Clinical Study Report Synopsis

Drug Substance	Saxagliptin
Study Code	D1680C00002
Date	01 July 2009

An 18-week, International, Multi-centre, Randomized, Parallel-group, Double-blind, Active-controlled Phase IIIb Study to Evaluate the Efficacy and Safety of Saxagliptin in Combination with Metformin in Comparison with Sitagliptin in Combination with Metformin in Adult Patients with Type 2 Diabetes Who Have Inadequate Glycaemic Control on Metformin Therapy Alone

Study dates:	First subject enrolled: 08 April 2008 Last subject completed: 13 March 2009
Phase of development:	Therapeutic confirmatory (IIIb)

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

Study center(s)

This study was conducted at 99 sites in the following countries: Argentina (14 sites), Belgium (11 sites), Denmark (9 sites), France (10 sites), Italy (9 sites), Mexico (4 sites), Norway (16 sites), South Africa (12 sites), and Sweden (14 sites).

Publications

None at the time of writing this report.

Objectives

The primary efficacy objective of this study was to assess if, after 18 weeks of oral administration of double-blind treatment, the change from baseline in glycosylated hemoglobin A1c (HbA1c) achieved with saxagliptin 5 mg per day added to metformin is non-inferior to sitagliptin 100 mg per day added to metformin in patients with type 2 diabetes who have inadequate glycemic control on 1500 mg or higher doses of metformin therapy alone.

Note: In order to clarify the primary objective of the study in this report, minor revisions have been made to the original wording stated in the clinical study protocol.

Secondary objectives

Efficacy

To compare the effects of saxagliptin 5 mg per day versus sitagliptin 100 mg per day given as add-on therapy to metformin after an 18-week, double-blind treatment period by evaluation of:

- Change from baseline in fasting plasma glucose (FPG), insulin, C-peptide, glucagon, and proinsulin.
- Proportion of patients achieving a therapeutic glycemic response defined as HbA1c ≤6.5%.
- Change from baseline in HbA1c in patients with baseline HbA1c ≥7.0%.
- Proportion of patients achieving a therapeutic glycemic response defined as HbA1c <7.0% in patients whose baseline HbA1c ≥7.0%.
- Change from baseline in β-cell function (as measured by homeostasis model assessment [HOMA-2] [Wallace et al 2004]).
- Change from baseline in the area under the curve (AUC) from 0 to 180 minutes for postprandial glucose, insulin, C-peptide, and glucagon response to an oral glucose tolerance test (OGTT) in a subset of patients.*
- Change from baseline in postprandial glucose (PPG) at 120 minutes during OGTT in a subset of patients.*

- Change from baseline in insulinogenic index (Phillips et al 1994) in a subset of patients.*

- Change from baseline in insulin sensitivity as measured by oral glucose insulin sensitivity model (OGIS) (Mari et al 2001) and Matsuda Index (Matsuda and DeFronzo 1999) in a subset of patients.*

* An extended OGTT was conducted for a subset of subjects within the Full analysis set. The target was to include 50 subjects in the subgroup.

Safety

Safety and tolerability were evaluated by assessment of adverse events (AEs, including AEs of special interest, such as localized edema and skin-related AEs and hypoglycemic events), laboratory values, electrocardiogram (ECG), pulse, blood pressure, body weight, and physical examination.

Study design

This was an 18-week, international, multicenter, randomized, parallel-group, double-blind, active-controlled phase IIIb study to evaluate the efficacy and safety of saxagliptin in combination with metformin in comparison with sitagliptin in combination with metformin in adult subjects with type 2 diabetes who had inadequate glycemic control on metformin therapy alone.

Target subject population and sample size

Men or women who are ≥18 years of age diagnosed with type 2 diabetes with inadequate glycemic control (HbA1c >6.5% 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 710 subjects randomized and treated (or 355 per treatment group), it was calculated that there would be 90% power to establish the non-inferiority comparison on change from baseline to Week 18 in HbA1c at the 5% level assuming that the standard deviation of change from baseline in HbA1c is 1.1%, with a non-inferiority limit set at 0.3% and an assumed zero true difference between the two randomized treatments. The sample size also assumed that 20% of the randomized subjects would be excluded from the Per Protocol (PP) analysis set (the primary analysis population).

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

All study medications were administered orally and consisted of film-coated tablets of saxagliptin 5 mg (Batch H2024-01-01), matching placebo tablets for saxagliptin (Batches H2014-01-01, H2014-01-02), encapsulated tablets of sitagliptin 100 mg (two 50-mg tablets and white to off-white powder that appeared as a granule or a plug in one 2-piece hard gelatine capsule) (Batches H2037-01-01-01, H2037-01-01-02, H2037-01-01-03), matching placebo capsules containing white to off-white powder that appeared as a granule or a plug for

sitagliptin (Batch H2038-01-01), and metformin hydrochloride tablets 500 mg (Batch H1605-04-01-01). Saxagliptin was administered at 5 mg once daily, sitagliptin was administered at 100 mg once daily, and metformin was administered at 1500 to 3000 mg per day, in 2 to 3 daily doses.

Duration of treatment

The total duration of treatment with study drug was 18 weeks. Subjects were treated with matching placebo tablets for saxagliptin and matching placebo capsules for sitagliptin 100 mg for a 2-week placebo lead-in period, followed by the 18-week, double-blind treatment period, in which subjects received their respective randomized treatment and matching placebo for comparator. All subjects received open-label metformin throughout the 2-week lead-in and 18-week, double-blind periods.

Criteria for evaluation - efficacy (main variables)

The primary variable for the study was absolute change in HbA1c from baseline to Week 18.

Secondary variables included:

- Change from baseline in FPG, insulin, C-peptide, glucagon, and proinsulin.
- Proportion of subjects achieving a therapeutic glycemic response defined as HbA1c ≤6.5%.
- Change from baseline in HbA1c in subjects with baseline HbA1c ≥7.0%.
- Proportion of subjects achieving a therapeutic glycemic response defined as HbA1c <7.0% in subjects whose baseline HbA1c ≥7.0%.
- Change from baseline in β-cell function as measured by HOMA-2.
- Change from baseline in PPG at 120 minutes during OGTT on a subset of subjects.
- Change from baseline in AUC from 0 to 180 minutes for PPG, insulin, C-peptide, and glucagon during OGTT on a subset of subjects.
- Change from baseline in insulinogenic index on a subset of subjects.
- Change from baseline in insulin sensitivity as measured by OGIS and Matsuda Index on a subset of subjects.

Criteria for evaluation - safety (main variables)

Safety was evaluated by incidence of AEs (including serious AEs [SAEs] and AEs of special interest); laboratory values; ECG, vital signs (pulse and blood pressure), physical examination, weight, height, and waist circumference; and plasma concentration of saxagliptin

and metabolite in subjects who experienced some predefined AEs or discontinued due to an AE.

Statistical methods

The primary efficacy analysis to establish non-inferiority with 0.3% non-inferiority limit on the change in HbA1c from baseline to Week 18 was performed on the PP analysis set using an analysis of covariance model (ANCOVA). The model used treatment group as a fixed effect and baseline value as a covariate. Within the framework of the ANCOVA model, point estimates and the 2-sided 95% CIs for the mean change within each treatment group, as well as for the mean change between the saxagliptin plus metformin treatment group and the sitagliptin plus metformin treatment group, were constructed. Saxagliptin plus metformin would be considered not inferior to sitagliptin plus metformin if the upper limit of the 2-sided 95% CI of the difference in change in HbA1c from baseline to Week 18 between saxagliptin plus metformin and sitagliptin plus metformin was less than 0.3%. For secondary continuous glycemic outcome variables, such as change from baseline in FPG at Week 18, a similar ANCOVA model was used; point estimates and the 2-sided 95% CIs for the mean change within each treatment group as well as for the differences in mean change between the 2 treatment groups were reported. Adjusted mean changes from baseline are adjusted for the baseline value (eg, adjusted mean changes from baseline in HbA1c are adjusted for baseline HbA1c).

Summaries of categorical endpoints (such as achieving HbA1c $\leq$6.5% at specific visits) provided frequencies and percents for each treatment group. In addition, the percent difference from sitagliptin + metformin with 95% CIs was estimated.

No a priori hypotheses for secondary objectives were proposed.

The PP analysis set, defined as a subset of the Full analysis set that includes subjects who had no significant protocol deviations and who completed the 18-week randomized treatment period, was the analysis set used for the primary efficacy analysis. The primary efficacy variable was also analyzed using the Full analysis set. All other efficacy variables were analyzed using the Full analysis set only. In last observation carried forward (LOCF) analyses at Week 18, the measurement designated as the Week 18 measurement was used. If no Week 18 measurement was available, the last available earlier post-baseline measurement was used.

The change in PPG from baseline to Week 18 of randomized treatment was evaluated for a subset of subjects within the Full analysis set for whom an extended OGTT was conducted. The target was to include 50 subjects in the subgroup. A total of 51 subjects underwent OGTT at 8 different South African sites, of whom 49 had glucose values measured at each required time point. South Africa was chosen for recruitment of this subject subset because, for logistic reasons, it was simpler to include subjects from 1 country and it was planned that South African sites would recruit a relatively high number of subjects.

Subject population

A total of 801 subjects were assigned to randomized treatment with either saxagliptin + metformin (n=403) or sitagliptin + metformin (n=398). Of 801 subjects who were assigned to randomized treatment, all subjects received at least 1 dose of study medication and more than 90% of subjects in each treatment group (92.3% of subjects overall) completed the 18-week, double-blind, randomized treatment period. The percentage of subjects discontinuing study treatment during double-blind treatment was similar overall between the 2 treatment groups. Overall, 124 (15.5%) of randomized subjects were excluded from the PP analysis set, 69 (17.1%) in the saxagliptin + metformin group and 55 (13.6%) in the sitagliptin + metformin group. The most common reasons for exclusion from the PP analysis set were no HbA1c data at Week 18 (8.2% of subjects) and, as a subset of those subjects, premature discontinuation from the study (7.7% of subjects).

Of the 801 randomized subjects, approximately 51% were female, 66% were White, and 51% were from Europe. The mean age was 58 years, and 71% were <65 years of age. Mean weight was 86 kg, and 54% had BMI ≥30 kg/m^2 (ie, overweight/obese population). Mean duration of type 2 diabetes mellitus was 6.3 years, mean baseline value HbA1c was 7.7%, and mean FPG level was 8.9 mmol/L (160.2 mg/dL). The mean baseline dose of metformin was 1829 mg/day. Baseline demographic and disease characteristics were well balanced across the 2 treatment groups in both the Randomized and PP analysis sets and were representative of subjects with uncontrolled type 2 diabetes treated with metformin monotherapy.

Summary of efficacy results

Table S1 summarizes the change in HbA1c from baseline to Week 18 of randomized treatment for the PP analysis set (the primary outcome).

Mean baseline HbA1c values were similar in the 2 treatment groups. Both treatments resulted in a reduction from baseline to Week 18 in HbA1c values (adjusted mean change from baseline -0.52 for saxagliptin + metformin and -0.62 for sitagliptin + metformin). Based on the difference in adjusted mean changes from baseline, treatment with saxagliptin + metformin group was non-inferior to treatment with sitagliptin + metformin in the PP analysis set (difference vs sitagliptin + metformin 0.09, 95% 2-sided CI -0.01 to 0.20). The upper limit of the 95% CI was below the predefined criterion for non-inferiority, an upper confidence limit of the estimate <0.3%.

Results of the PP analysis were confirmed in the Full analysis set.

Table S1 Change in HbA1c from baseline to Week 18 (PP analysis set)

	Saxa + Met (N=334)	Sita + Met (N=343)
n	334	343
Baseline mean (SE)	7.68 (0.052)	7.69 (0.047)
Week 18 Mean (SE)	7.16 (0.052)	7.07 (0.051)
Mean change from baseline (SE)	-0.52 (0.041)	-0.62 (0.042)
Adjusted change from baseline		
Mean (SE)	-0.52 (0.039)	-0.62 (0.038)
95% 2-sided CI	-0.60, -0.45	-0.69, -0.54
Difference vs sitagliptin + metformin[a]		
Mean (SE)[b]	0.09 (0.055)	NA
95% 2-sided CI[c]	-0.01, 0.20	NA

[a] Difference in adjusted change from baseline vs sitagliptin + metformin.
[b] Estimate=adjusted mean change for saxagliptin + metformin – adjusted mean change from sitagliptin + metformin.
[c] Saxagliptin + metformin is considered non-inferior to sitagliptin + metformin if the upper confidence limit of the estimate is <0.3%.
CI Confidence interval; HbA1c Glycosylated hemoglobin; Met Metformin; NA Not applicable.
PP Per protocol; Saxa Saxagliptin; SE Standard error; Sita Sitagliptin.

Secondary efficacy findings included:

- Proportions of subjects achieving a therapeutic glycemic response, defined as HbA1c ≤6.5%, were comparable in the 2 treatment groups (95% CI: -9.0 to 3.5% for the between-treatment difference).
- Sitagliptin added to metformin produced a numerically greater decrease from baseline in FPG compared with saxagliptin added to metformin (95% CI: 0.08 to 0.53 mmol/L for the between-treatment difference).

Summary of safety results

The numbers of subjects experiencing any AE or SAE during the 18-week, randomized treatment period were low and similar between the treatment groups. Overall incidence of AEs was 47.1% among saxagliptin + metformin-treated subjects and 47.2% in sitagliptin + metformin-treated subjects. There were no deaths during the study. A total of 12 subjects experienced SAEs during the randomized treatment period, 7 (1.7%) in the saxagliptin + metformin group and 5 (1.3%) in the sitagliptin + metformin group. Nine subjects in each treatment group discontinued treatment due to AEs, 2 (0.5%) of which were discontinuations due to SAEs in the saxagliptin + metformin group. There were 1 (0.2%) and 2 (0.5%) SAEs in the saxagliptin + metformin and sitagliptin + metformin groups, respectively, that were

considered by the investigator to be treatment related. The majority of AEs in both treatment groups were mild or moderate in intensity.

The system organ class (SOC) with the greatest frequency of AEs in both groups was Infections and Infestations (25.1% of subjects in each group). The numbers of subjects with skin disorders, based on either total AEs in the SOC Skin and Subcutaneous Tissue Disorders, or AEs considered by the investigator to be related to treatment, were higher in the sitagliptin + metformin group compared with the saxagliptin + metformin group (overall incidence by SOC: 20 [5.0%] in the sitagliptin + metformin group compared with 8 [2.0%] in the saxagliptin + metformin group). The numbers of subjects with any hypoglycemic events, either by preferred term or Committee for Proprietary Medicinal Products classification (now known as Committee for Medicinal Products for Human Use), were low and similar between the treatment groups. The numbers of subjects with marked laboratory abnormalities were low and similar between the treatment groups. There was a small mean decrease in body weight in both treatment groups.

Date of the report

01 July 2009