Clinical Study Report Synopsis

Drug Substance	Saxagliptin
Study Code	D1680C00008
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A 24-Week National, Multi-centre, Randomized, Parallel-group, Double-blind, Placebo-controlled, Phase IIIb study in India to Evaluate the Efficacy and Safety of Saxagliptin in Adult Patients with Type 2 Diabetes who have Inadequate Glycaemic Control with Diet and Exercise

Study dates: First subject enrolled: 27 May 2009
Last subject last visit: 22 July 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 national multicentre study was conducted at 12 study centres in India.

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 key secondary objectives and outcome variables

Objectives	Outcome variables	Type
Primary	**Primary**	
To compare, after a 24-week oral administration of double-blind treatment, the absolute change from baseline in HbA1c achieved with saxagliptin versus placebo in treatment-naïve patients with T2DM who had inadequate glycaemic control with diet and exercise alone	Absolute change from baseline to Week 24 in HbA1c	Efficacy
Secondary	**Secondary**	
To compare the effects of saxagliptin versus placebo after a 24 week double-blind treatment for:	• Change from baseline to Week 24 in FPG • Proportion of patients achieving a therapeutic glycaemic response defined as HbA1c <7.0% at Week 24	Efficacy
Safety and tolerability were evaluated by assessment of:	• AEs (including AEs of special interest[a]) • Laboratory values • ECG • Vital signs (pulse, blood pressure, weight[b]) • Physical examination	Safety

[a] AEs of special interest included hypoglycaemic AEs and other selected AEs, including lymphopaenia, thrombocytopaenia, skin disorders, localized oedema AEs, infections, cardiovascular, hypersensitivity, fracture, pancreatitis, and gastrointestinal AEs.

[b] Changes from baseline in BMI, weight, and waist circumference were analysed only as efficacy variables using the Full analysis set, and were not additionally analysed using the Safety analysis set, as a change to the planned analysis.

AE Adverse events; BMI Body mass index; ECG Electrocardiogram; FPG Fasting plasma glucose; HbA1c Glycosylated haemoglobin; T2DM Type 2 diabetes mellitus.

Study design

This study was a 24-week national, multicentre, randomised, parallel-group, double-blind, placebo-controlled, Phase 3b study, which was performed in India to evaluate the efficacy and safety of saxagliptin in adult drug-naïve subjects with type 2 diabetes mellitus (T2DM) who had inadequate glycaemic control with diet and exercise.

Drug-naïve subjects with T2DM were eligible to enrol in the study.

Eligible subjects with inadequate glycaemic control (glycosylated haemoglobin [HbA1c] ≥7.2% and ≤10.0% and fasting plasma glucose [FPG] <270 mg/dL [15 mmol/L]) were given placebo in a single-blind fashion (blind to the subject) at Visit 2 (4 weeks prior to randomisation) during a 4-week lead-in period (Period B). Visit 3 was done 1 week (±3 days) before randomisation. HbA1c, FPG, and safety laboratory measurements were conducted to confirm the subject remained eligible for the study.

Subjects with HbA1c ≥7.0% and ≤10.0% and FPG<270 mg/dL (15 mmol/L) at Visit 3 were eligible for randomisation. At Visit 4 (Week 0/baseline), eligible subjects were randomly assigned to double-blind treatment with either saxagliptin 5 mg or placebo for a 24-week, double-blind treatment period (Period C, Visits 4 through 12). Starting at Week 4 (Visit 6) during Period C, subjects with lack of adequate glucose control were eligible for the addition of open-label metformin as a rescue from continued hyperglycaemia.

Target subject population and sample size

Drug-naïve male and female subjects with T2DM, ≥18 years of age, were eligible for enrolment. Subjects with HbA1c of ≥7.2% and ≤10.0% and FPG<270 mg/dL (15 mmol/L) at Week -4 were eligible to continue. Subjects were assessed for randomisation on Day -7 and those with HbA1c ≥7.0% and ≤10.0% and FPG<270 mg/dL (15 mmol/L) were eligible for randomisation at Week 0.

With a total of 206 subjects randomised and treated (or 103 per treatment group), there would be 90% power to detect 0.5% difference between the 2 randomised treatment groups in absolute change from baseline to Week 24 in HbA1c at the 5% level assuming the standard deviation of change from baseline in HbA1c was 1.1%. A total of 218 subjects were expected to be randomised to account for 5% of subjects being unevaluable for the primary endpoint analysis.

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 09-002026AZ) and matching placebo tablets for saxagliptin (Batch 09-001978AZ). Saxagliptin 5 mg (or its matching placebo) was administered once daily. Subjects with unacceptable hyperglycaemia who met protocol-specified FPG criteria received metformin 500 mg once daily in an open-label fashion as add-on to their current study medication regimen (titration could occur in 500-mg increments at 2-week intervals up to a maximum of 2500 mg, given as divided daily doses with meals).

Duration of treatment

Subjects were treated with placebo for a 4-week lead-in period, followed by the 24-week, double-blind treatment period, in which subjects received their respective randomised treatment and matching placebo for comparator.

Statistical methods

Data recorded on or after rescue medication were excluded from all analysis of efficacy data. The missing Week 24 efficacy endpoints were replaced by the last observed value prior to rescue medication after baseline.

The primary efficacy analysis (change in HbA1c from baseline to Week 24) was assessed using an analysis of covariance (ANCOVA) model of that endpoint (last observation carried forward), with the treatment group as a fixed effect and baseline HbA1c value as covariate. It included subjects in the Full analysis set who took at least 1 dose of investigational product and had both baseline and post-baseline efficacy data. 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 group and the placebo group were calculated.

To assess the robustness of the primary efficacy analysis, the modelling of the primary analysis was repeated utilising repeated measures analysis (using mixed model). This model contained terms for treatment group, baseline measurement, time, and time by treatment group. Subgroup analyses for the primary efficacy variable included 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 T2DM since diagnosis (≤1.5 years, ≤3 years, >3 years to <5 years, ≥5 years, and ≥10 years); and baseline body mass index (BMI) (<30 kg/m^2 and ≥30 kg/m^2).

The 2 key secondary efficacy endpoints were identified for significance testing with the overall primary endpoints in a fixed-sequence testing procedure. The fixed-sequence test method was applied to these variables in the following sequential order:

1. Change from baseline to Week 24 in FPG using ANCOVA model as done for the primary efficacy analysis

2. Proportion of subjects achieving a therapeutic glycaemic response, defined as HbA1c<7.0%; compared between treatment groups using a 2-sided Fisher's Exact text

Statistical inference began with the overall primary efficacy variable. If the saxagliptin group was statistically significantly superior in the change from baseline in HbA1c at Week 24 over the placebo group at the 5% level, then statistical inference continued with the first key secondary efficacy variable (1); otherwise, statistical inference of the overall efficacy variable was stopped. Similarly, if the saxagliptin group was statistically significantly superior in the change from baseline in FPG to Week 24 over the placebo group at the 5% level, then statistical inference continued with the second key secondary efficacy variable (2); otherwise, statistical inference to the overall efficacy variable was stopped. (If testing is interrupted at any nonsignificant findings at the 5% level, 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).

The remaining 'other secondary' endpoints were analysed by linear models using baseline value as a covariate similar to the method used for the primary variable.

For all safety variables, the primary safety analyses excluded data collected on or after rescue medication. Sensitivity analyses on all data collected regardless of rescue up to and including Week 24 utilising the Safety analysis set were performed for selected AE analyses and selected laboratory analyses. Analyses 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 213 subjects were assigned to randomised treatment with either saxagliptin (n=107) or placebo (n=106). The proportion of subjects who completed the 24-week, double-blind, randomised treatment period (regardless of rescue) was high (94.4% overall) and similar in the 2 treatment groups (94.4% in the saxagliptin group and 94.3% in the placebo group). The proportion of subjects who completed the study without receiving rescue was high (88.7% overall; 90.7% in the saxagliptin group and 86.8% in the placebo group). The most common reason for discontinuation in both treatment groups (regardless of rescue) was voluntary discontinuation by subject (n=4, 3.7% in the saxagliptin group and n=4, 3.8% in the placebo group); no subjects discontinued study treatment due to study-specific discontinuation criteria during double-blind treatment. Overall, the proportion of subjects receiving rescue medication during the randomised treatment period was low (5.6%) but was higher in the placebo group compared with the saxagliptin group (7.5% vs 3.7%).

Of the 213 randomised and treated subjects, 56.3% were male and the mean age was 48.68 years (range: 25 to 75 years). A total of 8 (3.8%) subjects were ≥ 65 years of age and 1 (0.5%) subject was ≥75 years of age. Mean body weight was 69.62 kg (range: 45 kg to 120 kg); 20.7% of the study population had a mean BMI ≥30 kg/m^2. All subjects were from the Indian population. Baseline demographic and disease characteristics were generally well balanced across the 2 treatment groups in the Randomised analysis set and were representative of subjects with drug-naïve T2DM who had inadequate glycaemic control with diet and exercise alone.

Summary of efficacy results

Primary efficacy finding:

- Treatment with saxagliptin significantly decreased HbA1c from baseline to Week 24 compared to placebo (adjusted mean changes of -0.51% and -0.05% in the saxagliptin and placebo groups, respectively, with a difference vs placebo of -0.46%; 2 sided 95% CI -0.73% to -0.18%, p=0.0011).

Key secondary efficacy findings included:

- Treatment with saxagliptin resulted in a numerically greater decrease in FPG from baseline to Week 24 compared to placebo (adjusted mean changes of -10.35 mg/dL

[-0.58 mmol/L] and -0.16 mg/dL [-0.00 mmol/L] in the saxagliptin and placebo groups, respectively, with a difference vs placebo of -10.19 mg/dL [-0.57 mmol/L]; 2-sided 95% CI -20.91 to 0.53 mg/dL [-1.17 to 0.02 mmol/L], p=0.0623). In this comparison, the p-value was not statistically significant at the 0.05 level per the fixed-sequence test procedure; therefore, statistical inference was stopped in the analysis of the other key secondary variable.

- The proportion of subjects achieving a therapeutic glycaemic response, defined as HbA1c <7%, at Week 24 was numerically higher in the saxagliptin group than the placebo group (22.1% and 13.3% for the saxagliptin and placebo groups, respectively, with a difference vs placebo of 8.8%; 2-sided 95% CI -1.7% to 19.3%).

Summary of safety results

The mean duration of exposure including rescue was similar in the saxagliptin group compared with placebo with the majority of subjects (92.5% and 90.6% of subjects, respectively) exposed to treatment (regardless of rescue) for ≥166 days. Overall, saxagliptin was safe and well tolerated with a safety profile comparable placebo. The overall proportion of subjects experiencing AEs (excluding events on or after rescue medication) was similar in the 2 treatment groups (47.7% and 45.3% in the saxagliptin and placebo groups, respectively). There were no deaths or nonfatal SAEs, and no subject in either treatment group discontinued IP due to an AE during the study.

There were no subjects with AEs of hypoglycaemia or other AEs of special interest including thrombocytopaenia, selected skin disorders, localized oedema, cardiovascular, hypersensitivity, fracture or pancreatitis. One subject in the placebo group had an AE of lymphopaenia. Overall, the incidence of infection-related AEs was numerically higher in the saxagliptin group compared to the placebo group (20.6% and 15.1%, respectively), primarily driven by a higher incidence of nasopharyngitis (4.7% vs 0.9%). The incidence of GI-related AEs was balanced between the 2 groups (7.5% and 8.5% in the saxagliptin and placebo groups, respectively).

The number of subjects with any marked laboratory abnormality was low and similar in the 2 treatment groups.

No clinically relevant changes in vital signs or electrocardiogram findings were observed for either treatment group.