Clinical Study Report Synopsis

Drug Substance	Saxagliptin
Study Code	D1680L00005
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An 18-Week, Multicenter, Randomized, Double-Blind Phase 3b Trial to Evaluate the Efficacy and Safety of Saxagliptin in Combination with Extended Release Metformin, 1500 mg versus Metformin Uptitrated to 2000 mg in Subjects with Type 2 Diabetes who have Inadequate Glycemic Control After Diet and Exercise and a Stable Dose of Metformin XR 1500 mg

Study dates:	First subject enrolled: 3 August 2009 Last subject last visit: 4 October 2010
Phase of development:	Therapeutic confirmatory (3b)

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

Study centers

This study was conducted at 50 sites in the following countries: United States (US) (23 sites) Columbia (5 sites), Costa Rica (4 sites), Mexico (8 sites), and Peru (10 sites).

Publications

None at the time of writing this report.

Objectives and criteria for evaluation

Table S1 presents the objectives and outcome variables for this study.

Table S1 Primary and secondary objectives and outcome variables

Objectives	Outcome variables	Type
Primary	**Primary**	
To compare, after a 18-week oral administration of double-blind treatment, the absolute change from baseline in HbA1c achieved with saxagliptin plus metformin XR versus uptitrating metformin XR in patients with T2DM who have inadequate glycemic control on 1500 mg of metformin in addition to diet and exercise.	Absolute change from baseline to Week 18 in HbA1c	Efficacy
Secondary	**Secondary**	
To compare the effects of saxagliptin plus metformin XR versus uptitrating metformin XR alone after an 18-week double-blind treatment period for the following:	• Change in 2 hour PPG following MMTT from baseline to Week 18 or end of treatment period • Change in FPG from baseline to Week 18 or end of treatment period • Proportion of subjects reaching goal (ie, therapeutic glycemic response defined as HbA1c <7%)	Efficacy
Safety and tolerability were evaluated by assessment of:	• AEs (including AEs of special interest[a]) • Laboratory values • ECG • Vital signs • Height, weight, BMI • Physical examination	Safety

[a] AEs of special interest included hypoglycemic AEs and other selected AEs, including lymphopenia, thrombocytopenia, skin disorders, localized edema AEs, infections, cardiovascular, hypersensitivity, fracture, pancreatitis, and gastrointestinal AEs.

AE Adverse events; BMI Body mass index; ECG Electrocardiogram; FPG Fasting plasma glucose; HbA1c Glycosylated hemoglobin; MMTT Mixed meal tolerance test; PPG Postprandial glucose; T2DM Type 2 diabetes mellitus; XR Extended-release.

Study design

This was a Phase 3b, randomized, 2-arm, parallel, double-blind, multicenter trial comparing the antihyperglycemic activity of saxagliptin added onto existing metformin extended-release (XR) therapy, versus uptitrated metformin XR in subjects with type 2 diabetes mellitus (T2DM) who had inadequate glycemic control (glycosylated hemoglobin [HbA1c] ≥7.0% and ≤10.5% at randomization) and were currently on a stable dose of metformin immediate release (IR) or XR of ≥850 mg and ≤1500 mg per day as monotherapy for at least 8 weeks.

Subjects with T2DM and inadequate glycemic control (HbA1c ≥7.5% and ≤11.0% at screening) on metformin IR or XR ≥850 and ≤1500 mg/day for at least 8 weeks prior to the screening visit were eligible to enroll in the study. Subjects were to continue taking their prescribed dose of metformin until the next visit (7 to 14 days after screening).

Qualified subjects were enrolled in the single-blind lead-in phase (Period B) for open-label treatment with metformin XR 1500 mg plus diet and exercise. During lead-in, subjects with prestudy metformin IR ≤1500 mg or XR <1500 mg were titrated to a maintenance dose of metformin XR 1500 mg. These subjects were to remain on metformin XR 1500 mg for 8 weeks. (Subjects already on metformin XR at 1500 mg had a 4-week lead in period, rather than 8 weeks.) The subjects were reassessed for glycemic control at Week -4 and could continue in the study if their HbA1c value was ≥7.0% and ≤11.0%.

Subjects with HbA1c ≥7.0% and ≤10.5% at Day -7 were eligible for randomization. At Week 0/Day 1 (baseline), eligible subjects were randomly assigned to double-blind treatment with either saxagliptin 5 mg or metformin XR 500 mg added to open-label metformin XR 1500 mg for an 18-week, double-blind treatment period (Period C).

Target subject population and sample size

Male and female subjects 18 to 78 years of age, inclusive, who had inadequate glycemic control (defined as HbA1c ≥7.5% and ≤11.0% at screening) on a stable daily dose of metformin IR or XR (≥850 mg and ≤1500 mg) monotherapy for at least 8 weeks prior to screening were eligible for enrollment. Subjects with HbA1c of ≥7.0% and ≤11.0% at Week -4 were eligible to continue. Subjects were assessed for randomization on Day -7 and those with HbA1c ≥7.0% and ≤10.5% were eligible for randomization at Week 0/Day 1.

With at least 133 subjects per treatment group (266 total), there was 90% power to detect a difference of 0.4% between the 2 treatment groups. Assuming approximately 5% of subjects would drop out without any valid post-baseline assessment at Week 18, a total of 280 (140 subjects per treatment group) needed to be randomized.

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 9D45693), matching placebo tablets for saxagliptin (Batch 9D45538), metformin XR tablets 750 mg (Batch 9C3001A), metformin XR tablets 500 mg

(Batch 7G31347), and matching placebo tablets for metformin XR (Batches 9F55884 and 5J05490). Saxagliptin was administered at 5 mg once daily and metformin XR was administered at 500 mg once daily. All subjects received concurrent metformin XR 1500 mg (750 mg × 2) once daily in an open-label fashion.

Duration of treatment

Subjects were treated with open-label metformin XR treatment for an 8-week lead-in period (but only 4 weeks for subjects already on metformin XR 1500 mg at the screening visit), 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 XR throughout the 4-to 8-week lead-in and 18-week double-blind treatment periods.

Statistical methods

The primary efficacy analysis (change in HbA1c from baseline to Week 18) was assessed using an analysis of covariance (ANCOVA) model of that endpoint (last observation carried forward [LOCF]), with the treatment group as a fixed effect and baseline HbA1c value as covariate. It included subjects in the Randomized analysis set who had HbA1c assessments at baseline and post-baseline. 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 plus metformin XR treatment group and the uptitrated metformin XR group were calculated. In addition, the change in HbA1c from baseline to each visit was summarized using observed values and LOCF methodology.

A fixed-sequence test method was adopted for the overall primary efficacy variable (HbA1c change from baseline to Week 18), and the 3 key secondary efficacy variables to control type I error rate not to exceed the 5% level. The fixed-sequence test method was applied to these variables in the following sequential order:

1. Change from baseline to Week 18 in 2-hour postprandial glucose (PPG) (or the last post-baseline measurement prior to Week 18, if no Week 18 assessment available); ANCOVA similar to the model used for the primary variable.

2. Change from baseline to Week 18 in fasting plasma glucose (FPG) (or the last post-baseline measurement prior to Week 18, if no Week 18 assessment available); ANCOVA similar to the model used for the primary variable.

3. Proportion of subjects achieving a glycemic response defined as HbA1c <7.0% was compared by 2-sided Fisher's Exact test.

Statistical inference began with the overall primary efficacy variable. If the saxagliptin + metformin XR treatment group was statistically significantly superior in the change from baseline in HbA1c at Week 18 over the uptitrated metformin XR group at the 5% level, then statistical inference continued with the first secondary efficacy variable (1); otherwise,

statistical inference of the overall efficacy variables was stopped. (The p-values that follow cannot be considered as significant in this confirmatory analysis when the fixed-sequence procedure is used to control the overall type 1 error rate, even if the p-value is less than 0.05.)

Similarly, if the saxagliptin + metformin XR treatment group was statistically significantly superior in the change from baseline in 2-hour PPG to Week 18 over the uptitrated metformin XR group at the 5% level, then statistical inference continued with the second secondary efficacy variable (2); otherwise, statistical inference to the overall efficacy variables was stopped.

Similar testing was followed with the prescribed order (1) to (3) as the above steps with the same decision rule at each of the variable evaluations until all 3 secondary variables were analyzed or testing was interrupted at any nonsignificant findings at the 5% level.

The primary efficacy endpoint of HbA1c (LOCF) was summarized for the subgroups defined on the basis of the categorized baseline HbA1c, (<8%, ≥8% and <9%, and ≥9%).

Other efficacy variables were exploratory in nature.

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

Subject population

A total of 282 subjects were assigned to randomized treatment with either saxagliptin + metformin XR (n=138) or uptitrated metformin XR (n=144). A greater proportion of subjects in the saxagliptin + metformin XR group completed the 18-week, double-blind, randomized treatment period than in the uptitrated metformin XR group (94.2% in the saxagliptin + metformin XR group and 82.6% in the uptitrated metformin XR group). The proportion of subjects discontinuing study treatment due to study-specific discontinuation criteria during double-blind treatment was low overall (1.8%), and lower in the saxagliptin + metformin XR group than in the uptitrated metformin XR group (0.7% [n=1] in the saxagliptin + metformin XR group and 2.8% [n=4] in the uptitrated metformin XR group). The proportion of subjects discontinuing study treatment due to adverse events (AEs) during double-blind treatment was low overall (2.8%), and lower in the saxagliptin + metformin XR group than in the uptitrated metformin XR group (0.7% [n=1] in the saxagliptin + metformin XR group and 4.9% [n=7] in the uptitrated metformin XR group). The most common reason for discontinuation was subject lost to follow-up in the saxagliptin + metformin XR group (n=3, 2.2%) and discontinuation due to AEs in the uptitrated metformin XR group (n=7, 4.9%).

Of the 282 randomized and treated subjects, 46.1% were male and 53.9% were female. In the saxagliptin + metformin XR group, there were more female than male subjects (58.7% female) whereas the uptitrated metformin XR group was more evenly distributed by gender (49.3% female). The mean age was 55.3 years (range: 29 to 77 years). A total of 231 (81.9%) subjects were <65 years of age, 51 (18.1%) were ≥ 65 years of age, and 6 (2.1%) were ≥75 years of age. Mean body weight was 79.93 kg (range: 44.0 kg to 134.0 kg).

Approximately 51% of the study population had a mean body mass index ≥30 kg/m^2. Approximately 80% of subjects were from Latin America. Baseline demographic and disease characteristics were generally well balanced across the 2 treatment groups in the Randomized analysis set and were representative of subjects with uncontrolled T2DM treated with metformin monotherapy.

Summary of efficacy results

Saxagliptin + metformin XR was superior to uptitrated metformin XR in lowering HbA1c from baseline to Week 18 (adjusted mean changes of -0.88% and -0.35% in the saxagliptin + metformin XR and uptitrated metformin XR groups, respectively, with a difference vs uptitrated metformin XR of -0.52%; 2 sided 95% CI -0.73% to -0.31%, p<0.0001).

Other key efficacy findings included:

- Saxagliptin + metformin XR significantly improved glycemic control compared to uptitrated metformin XR as demonstrated by:
  - A significantly greater reduction in 2-hour PPG following a mixed meal tolerance test (MMTT) at Week 18 (difference in adjusted mean changes vs uptitrated metformin XR of -23.32 mg/dL [-1.29 mmol/L]; 2-sided 95% CI -37.36 to -9.28 mg/dL [-2.07 to -0.51 mmol/L], p=0.0013).
  - A significantly greater reduction in FPG at Week 18 (difference in adjusted mean changes vs uptitrated metformin XR of -13.18 mg/dL [-0.73 mmol/L]; 2-sided 95% CI -21.86 to -4.50 mg/dL [-1.21 to -0.25 mmol/L], p=0.0030).
  - A significantly higher proportion of subjects achieving a therapeutic glycemic response defined as HbA1c <7% at Week 18 (difference in proportions vs uptitrated metformin XR of 11.2%; 2-sided 95% CI 0.2% to 22.0%, p=0.0459).

Summary of safety results

The mean duration of exposure to blinded study medication was longer in the saxagliptin + metformin XR group than in the uptitrated metformin XR group (123 vs 116 days), reflecting a greater number of subjects completing the 18-week study in the saxagliptin + metformin XR group. Overall, saxagliptin + metformin XR was safe and well tolerated with a safety profile comparable to uptitrated metformin XR. The overall proportion of subjects experiencing AEs (excluding hypoglycemic events) was similar in the 2 treatment groups (51.4% in the saxagliptin + metformin XR group and 47.2% in the uptitrated metformin XR group). The number of subjects who discontinued due to an AE was low in both treatment groups, and lower in the saxagliptin + metformin XR group compared with the uptitrated metformin XR group (1 vs 6 subjects). There were no deaths during the study; all serious adverse events reported during the study occurred in the uptitrated metformin XR group (3 subjects).

Few subjects had AEs of hypoglycemia during the study, with a slightly higher incidence observed in the saxagliptin + metformin XR group compared to the uptitrated metformin XR group (5 vs 2 subjects). Two subjects in the saxagliptin + metformin XR group had

symptomatic confirmed hypoglycemia AEs (fingerstick plasma glucose ≤2.8 mmol/L [≤50 mg/dL]) compared with no subjects in the uptitrated metformin XR group.

The number of subjects with AEs of special interest of thrombocytopenia, cardiovascular, hypersensitivity, or fractures was low and similar between the 2 treatment groups; no subject in either treatment group had lymphopenia, a selected skin disorder, localized edema, or pancreatitis. The incidence of infection-related AEs was balanced between the 2 treatment groups.

The numbers of subjects with any marked laboratory abnormality were low and similar between the 2 treatment groups, and there were no clinically relevant ECG findings in either treatment group.