between treatment groups in fasting insulin, fasting C-peptide, or fasting glucagon.
- Saxagliptin added to metformin resulted in numerically greater increases compared with placebo added to metformin in C-peptide AUC (0 to 180 minutes) during MMTT (adjusted mean difference of 9.4 nmol•min/L [28.4 ng•min/mL]; 2-sided 95% CI -10.7 to 29.4 nmol•min/L [-32.2 to 88.9 ng•min/mL]).
- There was a greater increase in calculated fasting β-cell function (HOMA-2β) in the saxagliptin + metformin group compared with the placebo + metformin group (11.6% and 5.0%, respectively). Calculated insulin sensitivity (Matsuda index) increased and calculated early insulin secretion (60 minutes insulinogenic index) decreased during MMTT in both treatment groups, with no apparent difference between treatment groups.
- In general, the proportions of subjects achieving a glycemic response, as defined by various HbA1c, FPG, and 120-minute PPG response thresholds, were numerically higher in the saxagliptin + metformin group compared with the placebo + metformin group.

- The reductions in body weight, BMI, and waist circumference were similar for both treatment groups.

- The mean percent changes from baseline for TG were numerically smaller for the saxagliptin + metformin group compared with the placebo + metformin group (-0.1% and 9.6%, respectively), whereas there was no apparent difference between the groups in change from baseline in fasting TC or LDL-C. Increases in HDL-C were observed in both treatment groups and were numerically greater in the placebo + metformin group.

- Saxagliptin added to metformin resulted in numerically smaller glucose excursions at 60-, 120-, and 180-minutes during MMTT compared with placebo added to metformin.

Summary of safety results

Mean exposure was similar in the 2 treatment groups, 160 and 155 days in the saxagliptin + metformin and placebo + metformin groups, respectively. The majority of subjects (88.7% and 85.4% of subjects, respectively) were exposed to treatment (regardless of interruption) for ≥166 days.

The proportions of subjects experiencing any AE were similar between the treatment groups (43.8% for saxagliptin + metformin and 41.5% for placebo + metformin). The SOC with the highest number of subjects with AEs in the saxagliptin + metformin group was Infections and Infestations, with 60 (21.2%) subjects in the saxagliptin + metformin group and 44 (15.3%) subjects in the placebo + metformin group. At the PT level, the most common AEs in the Infections and Infestations SOC were upper respiratory tract infection (6.7% in the saxagliptin + metformin group and 4.5% in the placebo + metformin group), nasopharyngitis (4.9% and 4.2%, respectively), and urinary tract infection (4.6% and 2.8%, respectively). The proportion of subjects with AEs within the SOC Metabolism and Nutrition Disorders was lower in the saxagliptin + metformin group (4.2%) compared with the placebo + metformin group (10.1%). At the PT level, the most common AEs in the Metabolism and Nutrition Disorders SOC were hypercholesterolemia (2.1% in the saxagliptin + metformin group and 2.4% in the placebo + metformin group) and hyperlipidemia (1.4% and 3.8%, respectively).

There were no deaths reported during the study. The incidence of SAEs was low in both treatment groups, but numerically higher in the saxagliptin + metformin group compared with the placebo + metformin group. A total of 11 subjects experienced SAEs during the randomized treatment period, 8 (2.8%) in the saxagliptin group and 3 (1.0%) in the placebo group. A total of 9 subjects discontinued IP due to AEs during the randomized treatment period, 6 (2.1%) in the saxagliptin + metformin group and 3 (1.0%) in the placebo + metformin group.

The numbers of subjects experiencing AEs indicative of an acute cardiovascular event were low and similar between the treatment groups (1 subject in each group). The numbers of subjects with hypoglycemic events were low and similar between the treatment groups

(4 subjects in each group). There were few fracture, hypersensitivity, lymphopenic, and localized edema AEs (all of which occurred in the saxagliptin + metformin group). No subjects in either treatment group had pancreatitis, thrombocytopenia, or selected skin disorder AEs.

There were no clinically relevant changes in mean values for any hematology or clinical chemistry laboratory parameters, and the numbers of subjects experiencing marked laboratory abnormalities were low in both treatment groups. There were no apparent treatment-related effects on changes in physical findings, vital signs, or ECGs in either treatment group. Both treatment groups had small reductions in systolic and diastolic BP after 24 weeks of treatment.