Clinical Study Report Synopsis

Drug Substance	Saxagliptin
Study Code	D1680C00001
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A 52-Week International, Multi-center, Randomized, Parallel-group, Double-blind, Active-controlled, Phase III study with a 52-Week Extension Period to Evaluate the Safety and Efficacy of Saxagliptin in Combination with Metformin compared with Sulphonylurea in Combination with Metformin in Adult Patients with Type 2 Diabetes who have Inadequate Glycemic Control on Metformin Therapy Alone

Study dates:	First subject enrolled: 11 December 2007 Last subject last visit: 28 August 2009
Phase of development:	Therapeutic confirmatory (III)

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

Study centre(s)

This study was conducted at 130 centers in the following countries: Germany (16 sites), Finland (10 sites), United Kingdom (14 sites), Hungary (14 sites), India (5 sites), South Korea (9 sites), Netherlands (12 sites), Norway (13 sites), Russia (27 sites), Slovakia (8 sites), and Vietnam (2 sites).

Publications

None at the time of writing this report.

Objectives

The primary efficacy objective of this study was to assess if, after a 52-week oral administration of double-blind treatment, the change from baseline in glycosylated hemoglobin A1c (HbA1c) achieved with saxagliptin added to metformin is non-inferior to glipizide (SU) added to metformin in patients with type 2 diabetes who have inadequate glycemic control on 1500 mg or higher doses of metformin alone.

Three secondary objectives, among all secondary objectives, were identified a priori for special attention to compare the effects of saxagliptin versus glipizide given as add-on therapy to metformin after a 52-week double-blind treatment period by evaluation of:

- Proportion of patients reporting at least one episode of hypoglycemic event at Week 52
- Change from baseline in body weight at Week 52
- Durability from Week 24 to 52 of the HbA1c effect observed at Week 24

Note: In order to clarify the primary and key secondary objective relating to HbA1c effect in this report, minor revisions have been made to the original wording stated in the CSP.

Other secondary efficacy objectives were to compare the effects of saxagliptin versus glipizide given as add-on therapy to metformin after a 52-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 $\leq$6.5%
- Change from baseline in HbA1c in patients with baseline HbA1c $\geq$7.0%
- Proportion of patients achieving a therapeutic glycemic response defined as HbA1c <7.0% in subjects whose baseline HbA1c $\geq$7.0%

- Change from baseline in β-cell function (as measured by homeostasis model assessment [HOMA-2])

- Change from baseline in the area under curve (AUC) from 0 to 180 minutes for postprandial glucose (PPG), insulin, C-peptide and glucagon during an oral glucose tolerance test (OGTT) on a subset of patients*

- Change from baseline in insulinogenic index on a subset of patients*

- Change from baseline in insulin sensitivity as measured by oral glucose insulin sensitivity model (OGIS) and Matsuda Index on a subset of patients*

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

- The population pharmacokinetic (PK) profile of saxagliptin and its pharmacologically active metabolite, BMS-510849, in patients assigned to saxagliptin treatment groups from a total of approximately 50 randomized patients who will undergo OGTT assessment*

* 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 and tolerability were evaluated by assessment of adverse events (AEs) (including SAEs and AEs of special interest, such as edema and skin-related AEs, and hypoglycemic events), laboratory values, electrocardiograms (ECGs), pulse, blood pressure (BP), body weight, and physical examination.

A tertiary objective was to assess the long-term safety, tolerability, and efficacy of saxagliptin versus glipizide given as add-on therapy to metformin after a 104-week double-blind treatment period (ie, 52-week short-term period + 52-week long-term extension period), using the same evaluations identified for the 52-week ST period. This objective will be evaluated upon completion of the long-term extension period; results will be reported separately.

Study design

This study was a 52-week, international, multicenter, randomized, parallel-group, double-blind, active-controlled phase 3 study with a 52-week extension period to evaluate the efficacy and safety of saxagliptin in combination with metformin compared with glipizide in combination with metformin in adult subjects with type 2 diabetes who have inadequate glycemic control (HbA1c >6.5% and ≤10.0%) on metformin therapy alone.

Target population and sample size

Men or women who were ≥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 838 patients randomized and treated (or 419 per treatment group), it was calculated that there would be 95% power to establish the non-inferiority comparison on change from baseline to Week 52 in HbA1c at the 5% level, assuming that the standard deviation of change from baseline in HbA1c was 1.1%, with a non-inferiority limit set at 0.35% and a zero true difference between the 2 randomized treatments. The sample size also assumed about 35% of the randomized patients 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 7J21765), matching placebo tablets for saxagliptin (Batch 7E23409), glipizide 5 mg capsules (opaque grey, size 0, 2-piece, hard gelatine capsule containing commercial glipizide) (Batches 8A33270, 7J32802, 7H21755, 7H21756, 7H21743, 8A33271), matching placebo capsules containing white to off-white powder that appeared as a hard gelatine capsule for glipizide (Batches 7H21749, 7M21041, 7H21739), and metformin hydrochloride tablets 500 mg (Batches 102583, H 1605-01-01-10, 102598, 102608). Saxagliptin was administered at 5 mg once daily, glipizide was administered at 5 mg once or twice 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 52 weeks. Subjects were treated with open-label metformin treatment for a 2-week placebo lead-in period, followed by the 52-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 52-week, double-blind periods.

Criteria for evaluation - efficacy and pharmacokinetics (main variables)

The primary variable for the study was the change from baseline to Week 52 in HbA1c level.

The secondary (*a priori*) variables were:

- Proportion of subjects reporting at least 1 hypoglycemic event at Week 52 (a safety outcome variable)
- Change from baseline in body weight at Week 52 (a safety outcome variable)
- Durability of HbA1c effect based on Week 24 over the 52 weeks (efficacy)

Other secondary efficacy variables were:

- Change from baseline in fasting 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 the AUC from 0 to 180 minutes for PPG, insulin, C-peptide, and glucagon, as well as change from baseline in 120-minute PPG* during an 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
- Change from baseline in TC, LDL-C, HDL-C and TG

*Change from baseline in 120-minute PPG added as a change to the planned analysis.

Population PK results will be reported separately.

Criteria for evaluation - safety (main variables)

Safety was evaluated by the incidence of AEs (including SAEs and AEs of special interest), laboratory values, ECGs, vital signs (pulse, BP), body weight (including the proportion of subjects with weight gain defined as ≥7% increase from baseline [added as a change to the planned analysis), physical examination and plasma concentration of saxagliptin and metabolite in subjects who experienced some predefined AEs or discontinued due to AE.

Statistical methods

The primary analysis to establish non-inferiority with 0.35% non-inferiority limit on the change in HbA1c from baseline to Week 52 was assessed using an analysis of covariance (ANCOVA) model, with the treatment group as a fixed effect and baseline HbA1c value as 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 differences in mean change between the saxagliptin plus metformin treatment group and the glipizide plus metformin treatment group, were estimated. Saxagliptin plus metformin would be considered not inferior to glipizide plus metformin if the upper limit of the 2-sided 95% CI of the difference in change in HbA1c from baseline to Week 52 between saxagliptin plus metformin and glipizide plus metformin was less than 0.35%.

Three key secondary variables (proportion of subjects reporting hypoglycemic events, change from baseline in body weight, and mean slopes of the regressions of change from baseline in HbA1c) were identified for special consideration in this study, in addition to the primary efficacy variable (non-inferiority of HbA1c). The Per Protocol (PP) analysis set (defined as a subset of the Full analysis set that includes subjects who had no significant protocol deviations, completed the 52-week, randomized treatment period, and had both a baseline and Week 52 HbA1c measurement) was the primary analysis set used for the primary efficacy and the key secondary efficacy analyses involving HbA1c. All efficacy endpoints were also analyzed using the Full analysis set (defined as a subset of the Randomized analysis set that includes subjects who took at least 1 randomized IP dose, and had at least 1 non-missing baseline and 1 post-baseline efficacy data assessments) (last observation carried forward [LOCF]). The safety endpoints were analyzed using the Safety analysis set. Body weight and proportion of hypoglycemic events were safety variables and were analyzed using the Safety analysis set (defined as a subset of the Randomized analysis set that includes subjects who took at least 1 dose of investigational product [IP]).

The proportion of subjects reporting at least 1 episode of hypoglycemic event over the 52-week treatment period was compared between the 2 treatment groups using a 2-sided Fisher's exact test.

An ANCOVA method comparing the 2 treatment groups was used for change from baseline in body weight at Week 52, where the model included treatment as a fixed effect and baseline as a covariate. The durability of HbA1c was assessed for each of the 2 treatment groups from mean slopes of the regressions of change in HbA1c from Week 24 to Week 52. A mixed model with subject-specific slopes was utilized, including treatment, time, and treatment by time as fixed effects and subject by time as a random effect in the model. Only observed values between the 2 visits, inclusive, were used for this analysis.

A fixed-sequence test was employed for analysis of the 3 variables of special interest in order to control overall type I error rate of the study. The testing was performed in the following sequential order:

1. Non-inferiority comparison of HbA1c: if non-inferiority was demonstrated on the PP analysis set and the Full analysis set (LOCF), then statistical inference would proceed to step 2; otherwise, inference would stop.

2. Superiority test for hypoglycemic events on the Safety analysis set: if significant ($p<0.05$) in favour of saxagliptin plus metformin treatment group, then statistical inference would proceed to step 3; otherwise, inference would stop.

3. Superiority test for weight changes on the Safety analysis set (LOCF): if significant ($p<0.05$) in favour of saxagliptin plus metformin treatment group, then statistical inference would proceed to step 4; otherwise, inference would stop.

4. Superiority inference for durability on the PP analysis set.

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

All other secondary outcome variables were supplemental and were not included in the multiple comparison scheme as outlined above.

Analyses of the secondary efficacy endpoints were change from baseline in glucose related endpoints, β-cell functions, and insulin sensitivity and were analyzed by ANCOVA method similar to that used for the primary analysis.

Fasting lipids were presented using descriptive statistics. Summary tables were presented for proportions of subjects achieving glycemic therapeutic response.

Subject population

A total of 858 subjects were randomized and treated (at least 1 dose) with either saxagliptin + metformin (n=428) or glipizide + metformin (n=430). The number of subjects who completed the 52-week, double-blind, randomized treatment period was high (73.8%) and was similar between the 2 treatment groups (72.9% in the saxagliptin + metformin group and 74.7% in the glipizide + metformin group). Overall, the percentage of subjects who discontinued study treatment during the double-blind treatment period due to study-specific discontinuation criteria was similar between the 2 treatments (16.4% in the saxagliptin + metformin group and 15.3% in the glipizide + metformin group); the most common reason for subjects discontinuing study treatment was HbA1c >8% at Week 30 or Week 39 (10.3% in the saxagliptin + metformin group and 9.5% in the glipizide + metformin group). A small but greater number of subjects in the saxagliptin + metformin group compared with the glipizide + metformin group discontinued study treatment due to high FPG at Week 18 (6/428, 1.4% vs 1/430, 0.2%) and Week 24 (8/428, 1.9% vs 3/430, 0.7%). More subjects in the glipizide + metformin group discontinued study treatment due to severe and/or frequent hypoglycemic events than in the saxagliptin + metformin group (2.6% vs 0%).

Of the 858 randomized and treated subjects, 51.7% were male, 83.2% were White, and the mean age was 57.6 years (range: 25 to 83 years). A total of 219 (25.5%) subjects were ≥ 65 years of age and 42 (4.9%) were ≥75 years of age. Mean body weight was 88.7 kg (range: 42.80 kg to 178.20 kg). Approximately 54% of the study population had a mean body mass index (BMI) ≥30.0 kg/m^2. The demographic characteristics of the Randomized analysis set were generally balanced across the randomized treatment groups. Baseline demographics in the PP analysis set were similar to those in the Randomized analysis set and balanced across the 2 treatment groups.

Summary of efficacy results

Table S1 summarizes the change in HbA1c from baseline to Week 52 of randomized treatment for the PP analysis set (the primary outcome).

The mean baseline HbA1c value was 7.46% and 7.53% in the saxagliptin + metformin and glipizide + metformin groups, respectively. Both treatments resulted in a reduction from baseline to Week 52 in HbA1c values (adjusted mean change from baseline -0.74% for

saxagliptin + metformin and -0.80% for glipizide + metformin). Based on the difference in adjusted mean changes from baseline, treatment with saxagliptin + metformin group was non-inferior to treatment with glipizide + metformin in the PP analysis set (difference vs glipizide + metformin 0.06%, 95% 2-sided CI -0.05 to 0.16%). The upper limit of the 95% CI was below the predefined criterion for non-inferiority, an upper confidence limit of the estimate <0.35%.

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

Table S1 Change in HbA1c (%) from baseline to Week 52 (PP analysis set)

	Saxa + Met (N=293)	**Glip + Met (N=293)**
n	293	293
Baseline mean (SE)	7.46 (0.045)	7.53 (0.045)
Week 52 Mean (SE)	6.74 (0.042)	6.71 (0.042)
Mean change from baseline (SE)	-0.72 (0.046)	-0.82 (0.046)
Adjusted change from baseline		
Mean (SE)	-0.74 (0.038)	-0.80 (0.038)
95% 2-sided CI	-0.81, -0.66	-0.87, -0.72
Difference vs glipizide + metformin[a]		
Mean (SE)[b]	0.06 (0.053)	NA
95% 2-sided CI[c]	-0.05, 0.16	NA

ANCOVA model: post - pre = pre + treatment.
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.
[a] Difference in adjusted change from baseline vs glipizide + metformin.
[b] Estimate=adjusted mean change for saxagliptin + metformin – adjusted mean change from glipizide + metformin.
[c] Saxagliptin + metformin is considered non-inferior to glipizide + metformin if the upper confidence limit of the estimate is <0.35%.
CI Confidence interval; Glip Glipizide; HbA1c Glycosylated hemoglobin; Met Metformin; NA Not applicable; PP Per protocol; Saxa Saxagliptin; SE Standard error.

Secondary efficacy findings included:

- The proportion of subjects with at least 1 hypoglycemic event over 52 weeks was low in the saxagliptin + metformin group (3.0%) and was clinically and statistically significantly lower than in the glipizide + metformin group (36.3%) (difference vs glipizide + metformin -33.2%, 95% CI -38.1% to -28.5%, p<0.0001).

- Body weight decreased in the saxagliptin + metformin group and increased in the glipizide + metformin group with a statistically significant difference in the change

from baseline between treatment groups (difference vs glipizide + metformin -2.2 kg, 95% CI -2.7 to -1.7 kg, p<0.0001).

- Treatment with saxagliptin + metformin resulted in a statistically significant smaller rise per week in HbA1c from Week 24 to Week 52 compared with glipizide + metformin (difference vs glipizide + metformin -0.002%, 95% CI -0.0046% to -0.0001%, p=0.040).

Summary of safety results

The proportion of subjects experiencing any AE was higher in the glipizide + metformin group (68.1%) than the saxagliptin + metformin group (60.7%). A greater proportion of subjects in the glipizide + metformin group had treatment-related AEs compared with the saxagliptin + metformin group (31.2% vs 9.8%); the difference between groups was driven by a higher incidence of hypoglycemic events in the glipizide + metformin group (36.3% vs 3.0% in the saxagliptin + metformin group). When hypoglycemic events were excluded, the proportion of subjects experiencing treatment-related AEs was similar between the 2 groups (9.8% and 7.7% in the glipizide + metformin and saxagliptin + metformin groups, respectively). There were 2 subjects with major hypoglycemic events based on CPMP classification in the glipizide + metformin group and none in the saxagliptin + metformin group. There was no subject with confirmed hypoglycemia by fingerstick plasma glucose level ≤2.8 mmol/L (50 mg/dL) in the saxagliptin + metformin group compared with 12.3% in the glipizide + metformin group, and 1.2% of subjects in the saxagliptin + metformin group and 26.3% in the glipizide + metformin group had confirmed hypoglycemia by fingerstick plasma glucose level >2.8 mmol (50 mg/dL) and ≤3.5 mmol/L (63 mg/dL).

The number of subjects with SAEs (9.1% and 7.4% in the saxagliptin + metformin and glipizide + metformin groups, respectively), or who discontinued due to an AE (1.9% in each group) was low and similar between the 2 treatment groups. There were 2 deaths in each of the treatment groups (cardiac failure and head injury in the saxagliptin + metformin group, and ischemic stroke and myocardial infarction in the glipizide + metformin group).

The numbers of subjects experiencing any AE indicative of acute CV events were low and similar between the 2 treatment groups (2%). A total of 6 events were confirmed by the adjudication committee as CV events (1 CV death, 1 silent myocardial infarction and 2 myocardial infarction in the saxagliptin + metformin group and 2 CV deaths in the glipizide + metformin group) and 1 event was confirmed to be a non-CV death (saxagliptin + metformin group. There were more AEs of fractures in the saxagliptin + metformin group than in the glipizide + metformin group (7 [1.6%] vs 1 [0.2%] subjects). Overall, 2 or fewer subjects in either treatment group had AEs of selected skin disorders, hypersensitivity, or pancreatitis.

The numbers of subjects with any marked laboratory abnormality were low and similar between the 2 treatment groups.

Date of the report

13 January 2010