Clinical Study Report Synopsis

Drug Substance	Saxagliptin
Study Code	D1680C00007
Edition Number	Final
Date	07 December 2009

A Short-term 12-Week, Multi-centre, Randomized, Parallel-group, Double-blind, Placebo-controlled Study to Evaluate the Treatment Effect of Saxagliptin compared with Placebo in Adult Patients with Type 2 Diabetes and Renal Impairment (Moderate, Severe, and End-Stage) with an Additional 40-week, Randomized, Parallel-group, Double-blind, Placebo-controlled Long-term Observational Period (Short-term Clinical Study Report)

Study dates:	First subject enrolled: 22 January 2008 Last subject completed (short-term period): 08 June 2009
Phase of development:	Therapeutic confirmatory (III)

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

Study centres

The study was conducted at 69 centres in 12 European countries and in the United States of America (USA) (6 centres in Belarus, 6 in Croatia, 4 in the Czech Republic, 1 in Estonia, 3 in Germany, 4 in Hungary, 2 in Latvia, 6 in Lithuania, 10 in Poland, 7 in Romania, 4 in Russia, 9 in Ukraine, and 7 in the USA).

The first subject was enrolled into the study on 22 January 2008.

Publications

None at the time of writing this report.

Objectives for the short-term period - 12 weeks

1. To evaluate the efficacy of saxagliptin 2.5 mg in adult subjects with type 2 diabetes and renal impairment (moderate, severe, and end-stage) compared with placebo by assessment of the absolute change from baseline in glycosylated haemoglobin A1c (HbA1c).

2. To evaluate the efficacy of saxagliptin 2.5 mg compared with placebo by assessment of the absolute change from baseline in fasting plasma glucose (FPG).

3. To evaluate the safety and tolerability of saxagliptin 2.5 mg compared with placebo by assessment of:

    - Adverse events (AEs) (including serious adverse events [SAEs] and AEs of special interest);
    - Laboratory values including estimation of creatinine clearance (CrCl), glomerular filtration rate (GFR) (modification of diet in renal disease), and urinary albumin:creatinine ratio;
    - Electrocardiogram (ECG);
    - Vital signs;
    - Body weight;
    - Physical examination;
    - Doubling of serum creatinine (SCr) or progression to end-stage renal impairment, a criterion introduced by protocol amendment number 1.

4. To characterise the pharmacokinetic (PK) properties of saxagliptin, by assessing the steady state plasma concentration-time data of saxagliptin and its metabolite, BMS-510849. The PK data obtained from this study, and presented in this report, will be pooled with data from other studies to build a population exposure model, and presented in a separate report. PK parameters (eg, apparent oral clearance, apparent oral volume of distribution, and absorption rate constant) and potential covariate effects on these parameters will be estimated.

The objectives of the long-term period will be presented and analysed in a separate report.

Study design

This was a 12-week, international, multi-centre, randomised, parallel-group, double-blind, placebo-controlled study to evaluate the treatment effect and tolerability of saxagliptin 2.5 mg compared with placebo in adult subjects with type 2 diabetes and renal impairment (moderate, severe, and end-stage). An additional 40-week, randomised, parallel-group, double-blind, placebo-controlled, long-term observational period to evaluate safety, tolerability, and efficacy is on-going, and will be evaluated in a separate report.

After a 2-week single-blind placebo lead-in period, subjects underwent stratified randomisation to double-blind treatment with either saxagliptin or placebo, in a 1:1 ratio within each renal impairment category. Randomisation was stratified by renal impairment category at baseline.

Target population and sample size

Main inclusion criteria at enrolment (Visit 1):

1. Provision of informed consent.

2. Diagnosed with type 2 diabetes.

3. Men or women who were ≥18 years of age at time of consenting at Visit 1.

4. Documented history of CrCl <50 mL/min within the 3 months prior to enrolment.

Main inclusion criteria at Visit 2 (laboratory values from Visit 1):

1. HbA1c ≥7.0% and ≤11.0%.

2. C-peptide level ≥0.33 nmol/L (≥1.0 ng/mL). This criterion was modified to correct a conversion factor error by protocol administrative change number 5.

3. Estimated CrCl <50 mL/min.

It was planned to randomise 168 subjects (84 per treatment group), giving 80% power to detect a 0.45% difference between the treatment groups in the primary endpoint (absolute

change from baseline to Week 12 in HbA1c) at the 5% level, assuming a standard deviation (SD) of change from baseline in HbA1c of 1.0%. The planned sample size allowed for the possibility that 5% of subjects would not have post-baseline HbA1c for the primary analysis.

170 subjects were included in the randomised analysis set, 85 in each treatment group.

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

Saxagliptin (BMS-477118) 2.5 mg and placebo tablets were used during the short-term treatment period as shown below.

Table S1 Details of saxagliptin and placebo dosing

Treatment	Formulation	Dose	Route of administration	Batch numbers
Saxagliptin	Tablet	2.5 mg once daily	Oral	H 2013-01-01-01
Placebo	Tablet	Once daily	Oral	H 2014-01-01-01, H 2014-01-01-02 and H 2014-01-01-03

Background oral antidiabetic and insulin therapy were continued throughout the study.

Duration of treatment

Short-term treatment period: 12 weeks.

Long-term treatment period: 40 weeks.

Criteria for evaluation - efficacy and pharmacokinetics (main variables)

The primary efficacy variable was absolute change from baseline to Week 12 in HbA1c. The main secondary efficacy variable was absolute change from baseline to Week 12 in FPG.

The main PK variable was steady state plasma concentration-time data of saxagliptin and its metabolite BMS-510849.

Criteria for evaluation - safety (main variables)

Safety variables were AEs, hypoglycaemic events, other AEs of special interest, and safety laboratory values including estimated CrCl, estimated GFR, and urinary albumin:creatinine ratio, ECG, vital signs, body weight, body mass index (BMI), waist circumference, physical examination, and doubling of SCr or progression to end-stage renal impairment.

Statistical methods

The primary efficacy endpoint (absolute change in HbA1c from baseline to Week 12) was compared between the treatment groups using an analysis of covariance (ANCOVA), with treatment group and baseline renal impairment group (moderate, severe, or end-stage) as fixed effects and the baseline value as a covariate in the model. The analysis used the full analysis set (FAS) (last observation carried forward [LOCF]). Within the framework of this ANCOVA model, the point estimates and 95% confidence intervals (CIs) for the absolute change from baseline within each treatment group were presented, as well as for the difference in absolute change from baseline between saxagliptin 2.5 mg and placebo. The treatment-by-baseline HbA1c interaction and treatment-by-baseline renal impairment interaction were tested and distributional assumptions assessed. Each of these tests was performed at the 0.10 level of significance.

Within the framework of an ANCOVA model (with treatment group as a fixed effect and the baseline value as a covariate), point estimates and 95% CIs for the absolute change from baseline to Week 12 within each treatment group were also presented stratified by baseline renal impairment category (moderate, severe, end-stage).

Secondary efficacy endpoint analyses included comparison of absolute change from baseline to Week 12 in FPG between treatment groups using ANCOVA.

HbA1c and FPG summaries and graphs were presented stratified by baseline renal impairment category and by insulin use (yes, no).

Subject population

It was planned to randomise 168 subjects (84 per treatment group). A total of 561 subjects entered the lead-in period and took at least 1 dose of placebo lead-in medication. Of these, 170 subjects were assigned to and took randomised treatment with either saxagliptin (N=85) or placebo (N=85). Of the randomised subjects, 90 subjects (52.9%) had moderate renal impairment at baseline, 41 subjects (24.1%) had severe renal impairment, and 39 subjects (22.9%) had end-stage renal impairment. Sixty-one (71.8%) saxagliptin-treated subjects and 68 (80.0%) subjects in the placebo group completed the 12-week, double-blind, randomised treatment period and continued to the long-term period of the study.

Of the 572 subjects enrolled, 561 subjects were included in the lead-in analysis set, and 170 subjects were randomised, took a least 1 dose of randomised study medication, and were included in the randomised analysis set. A total of 164 (96.5%) of the subjects from the randomised analysis set were included in the FAS. Fourteen subjects in the FAS experienced significant protocol deviations that led to complete data exclusion, leading to the inclusion of 150 (88.2%) of the subjects in the randomised analysis set in the PP analysis set. The safety analysis set included all 170 (100%) subjects in the randomised analysis set. The 2 treatment groups were well balanced with regard to inclusion in the respective analysis sets.

Baseline demographic and disease characteristics were generally balanced across the 2 treatment groups in both the randomised and PP analysis sets and were representative of subjects with poorly-controlled type 2 diabetes and renal impairment. There were a higher percentage of female subjects and subjects who were receiving background insulin therapy in the saxagliptin group compared with the placebo group. In contrast, there was a higher percentage of subjects who were taking oral blood glucose lowering drugs in the placebo group compared with the saxagliptin group. In addition, mean baseline HbA1c and FPG were higher in the saxagliptin group compared with the placebo group (HbA1c: 8.5% versus 8.1%, respectively; FPG: 187.9 mg/dL versus 168.6 mg/dL [10.4 mmol/L versus 9.4 mmol/L], respectively).

Summary of efficacy results

There was a reduction in mean HbA1c from baseline in both treatment groups at Week 12 (LOCF) (adjusted mean [SE] change from baseline -0.86% [0.112%] for the saxagliptin group and -0.44% [0.109%] for the placebo group). The reduction was statistically significantly greater with saxagliptin than with placebo (mean [SE] treatment difference: -0.42% [0.151%]; 95% CI: -0.71% to -0.12%; p=0.007).

Numerically larger adjusted mean reductions from baseline to Week 12 in HbA1c were observed with saxagliptin compared with placebo in subjects with moderate baseline renal impairment (adjusted mean [SE] change from baseline -0.64% [0.134%] for the saxagliptin group and -0.05% [0.139%] for the placebo group) and in subjects with severe baseline renal impairment (adjusted mean [SE] change from baseline -0.95% [0.228%] for the saxagliptin group and -0.50% [0.201%] for the placebo group). In subjects with end-stage baseline renal impairment, the adjusted mean (SE) change from baseline to Week 12 in HbA1c was -0.84% (0.243%) in the saxagliptin group and -0.87% (0.243%) in the placebo group.

Due to a statistically significant treatment-by-baseline renal impairment interaction, FPG results were analysed separately for each baseline renal impairment category. In the moderate baseline renal impairment category, the adjusted mean change from baseline to Week 12 in FPG was numerically larger in the saxagliptin group (-15.22 mg/dL [-0.84 mmol/L]) compared with the placebo group (-2.88 mg/dL [-0.16 mmol/L]; mean treatment difference versus placebo: -12.34 mg/dL [-0.68 mmol/L]; 95% CI: -37.91 mg/dL to 13.22 mg/dL [-2.10 mmol/L to 0.74 mmol/L]; p=0.339). In the severe baseline renal impairment category, the adjusted mean change from baseline to Week 12 in FPG was numerically larger in the saxagliptin group (-34.28 mg/dL [-1.89 mmol/L]) compared with the placebo group (-29.91 mg/dL [-1.66 mmol/L]; mean treatment difference versus placebo: -4.36 mg/dL [-0.24 mmol/L]; 95% CI: -38.65 mg/dL to 29.93 mg/dL [-2.14 mmol/L to 1.67 mmol/L]; p=0.798). In the end-stage group, mean FPG increased from baseline to Week 12 in the saxagliptin group (32.82 mg/dL [1.81 mmol/L]), compared with a small decrease in the placebo group (-11.18 mg/dL [-0.62 mmol/L]; mean treatment difference versus placebo: 44.01 mg/dL [2.44 mmol/L]; 95% CI: -18.93 mg/dL to 106.94 mg/dL [-1.05 mmol/L to 5.93 mmol/L]; p=0.164).

Summary of pharmacokinetic results

The mean (SD) saxagliptin plasma concentrations at the nominal collection times of pre-dose, 1, 2, and 4 hours post-dose were generally similar across all of the baseline renal impairment categories studied. Based on mean pre-dose plasma concentrations of saxagliptin, a small amount of saxagliptin accumulation was observed in all categories of baseline renal impairment studied, but there was no clear pattern to the extent of accumulation associated with baseline renal impairment category. The peak mean plasma concentrations of saxagliptin were observed at the first post-dose nominal sampling time point of 1 hour in all groups.

The mean (SD) plasma concentrations of the active metabolite of saxagliptin, BMS-510849, at the nominal collection times were generally higher with increasing severity of baseline renal impairment. Based on mean pre-dose concentrations of BMS-510849, accumulation of BMS-510849 was observed in all categories of baseline renal impairment studied. The extent of accumulation of BMS-510849 was generally higher with increasing severity of baseline renal impairment. The peak mean plasma concentrations of BMS-510849 were observed at the last nominal sampling time point of 4 hours post-dose in all groups.

Summary of safety results

Mean exposure to randomised study medication was 74.5 days in the saxagliptin group and 80.3 days in the placebo group. The number and percentage of subjects experiencing any AE during the short-term treatment period was similar between the treatment groups (saxagliptin: 49 [57.6%] subjects; placebo: 46 [54.1%] subjects). The number and percentage of subjects experiencing SAEs was low overall, although higher in saxagliptin-treated subjects compared with placebo subjects (12 [14.1%] subjects and 7 [8.2%] subjects respectively). The number and percentage of subjects experiencing AEs leading to discontinuation of study medication was also low overall, although higher in saxagliptin-treated subjects compared with placebo subjects (5 [5.9%] subjects and 1 [1.2%] subject, respectively). The most common AEs by system organ class (SOC) were Infections and Infestations in both treatment groups. The most common AEs by preferred term (PT) were urinary tract infection in the saxagliptin group and hypertension and anaemia in the placebo group. There were no clinically relevant differences between the treatment groups in the incidence and type of AEs within the 3 baseline renal impairment categories and according to insulin use. The incidence of AEs related to study medication (excluding hypoglycaemia events) was low; 5 (5.9%) subjects in the saxagliptin group and 2 (2.4%) subjects in the placebo group.

No AEs were reported that matched any defined lists of PTs (or LLTs for localised oedema events) for lymphopenia, thrombocytopenia, skin disorders, localised oedema, hypersensitivity, and pancreatitis. The incidence of AEs in the SOC Infections and Infestations was similar in the 2 treatment groups: 10.6% of subjects in the saxagliptin group and 11.8% of subjects in the placebo group. The most common infections were urinary tract infection in the saxagliptin group (4.7%) and urinary tract infection (2.4%) and nasopharyngitis (2.4%) in the placebo group. No AEs in the placebo group and 1 AE in the saxagliptin group (myocardial infarction in subject E2301014, reported as an SAE) was considered an acute cardiovascular event based on a list of defined PTs. Cardiovascular AEs

experienced by 4 subjects in the saxagliptin group were sent to the Montreal Heart Institute Coordinating Center for adjudication (includes event of myocardial infarction in subject E2301014 mentioned above); none of these events was considered by the committee to be a myocardial infarction. Only 2 subjects experienced fracture AEs (rib fracture in subject E2102002 and upper limb fracture in subject E1703016), both of whom were in the placebo group. The upper limb fracture was reported as an SAE. The number and percentage of subjects with any hypoglycaemic events were similar between the treatment groups (saxagliptin: 17 [20%] subjects; placebo:19 [22.4%] subjects).

Abnormalities were most commonly reported for serum creatinine, alkaline phosphatase, and potassium, with a similar incidence in both treatment groups. The number and percentage of subjects with other marked laboratory abnormalities were low and similar between the treatment groups. There were no clinically relevant changes from baseline in vital sign or ECG measurements, body weight, BMI, or waist circumference in either treatment group.

Date of the report

07 December 2009