**Clinical Study Report Synopsis**

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| Drug Substance | Saxagliptin |
| Study Code | D1680L00006 |
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# A 24-week, Multicentre, Randomised, Double-Blind, Placebo-Controlled Phase IIIb Study to Evaluate the Efficacy and Safety of Saxagliptin in Combination with Metformin and Sulfonylurea in Subjects with Type 2 Diabetes who have Inadequate Glycaemic Control with the Combination of Metformin and Sulfonylurea

**Study dates:** First subject enrolled: 30 June 2010
Last subject last visit: 14 June 2011

**Phase of development:** Therapeutic confirmatory (IIIb)

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

## Study centres

This study was conducted in the following 6 countries: United Kingdom (12 sites), Canada (4 sites), Australia (7 sites), India (6 sites), Korea (4 sites), and Thailand (2 sites).

## Publications

None at the time of the writing of this report.

## Objectives and criteria for evaluation

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

**Table S1 Objectives and outcome variables**

| Objective | | | Outcome Variable |
|---|---|---|---|
| **Priority** | **Type** | **Description** | **Description** |
| Primary | Efficacy | Compare the difference between saxagliptin 5 mg QD + metformin + SU vs placebo + metformin + SU, in subjects with T2DM, as determined by the change in HbA1c levels from baseline to Week 24 | Change in HbA1c from baseline (Visit 3) to Week 24 |
| Secondary | Efficacy | Compare the effects of saxagliptin 5 mg QD + metformin + SU vs placebo + metformin + SU after a 24-week double-blind treatment period for: | • Change in PPG (measured 2 hours after breakfast) from baseline to Week 24<br>• Change in FPG from baseline to Week 24<br>• Proportion of subjects achieving a therapeutic glycaemic response at Week 24, defined as HbA1c <7% |
| | Other efficacy | Compare the effects of saxagliptin 5 mg QD + metformin + SU vs placebo + metformin + SU after a 24-week double-blind treatment period for: | • Change in TC, LDL-C, HDL-C, and TG from baseline to Week 24<br>• Subject-reported endpoints using the EQ-5D questionnaire<br>• Change in insulin, C-peptide, and glucagon from baseline to Week 24 |
| Safety | Safety | Safety and tolerability were evaluated by assessment of: | • All AEs, including hypoglycaemic events[a]<br>• Laboratory values<br>• Changes in renal function by estimation of CrCl (Cockcroft Gault) and urinary albumin:creatinine ratio<br>• 12-Lead ECG<br>• Vital signs (pulse and blood pressure)<br>• Body weight[b]<br>• Physical examination |

[a] AEs of special interest included those related to hypoglycaemia, hepatic disorders, lymphopaenia, thrombocytopaenia, skin disorders, localised oedema, infections, hypersensitivity, fractures, pancreatitis, gastrointestinal disorders, and cardiovascular AEs.

[b] Height and waist circumference were also assessed.

AE Adverse event; CrCl Creatinine clearance; ECG Electrocardiogram; EQ-5D EuroQoL-5 Dimension; FPG Fasting plasma glucose; HbA1c Glycosylated haemoglobin; HDL-C High-density lipoprotein–

cholesterol; LDL-C Low-density lipoprotein–cholesterol; PPG Postprandial glucose; QD Once daily; SU Sulfonylurea; T2DM Type 2 diabetes mellitus; TC Total cholesterol; TG Triglycerides

## Study design

The study was a 24-week, multicentre, randomised, parallel-group, double-blind, placebo-controlled Phase 3b study to evaluate the efficacy and safety of saxagliptin as add-on therapy to stable combination treatment with metformin plus a sulfonylurea (SU) compared with placebo as add-on therapy to stable combination treatment with metformin plus SU in subjects with type 2 diabetes mellitus (T2DM) who have inadequate glycaemic control (HbA1c ≥7% and ≤10%).

## Target subject population and sample size

Male and female subjects ≥18 years of age with body mass index ≤40 kg/m$^2$ and with a clinical diagnosis of T2DM with uncontrolled glycaemia in spite of being on the combination of metformin extended release (XR) or immediate release (IR) (at maximum tolerated dose [MTD], minimum dose for enrolment being 1500 mg) plus SU (at MTD, with minimum dose for enrolment being ≥50% of the maximum recommended dose) daily for at least 8 weeks prior to Visit 1 were eligible for enrolment. Blood samples for assessment of inclusion and exclusion criteria were taken; subjects with HbA1c ≥7% and ≤10%, as confirmed by the central laboratory and who met all the eligibility criteria were eligible for randomisation.

To demonstrate a significant difference between saxagliptin and placebo, as add-on therapy to the combination of metformin plus SU, in the change in HbA1c from baseline to Week 24, a total of 240 subjects randomised and treated (120 subjects per treatment group) was needed to provide approximately 80% power at a 2-sided significance level of 0.05, assuming a true difference of 0.40% and a standard deviation (SD) of 1.1%. Assuming a 4% drop-out rate of subjects who were randomised but did not return for a post-baseline assessment, a total of 250 subjects was required for randomisation. Assuming a 10% screening failure rate for subjects who were consented and enrolled but were not eligible for randomisation, a total of 275 subjects was planned for enrolment/screening.

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

Investigational products were administered orally, once daily with breakfast, and consisted of film-coated tablets of saxagliptin 5 mg (Batches 7J21765, 9D45693; Bristol-Myers Squibb) or matching placebo tablets for saxagliptin (Batches 7E23409, 9D45538; Bristol-Myers Squibb). During the enrolment/screening and 24-week double-blind treatment periods, subjects continued their own (open-label) metformin plus SU at the doses ascertained during enrolment; metformin and SU were not supplied as part of the investigational products.

## Duration of treatment

The study consisted of 2 periods: a 2-week enrolment/screening period and a 24-week double-blind treatment period. Subjects were required to be on a stable combined dose of

metformin (XR or IR) plus SU for at least 8 weeks prior to enrolment. Subjects continued to receive a stable combined dose of metformin plus SU (at the doses ascertained during enrolment) during the 2-week enrolment/screening period. During the 24-week double-blind treatment period, subjects were treated with saxagliptin 5 mg or matching placebo for comparator as add-on therapy to the stable dose of metformin plus SU.

**Statistical methods**

Primary endpoint

The primary efficacy endpoint (change from baseline to Week 24 in glycosylated haemoglobin [HbA1c]) was analysed using an analysis of covariance (ANCOVA) model with treatment group and country as fixed effects and baseline HbA1c value as a covariate. The analysis was based on the Full analysis set, which included subjects who took at least 1 dose of investigational product and had both baseline and post-baseline efficacy data. Missing Week 24 values were imputed with the latest post-baseline value using the last observation carried forward (LOCF) method. The model was used to derive a least squares estimate of the treatment difference in the mean change from baseline with corresponding 2-sided 95% confidence interval (CI) and 2-sided p-value. In addition, 2-sided 95% CIs for the mean change within each treatment group were calculated. For this study, a sensitivity analysis was to be performed for the Per Protocol analysis set only if >10% of subjects in either treatment group of the Full analysis set had significant deviations from the protocol,

Sequential testing methodology

A fixed-sequence test method was adopted for the overall primary efficacy variable and the 3 secondary efficacy variables to control the Type I error rate so as 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 24 in 2-hour postprandial glucose (PPG) (or the last post-baseline measurement prior to Week 24 if no Week 24 assessment was available).

2. Change from baseline to Week 24 in fasting plasma glucose (FPG) (or the last post-baseline measurement prior to Week 24 if no Week 24 assessment was available).

3. Proportion of subjects achieving a glycaemic response defined as HbA1c <7.0%.

Statistical inference began with the overall primary efficacy variable. If the saxagliptin treatment 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 (1) in the sequence above—the first secondary efficacy variable (2-hour PPG); otherwise, statistical inference of the overall efficacy variables was stopped (any p-value that follows cannot be considered as significant in this confirmatory analysis when the fixed-sequence procedure is used to control the overall Type I error rate, even if the p-value is <0.05).

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

Secondary efficacy endpoints

The changes from baseline to Week 24 in PPG and FPG were also analysed using an ANCOVA model with treatment group and country as fixed effects and the baseline value as a covariate. Similar to the primary efficacy variable, the LOCF method was applied and the model was used to derive point estimates and 2-sided 95% CIs for the mean change from baseline within each treatment group as well as for the difference in mean change from baseline between the 2 treatment groups.

The proportions of subjects with a therapeutic glycaemic response (HbA1c <7% at Week 24) were summarised per treatment group using counts and proportions. Comparisons of proportions between the treatment groups were performed using a logistic regression model with treatment group and country as fixed effects and the baseline value of the associated continuous variable (ie, HbA1c) as a covariate.

Other efficacy endpoints

For the other efficacy endpoints of lipids (total cholesterol [TC], low-density lipoprotein-cholesterol [LDL-C], high-density lipoprotein-cholesterol [HDL-C], and triglycerides [TG]), insulin, C-peptide, glucagon, and the responses to the Euro Quality of Life - 5 Dimension (EQ-5D) questionnaire and visual analogue scale, standard descriptive summary statistics were calculated for the changes from baseline to Week 24.

Sensitivity analyses

Sensitivity analyses for the efficacy endpoints were performed with observed values. The first analysis was performed for HbA1c, PPG, and FPG employing the same ANCOVA model as in the primary analysis. The second was a repeated measures analysis (mixed models framework) using observed cases for all post-treatment visits for the HbA1c and FPG endpoints. PPG was not analysed with the latter technique since PPG was only measured at baseline and at Week 24.

Safety analysis

The Safety analysis set was used for the analysis of the safety and tolerability data. Adverse events (AEs) were coded to a System Organ Class (SOC) and Preferred Term (PT) using the Medical Dictionary for Regulatory Activities (MedDRA version 14.0). The number and percentage of subjects with an event, including AEs, serious adverse events (SAEs), deaths, events leading to discontinuation, and events of special interest were summarised for each treatment group from the first day of double-blind treatment until the last dosing date. In addition, the incidence of hypoglycaemic events was presented by treatment group. Confirmed hypoglycaemia events (symptomatic hypoglycaemia with a fingerstick glucose

value of ≤2.8 mmol/L [50 mg/dL]) was summarised. Hypoglycaemic events were also classified as being major, minor, or suggestive of hypoglycaemia.

Changes from baseline to each scheduled time point for each clinical laboratory test, vital signs, and ECG were summarised by treatment group. The number and percentage of subjects with a predefined marked abnormality in clinical laboratory tests was summarised by treatment group.

There were no hypotheses proposed *a priori* for any of these safety endpoints; no formal statistical testing of these endpoints was performed.

**Subject population**

A total of 257 subjects were assigned to randomised double-blind treatment with either saxagliptin + metformin + SU (n=129) or placebo + metformin + SU (n=128). The proportion of subjects who completed the 24-week, double-blind, randomised treatment period was high and similar in the 2 treatment groups (approximately 88%). The proportion of subjects discontinuing study treatment during the double-blind treatment period was low overall and similar between the 2 treatment groups (12.4% for saxagliptin and 11.7% for placebo). The most common reason for discontinuation in both treatment groups was worsening of T2DM (6.2% [n=8] in the saxagliptin group and 5.5% [n=7] in the placebo group). One subject (0.8%) in each treatment group withdrew due to a calculated creatinine clearance of <60 mL/min or an increase in serum creatinine of ≥44.2 µmol/L (≥0.5 mg/dL) above baseline. The proportion of subjects discontinuing study treatment due to an AE during double-blind treatment was low overall and lower in the saxagliptin group than in the placebo group (0.8% [n=1] in the saxagliptin group and 2.3% [n=3] in the placebo group).

The demographic and key baseline characteristics were generally balanced across the 2 treatment groups. The subjects ranged in age from 25 to 83 years with a mean (SD) age of 57.0 (10.54) years. A total of 196 subjects (76.3%) were <65 years of age. Of the 257 randomised and treated subjects, the majority of subjects in each treatment group were male (62.0% and 57.8% in the saxagliptin and placebo groups, respectively). Body weight ranged from 40 to 155 kg with a mean (SD) of 82.4 (19.86) kg and 80.3 (18.47) kg for the saxagliptin and placebo groups, respectively. The respective mean (SD) BMI was 29.4 (5.26) $kg/m^2$ and 29.1 (4.93) $kg/m^2$ for the saxagliptin and placebo groups.

The baseline disease characteristics of HbA1c, PPG, and FPG were representative of subjects with uncontrolled T2DM who have inadequate glycaemic control when treated with combination therapy with metformin plus SU. The mean baseline values for these 3 parameters were slightly higher in the saxagliptin group compared with the placebo group. For HbA1c, the mean (SD) value at baseline was 8.38% (0.856%) and 8.19% (0.832%) in the saxagliptin and placebo groups, respectively.

**Summary of efficacy results**

Saxagliptin + metformin + SU was superior to placebo + metformin + SU in lowering HbA1c from baseline to Week 24 (adjusted mean changes of -0.74% for the saxagliptin group and

-0.08% for the placebo group). The difference in adjusted mean changes between the 2 groups (saxagliptin minus placebo) was -0.66% (2-sided 95% CI, -0.86% to -0.47%; p<0.0001). Similar results were obtained in the Per Protocol analysis as well as in the Full analysis set using observed values and in the repeated measures analysis.

Treatment with saxagliptin + metformin + SU resulted in a significantly greater reduction in 2-hour PPG at Week 24 compared with placebo + metformin + SU. The difference in adjusted mean changes between the 2 groups (saxagliptin minus placebo) was -0.93 mmol/L (-16.74 mg/dL) (2-sided 95% CI, -1.77 to -0.09 mmol/L [-31.85 to -1.62 mg/dL]; p=0.0301).

Saxagliptin + metformin + SU produced a numerically greater reduction compared with placebo + metformin + SU in FPG at Week 24. The difference in adjusted mean changes between the 2 groups (saxagliptin minus placebo) was -0.44 mmol/L (-7.90 mg/dL) (2-sided 95% CI, -0.94 to 0.06 mmol/L [-16.96 to 1.15 mg/dL]; p=0.0868).

The proportion of subjects achieving a therapeutic glycaemic response, defined as HbA1c <7.0% at Week 24, was higher in the saxagliptin group (30.7%) than in the placebo group (9.4%). The adjusted odds ratio for the difference in proportions between the 2 groups (saxagliptin/placebo) was 9.006 (2-sided 95% CI, 3.852 to 21.05).

Other efficacy findings included:

- Saxagliptin + metformin + SU compared with placebo + metformin + SU had similar non–clinically relevant effects on mean changes from baseline to Week 24 in fasting plasma lipids as well as on fasting levels of insulin, C-peptide, and glucagon.

- The changes from baseline to Week 24 were similar in the saxagliptin and placebo groups in subject-reported health status assessed with the EQ-5D.

**Summary of safety results**

Mean (SD) exposure to investigational product was similar in both treatment groups (158.9 [31.41] days in the saxagliptin group and 160.1 [29.73] days in the placebo group), with median exposures of 168 days in both treatment groups.

The safety and tolerability profile of saxagliptin + metformin + SU was similar to that of placebo + metformin + SU. The proportion of subjects experiencing any AE was lower in the saxagliptin group compared with the placebo group (62.8% and 71.7% in the saxagliptin and placebo groups, respectively; 59.7% and 69.5%, respectively, when hypoglycaemic events were excluded). The most common AEs (≥5%) in the saxagliptin group were nasopharyngitis (6.2%), diarrhoea (5.4%), and hypertension (5.4%); the most common AEs in the placebo group were nasopharyngitis (9.4%), urinary tract infection (6.3%), and dyslipidaemia (5.5%). The proportion of subjects experiencing any treatment-related AE was higher in the saxagliptin group compared with the placebo group (16.3% and 10.2% in the saxagliptin and

placebo groups, respectively; 11.6% and 7.0%, respectively, when hypoglycaemic events were excluded).

There were no deaths during the study. SAEs were reported in a total of 10 subjects: 3 (2.3%) subjects in the saxagliptin group (lower respiratory tract infection, laryngeal cancer, and hepatitis in 1 subject each) and 7 (5.5%) subjects in the placebo group (influenza, osteomyelitis, squamous cell carcinoma, cartilage injury, renal colic, and asthma in 1 subject each; arthritis and musculoskeletal stiffness in 1 subject). Of these, only 1 SAE (hepatitis) was considered by the investigator to be possibly related to saxagliptin. The subject, although asymptomatic, was diagnosed with hepatitis, pancreatitis, and calculus cholecystitis after the subject's end-of-study laboratory evaluations revealed elevated transaminases and total bilirubin. Few subjects discontinued due to an AE in either treatment group; 1 (0.8%) subject in the saxagliptin group discontinued due to an AE (headache) and 3 (2.3%) subjects in the placebo group discontinued due to an AE (abdominal distension, diabetes mellitus inadequate control, and asthma).

The incidence of hypoglycaemic AEs was low in both treatment groups but was higher in the saxagliptin group compared with the placebo group (10.1% and 6.3%, respectively); only 2 subjects (saxagliptin group) had confirmed hypoglycaemia (symptomatic with fingerstick plasma glucose ≤2.8 mmol/L [50 mg/dL]). An AE indicative of an acute cardiovascular event (carotid artery occlusion) was reported in 1 saxagliptin-treated subject who had a history of hypercholesterolaemia and heart valve regurgitation. The event was judged to not be a cardiovascular event upon adjudication. Infections overall were reported less frequently in the saxagliptin group than in the placebo group; there were no events of opportunistic infections. The incidence of gastrointestinal AEs was similar for the 2 treatment groups. Other AEs of special interest identified with the prespecified lists of PTs did not reveal any imbalances or new findings.

One subject in the saxagliptin group had a clinically important ECG finding (T-wave inversion) during the double-blind treatment period that was not present at baseline; this event was adjudicated and the final adjudication confirmed that there were non-specific ST–T-wave ECG changes compatible with lanoxin therapy and no clinical evidence of myocardial infarction. There were no other clinically relevant changes in clinical laboratory values, vital signs, or ECGs. No indications of renal or other system impairments were reported throughout the study.