AstraZeneca

Clinical Study Report Synopsis

Drug Substance	Saxagliptin
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A 24-Week, Randomised, Double-Blind, Active-Controlled, Multi-Centre Phase IIIb/IV Study to Evaluate the Efficacy and Tolerability of Saxagliptin Add-On Compared to Uptitration of Metformin in Patients with Type 2 Diabetes Mellitus With Inadequate Glycaemic Control on Sub-Maximal Doses of Metformin

Study dates: First patient enrolled: 20 October 2009
Last patient last visit: 3 December 2010

Phase of development: Therapeutic confirmatory/use (IIIb/IV)

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

Study centre(s)

This study was conducted at 56 sites in the following seven countries: Belgium (11 sites), France (6 sites), Germany (7 sites), Italy (9 sites), Spain (11 sites), Turkey (3 sites) and the United Kingdom (9 sites).

Publications

None at the time of writing this report.

Objectives and criteria for evaluation

Table S1 Primary and secondary objectives and outcome variables

Objectives	Outcome variables	Type
Primary	Primary	
To show superiority of saxagliptin 5 mg once daily added on to metformin 1500 mg daily, compared to metformin uptitrated to a maximum of 2500 mg daily, in improving glycaemic control as determined by the absolute change in HbA_{1c} levels from baseline to Week 24, in patients with type 2 diabetes who have inadequate glycaemic control on a submaximal total daily dose of 1500 mg of metformin.	Change from baseline to Week 24 in HbA_{1c} level	Efficacy
Secondary	Secondary	
To compare the effects of saxagliptin 5 mg once daily added on to metformin 1500 mg daily, compared to metformin uptitrated to a maximum dose of 2500 mg daily, after 24 weeks of treatment, by evaluation of the following efficacy variables:	Change from baseline to Week 24 in fasting plasma glucose and fasting insulin Proportion of patients achieving a therapeutic glycaemic response at Week 24 defined as HbA_{1c} <7.0% or ≤6.5% Change from baseline to Week 24 in β-cell function as measured by Homeostasis Model Assessment-2β (HOMA-2β)	Efficacy
Safety	Safety	
Safety and tolerability were evaluated by assessment of the following safety variables:	Incidence of AEs (including SAEs and AEs of special interest[a]) Laboratory values Electrocardiogram Vital signs (pulse, blood pressure) Body weight Physical examination	Safety

[a] AEs of special interest included hypoglycaemic AEs and other selected AEs, including hepatic disorders, lymphocytopenia, thrombocytopenia, infections, opportunistic infections, skin related disorders, localised oedema, cardiovascular events, hypersensitivity, fractures and pancreatitis.

For exploratory objectives see the Clinical Study Report (CSR). Results of exploratory objectives are not included in this synopsis, but can be found in the CSR.

AE Adverse Event; HbA_{1c} Glycosylated Haemoglobin A_{1c}; SAE Serious Adverse Event.

Study design

This study was a 24-Week, multi-centre, randomised, parallel-group, double-blind (double-dummy), active-controlled Phase IIIb/IV trial to evaluate the efficacy and safety of saxagliptin compared with uptitration of metformin in patients with type 2 diabetes who had inadequate glycaemic control (defined as HbA_{1c} ≥7.0% and ≤10.0%) on a sub-maximal dose of metformin.

Target patient population and sample size

The target patient population was males and females, ≥18 years old, with diagnosis of type 2 diabetes who had inadequate glycaemic control, defined as HbA_{1c} levels ≥7.0% and ≤10.0%, on a prescribed treatment with metformin alone (any formulation) on stable doses of 1500 to 1700 mg per day for at least 8 weeks prior to Visit 1.

To demonstrate superiority of saxagliptin compared to uptitration of metformin in change from baseline to Week 24 in HbA_{1c}, a total of 240 randomised and treated patients (120 patients per treatment group) were needed to provide approximately 80% power at a two-sided significance level of 0.05 to show the difference between treatment groups, assuming a true difference of 0.4% and a standard deviation of 1.1%.

With an assumed 10% of patients dropping out prior to treatment with study medication, approximately 268 patients (134 patients per treatment group) were planned for randomisation.

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

Table S2 Investigational products

Investigational product	Dosage form, strength, dosing schedule, and route of administration	Manufacturer	Formulation number	Batch number
Metformin hydrochloride (open-label)	Film-coated, white to off-white round tablet, 500 mg, 3 tablets daily, administered orally	Bristol-Myers Squibb	309403-KXXX-011	6H16141
Saxagliptin	Plain, yellow, biconvex, round, film coated tablet, 5 mg, once daily, administered orally	Bristol-Myers Squibb	477118-K005-111	9D45693
Placebo for saxagliptin	Plain, yellow, biconvex, round, film coated tablet to match saxagliptin, 5 mg, once daily, administered orally	Bristol-Myers Squibb	477118-K000-112	9D45538

Investigational product	Dosage form, strength, dosing schedule, and route of administration	Manufacturer	Formulation number	Batch number
Metformin hydrochloride (double-blind)	Film-coated, white to off-white round tablet, 500 mg, added once or twice daily (if second uptitration step indicated), administered orally	Bristol-Myers Squibb	309403-KXXX-011	6H16141
Placebo for metformin hydrochloride	Film-coated, white to off-white round tablet to match metformin, 500 mg, added once or twice daily (if second uptitration step indicated), administered orally	Bristol-Myers Squibb	309403-K000-013	7J30710

Qualified patients entering the 4-Week lead-in period received open-label metformin (500 mg tablets) at a daily dose of 1500 mg (i.e. background treatment). This open-label treatment of metformin 1500 mg was to remain constant throughout the whole study period.

Eligible patients entering the 24-Week double-blind treatment period were randomly assigned to either the saxagliptin group, i.e. saxagliptin (5 mg) once daily added on to open-label treatment of metformin, or the uptitration of metformin group, i.e. double-blind metformin (500 mg) once or twice daily (depending on final titration level) added on to open-label treatment of metformin.

The investigator had the possibility of uptitrating the metformin dose by adding a second double-blind tablet of metformin 500 mg or matching placebo (for patients in the saxagliptin group) between Visit 5 (Week 2) and Visit 7 (Week 12). This decision was based on blood glucose measurements made by the patient prior to Visit 5, the gastrointestinal tolerability and the fasting plasma glucose (FPG) value (performed at the Central Laboratory at Visit 5). Titration of metformin should aim at FPG ≤6.1 mmol/L (or ≤110 mg/dL) or the highest tolerable dose during the first 12 weeks. No uptitration was allowed beyond Week 12 to ensure a steady-state effect of the HbA_{1c}, which was the primary endpoint of the present study. The metformin dose of the non-background treatment could be down-titrated at any time during the study if necessary and felt appropriate by the investigator.

Duration of treatment

The duration of the double-blind treatment period was 24 weeks. Patients had a 2-Week enrolment period and a 4-Week lead-in period before the day of randomisation.

Statistical methods

The primary efficacy analysis was to show the superiority of saxagliptin compared to uptitration of metformin to a maximum dose of 2500 mg per day in improving glycaemic control in patients with type 2 diabetes, as determined by the change in HbA_{1c} levels from

baseline to Week 24. This analysis was performed using the full analysis set. The absolute change from baseline to Week 24 in HbA_{1c} was analysed with an analysis of covariance model (ANCOVA) using the treatment group as a factor and the baseline HbA_{1c} measurement as a covariate. Missing post-baseline values were replaced by using the last observation carried forward (LOCF) after baseline. The model was used to derive a least squares estimate of the treatment difference in mean change with corresponding two-sided 95% confidence interval (CI) and two-sided p-value. Further, two-sided 95% CIs for the mean change within each treatment group were calculated.

Continuous secondary and other relevant variables were analysed by means of an ANCOVA for change from baseline to Week 24 using the treatment group as a factor and their baseline value as a covariate. By analogy to the primary efficacy variable, the LOCF methodology was applied and the model was used to derive point estimates and two-sided 95% CIs for the mean change within each treatment group as well as for the difference in mean change between the two treatment groups.

No control of type I error was performed for the secondary endpoints. Nominal two-sided p-values for the difference between the treatment groups were provided.

Categorical secondary efficacy variables were analysed using the methodology of Zhang, Tsiatis and Davidian (Zhang et al 2008), and Tsiatis, Davidian, Zhang and Lu (Tsiatis et al 2007). The difference in response rate between the saxagliptin and uptitration of metformin group was displayed along with the 95% CIs in the overall population. Nominal p-values for the difference between the saxagliptin and uptitration of metformin group were provided for the overall population.

Patient population

In total, 343 patients were enrolled in this study and 332 patients (96.8%) completed the enrolment period. 286 patients (83.4%) completed the lead-in period and were randomised to enter the double-blind treatment period. Most common reasons for not being randomised were voluntary discontinuation and not fulfilling all the inclusion criteria or fulfilling at least one exclusion criterion summarised as “incorrect enrolment”. A total of 119 (81%) patients in the saxagliptin group and 107 (77%) patients in the uptitration of metformin group completed the 24 weeks of double-blind treatment (overall completion rate of 79%). The most common reason for not completing the double-blind treatment period was development of study-specific discontinuation criteria (refer to Section 5.3.4.1 in the CSR for description of these specific discontinuation criteria) in both treatment groups (16 patients (10.9%) in the saxagliptin group and 23 patients (16.5%) in the uptitration of metformin group). The proportion of patients not completing the double-blind treatment period due to voluntary discontinuation and occurrence of an adverse event were low overall (2.7% and 1.4% in the saxagliptin group, respectively, and 1.4% and 2.2% in the uptitration of metformin group, respectively).

All of the 286 randomised patients took at least one dose of double-blind study medication, i.e. both the randomised analysis set and the safety analysis set comprised 286 patients (147 patients in the saxagliptin group and 139 patients in the uptitration of metformin group).

In general, the treatment groups were balanced with respect to demographic, baseline characteristics, patient lifestyle and tobacco usage. Of the 286 randomised patients, 57.3% were male and 42.7% were female. The mean age was 58.7 years. Overall, 70.6% of the patients were aged below 65 years and 5.9% were 75 years or elder. The majority of patients were White (97.9%). 29.4% of the patients were overweight (BMI ≥25 and <30 kg/m^2) and 57.3% were obese (BMI ≥30 kg/m^2). Most patients (57.3%) were from the North Sea region, whilst 42.7% were from the Mediterranean region. Mean duration of type 2 diabetes was 6.5 years. The proportion of patients diagnosed with type 2 diabetes ≥5 years before the start of the study was overall 51.4%, and overall 22.0% for patients diagnosed ≥10 years. The mean baseline HbA_{1c} was 7.76% and 9.1% of the patients had a baseline HbA_{1c} ≥9%. The mean baseline FPG was 9.38 mmol/L, fasting insulin was 14.5 µU/mL and β-cell function based on Homeostasis Model Assessment-2β (HOMA-2β) was 49.86%. The mean daily metformin dose was 1613 mg before the start of the study.

Summary of efficacy results

Saxagliptin added to metformin was not significantly superior to uptitration of metformin in lowering HbA_{1c} from baseline to Week 24 (adjusted mean changes of –0.47% and –0.38% in the saxagliptin and uptitration of metformin group, respectively, with a difference versus uptitration of metformin of –0.10%; two-sided 95% confidence interval –0.26% to 0.07%, p-value 0.26).

Key secondary efficacy findings:

Patients in both treatment groups showed an adjusted mean reduction in FPG (-1.07 mmol/L in the saxagliptin group and -1.14 mmol/L in the uptitration of metformin group). The difference between treatment groups was 0.07 (95% CI [-0.38, 0.52]).

Patients in both treatment groups showed an adjusted mean reduction in fasting insulin (-1.9 µU/mL in the saxagliptin group and -2.3 µU/mL in the uptitration of metformin group). The difference between treatment groups was 0.3 (95% CI [-2.0, 2.7]).

The adjusted proportion of patients achieving HbA_{1c} <7.0% was numerically higher in the saxagliptin group (42.2%) than in the uptitration of metformin group (36.4%). The difference between treatment groups was 5.8% (95% CI [-5.6, 17.1]).

The adjusted proportion of patients achieving HbA_{1c} ≤6.5% was 19.7% in the saxagliptin group and 17.4% in the uptitration of metformin group. The difference between treatment groups was 2.3% (95% CI [-6.7, 11.3]).

The adjusted mean increase in HOMA-2ß was 4.70% in the saxagliptin group and 2.34% in the uptitration of metformin group at Week 24. The difference between treatment groups was 2.36% (95% CI [-6.22, 10.93]).

Summary of safety results

The overall proportion of patients experiencing at least one AE (excluding hypoglycaemic events) was 51.0% (n=75) in the saxagliptin group and 43.9% (n=61) in the uptitration of metformin group. The incidence of treatment related AEs was low in both treatment groups, with 7.5% (n=11) of the patients in the saxagliptin group and 5.0% (n=7) of the patients in the uptitration of metformin group. The proportion of patients who discontinued due to an AE was low in both treatment groups (2.7% (n=4) of the patients in the saxagliptin group and 3.6% (n=5) of the patients in the uptitration of metformin group).

The incidence of infections and infestations related AEs was higher in the saxagliptin group compared with the uptitration of metformin group; this was mainly driven by the frequency of AEs of nasopharyngitis (5.4% vs. 1.4% for the saxagliptin and uptitration of metformin group, respectively). The incidence of gastrointestinal disorder related AEs was higher in the uptitration of metformin group compared with the saxagliptin group; this was mainly driven by the frequency of AEs of diarrhoea (6.1% vs. 12.2% for the saxagliptin and uptitration of metformin group, respectively).

A total of 12 patients experienced SAEs during the double-blind treatment period, 6 patients in each treatment group (4.1% of the patients in the saxagliptin group and 4.3% of the patients in the uptitration of metformin group). Two patients died during the double-blind treatment period, one patient in each treatment group. The patient in the saxagliptin group died from aortic dissection and the patient in the uptitration of metformin group died from tongue neoplasm malignant stage unspecified. There were no treatment related SAEs reported in the two treatment groups.

Few patients had hypoglycaemia during the study, with a slightly higher incidence observed in the saxagliptin group compared to the uptitration of metformin group (10 patients (6.8%) in the saxagliptin group and 3 patients (2.2%) in the uptitration of metformin group). In the saxagliptin group, the vast majority of the hypoglycaemic events was classified as other based on the CPMP classification, defined as suggestive event not meeting the criteria for major or minor events (5.4% vs. 0.7% for the saxagliptin and uptitration of metformin group, respectively). One patient in the uptitration of metformin group (none in the saxagliptin group) experienced a hypoglycaemic event classified as major event. Two patients in each treatment group experienced minor hypoglycaemic events confirmed by a capillary or plasma glucose level of <3.0 mmol/L (<54 mg/dL).

The proportion of patients with AEs of special interest of localised oedema, cardiovascular, hypersensitivity, or fracture was low and similar between the two treatment groups. No patients in either treatment group had AEs of lymphocytopenia, thrombocytopenia, opportunistic infections, skin related events or pancreatitis.

The proportion of patients with marked laboratory abnormality was low and similar between the two treatment groups, and there were no clinically relevant ECG findings in either treatment group.

There were no clinically meaningful changes from baseline observed for systolic and diastolic blood pressure or for heart rate in either treatment group.

Patients in both treatment groups showed a mean reduction in body weight at Week 24 compared to baseline, with the uptitration of metformin group showing a slightly greater mean reduction compared to the saxagliptin group, -1.6 kg (95% CI [-2.1, -1.1]) vs. -1.1 kg (95% CI [-1.7, -0.4]), respectively.