AstraZeneca

Clinical Study Report Synopsis

Drug Substance	Saxagliptin
Study Code	D1680L00002
Edition Number	1
Date	3 October 2012

A 52-Week, Randomised, Double Blind, Active-Controlled, Multi-Centre Phase 3b/4 Study to Evaluate the Efficacy and Tolerability of Saxagliptin Compared to Glimepiride in Elderly Patients with Type 2 Diabetes Mellitus Who Have Inadequate Glycaemic Control on Metformin Monotherapy

Study dates: First subject enrolled: 20 October 2009
Last subject last visit: 14 June 2012

Phase of development: Therapeutic confirmatory/use (3b/4)

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

Study centre(s)

This study was conducted in the following 13 countries: Austria (8 sites), Denmark (11 sites), Finland (13 sites), France (7 sites), Germany (16 sites), Greece (7 sites), Hungary (7 sites), Italy (9 sites), Mexico (5 sites), Norway (21 sites), Spain (10 sites), Sweden (17 sites) and the United Kingdom (21 sites).

Publications

There were no publications at the time of writing this synopsis.

Objectives and criteria for evaluation

Table S1 Primary and secondary objectives and outcome variables

Objectives	Outcome variables	Type
Primary	**Primary**	
To show the superiority of saxagliptin compared to glimepiride in bringing elderly patients (≥65 years) with type 2 diabetes to HbA1c target <7% without hypoglycaemia (confirmed or severe) over a 52-week treatment period. Saxagliptin or glimepiride was administered as an add-on therapy to a background therapy with metformin.	Proportion of patients reaching HbA1c <7% after 52 weeks of treatment without confirmed or severe hypoglycaemia	Efficacy
Secondary	**Secondary**	
To compare the effects of saxagliptin versus glimepiride given as add-on to a metformin therapy after 52 weeks of double-blind treatment period by evaluation of the following secondary safety variable:	Proportion of patients having experienced at least one hypoglycaemic event (confirmed or severe) over the 52-week double-blind treatment period	Key Secondary Safety
To compare the effects of saxagliptin versus glimepiride given as add-on to a metformin therapy after 52 weeks of double-blind treatment period by evaluation of the following secondary efficacy variables:	Change from baseline to Week 52 in HbA1c Proportion of patients achieving a therapeutic glycaemic response at Week 52 defined as HbA1c <7.0% or <6.5% Change from baseline to Week 52 in fasting plasma glucose (FPG) and insulin Change from baseline to Week 52 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:	Adverse events (AEs) Laboratory values Electrocardiogram (ECG) Pulse rate, blood pressure Body weight Physical examination	Safety

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.

HbA1c Glycosylated Haemoglobin A1c.

Study design

This study was a 52-week, multi-centre, randomised, parallel-group, double-blind, active-controlled Phase 3b/4 trial to evaluate the efficacy and safety of saxagliptin compared with glimepiride in elderly patients (≥65 years old) with type 2 diabetes who had inadequate glycaemic control (defined as HbA1c ≥7.0% and ≤9.0%) on a stable dose of metformin monotherapy for at least 8 weeks. The randomisation was stratified by age (<75 and ≥75 years). The cohorts were approximately 60% of the patients for age group 65 years to 75 years and 40% for age group ≥75 years.

Target subject population and sample size

The target patient population was males and females, ≥65 years of age, with diagnosis of type 2 diabetes who had inadequate glycaemic control, defined as HbA1c levels ≥7.0% and ≤9.0%, on a prescribed treatment with metformin alone at a stable dose (any dose) for at least 8 weeks prior to Visit 1.

To detect superiority with a two-sided significance level of α=0.05 and 80% power sample size calculations based on the Cochran-Mantel-Haenszel (CMH) method using continuity correction and assuming equality of Odds Ratios (OR) across strata, a total of 698 patients, randomised and treated (349 patients in each treatment arm) were needed. It was estimated that the selected sample size should result in a total number of 140 randomised and treated patients aged ≥75 years per treatment arm (40% of 349).

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

Qualified patients entering the 2-week single-blind (blind to patient only) lead-in period received matching placebo tablets for saxagliptin 5 mg and matching placebo-encapsulated tablets for glimepiride 1 mg.

Eligible patients entering the 52-week double-blind treatment period were randomly assigned to either the saxagliptin group, ie saxagliptin (5 mg) once daily added on to the prescribed stable metformin monotherapy, or the glimepiride group, ie glimepiride (1, 2 or 4 mg with dosing 1 to 6 mg, depending on final titration level) once or twice daily added on to the prescribed stable metformin monotherapy. To ensure blinding of the investigational products (IPs), the patients received placebo capsules/tablets using a double-dummy technique.

During the first 12 weeks (the titration period), the glimepiride/placebo dose was titrated in a stepwise fashion depending on glycaemic control. The glimepiride/placebo dose was to be titrated to optimal effect (Fasting plasma glucose [FPG] ≤6.1 mmol/L or ≤110 mg/dL) or the highest tolerable dose during the first 12 weeks. The starting dose for glimepiride/placebo was 1 mg per day (once daily), and the dose was titrated at 3-week intervals to a maximum of 6 mg per day. The titration steps were 2 mg per day (once daily) followed by 3 mg, 4 mg or

6 mg (once daily), if needed only. In patients for whom titration was not medically indicated at Week 3 (Visit 4), re-assessment for titration occurred at Week 6 (Visit 5), Week 9 (Visit 6) and Week 12 (Visit 7).

The glimepiride/placebo dose could be downtitrated during the titration period if hypoglycaemic events occurred. The treatment could thereafter be uptitrated once during the titration period

After the titration period, the patient remained on the patient optimal dose of IP for 40 weeks to assess efficacy and safety of the treatment. The dose of glimepiride/placebo could be downtitrated at any time during this period to mitigate recurrent hypoglycaemic events at the discretion of the investigator. No up titration was allowed during the maintenance treatment period (ie, if the dose was lowered it would then be left on this lower dose level).

The saxagliptin dose (5 mg) and the patients' prescribed stable dose of metformin remained constant throughout the study.

Duration of treatment

The duration of the double-blind treatment period was 52 weeks. The double-blind treatment period consisted of a 12-week titration period and a 40-week maintenance treatment period. Patients had a 2-week enrolment period and a 2-week single-blind (blind to patient only) placebo lead-in period before the day of randomisation.

Statistical methods

The hypothesis tested was to show the superiority of saxagliptin compared to glimepiride in bringing elderly patients (≥65 years old) with type 2 diabetes to HbA1c target <7% without hypoglycaemia (confirmed or severe) over a 52-week treatment period. The proportion of patients reaching HbA1c <7% without confirmed or severe hypoglycaemia was analysed using the CMH method for the OR, including a stratification variable for the age group (<75 versus ≥75 years).

The primary efficacy analysis was performed on the safety analysis set using the above mentioned CMH approach providing statistical test results and 95% confidence intervals (CI) for the OR comparing treatments. There was no re-assignment of treatments for this analysis, each patient was analysed as randomised.

Any patient who did not complete the 52-week treatment period was considered as a non-responder, ie, as having not achieved the HbA1c target without confirmed or severe hypoglycaemia. In order to assess the influence of including all drop-outs, irrespective of their reason, into the group of non-responders, a sensitivity analysis of the primary efficacy endpoint was conducted for the subgroup of the safety analysis set, excluding all patients who terminated due to a reason not related to glycaemic control. Patients who discontinued due to glycaemic control reasons continued to be counted as non-responders.

The key secondary objective (safety analysis), the proportion of patients having experienced at least one hypoglycaemic event (confirmed or severe) over the 52-week double-blinded treatment period, was analysed using the same approach as in the analysis of the primary endpoint. Superiority of saxagliptin was tested in the safety analysis set.

To preserve the type I error rate ≤0.05 (two-sided) across the primary and the key secondary endpoints, a hierarchical testing procedure was used to interpret the statistical significance of these treatment comparisons. The primary endpoint was tested first followed by the key secondary endpoint. Both comparisons were tested at a two-sided significance level of α=0.05. However, a comparison of the key secondary objective would only be confirmed as statistically significant if the preceding primary comparison were statistically significant.

The remaining secondary analyses included both continuous and categorical endpoints and were considered exploratory. No multiplicity adjustments were performed. The time course of the continuous variables was presented using standard descriptive summary statistics. Analyses of continuous endpoints were performed using analysis of covariance (ANCOVA) methods for the change from baseline. The ANCOVA model used the factors treatment group and age (<75 versus ≥75 years) as a fixed effect and the respective baseline value as covariate. Within the framework of the ANCOVA model, point estimates and the two-sided 95% CIs for the mean change within each treatment group, as well as for the differences in mean change between the two treatment groups, were reported. Repeated measurement analysis by analogy with the ANCOVA model was conducted.

The categorical secondary variables were summarized by counts, proportions, and if appropriate, corresponding 95% CIs. Exploratory secondary analyses of categorical endpoints used the same approach as for the primary endpoint.

The last observation carried forward (LOCF) approach was applied to the exploratory secondary endpoints only. This means that for a specific time-point post-baseline, analyses were based on measurements available at that time-point or the last post-baseline measurement prior to the time-point, if no measurement was available at that time-point.

The safety analysis set was used for all summaries of safety data in the double-blind treatment period. All safety data was summarised by treatment group and for the overall population. Adverse events (AEs) were classified by primary system organ class and preferred term according to Medical Dictionary for Regulatory Activities. No statistical tests were performed to compare AE rates between treatment groups.

Subject population

In total, 957 patients were enrolled in this study and 942 patients (98.4 %) completed the enrolment period. Seven hundred and twenty patients (75.2 %) completed the lead-in period and were randomised to enter the double-blind treatment period. The most common reason for not being randomised was subject did not meet randomisation criteria (20.7%), and the second most common reason was voluntary discontinuation (2.9%).

Of the 720 patients who were randomised 574 patients (79.8%) completed the 52-week treatment period (289 patients [80.3%] in the saxagliptin group and 285 patients [79.2%] in the glimepiride group). The most common reason for not completing the double-blind treatment period in both treatment groups was development of study-specific discontinuation criteria (9.2 % in the saxagliptin group and 9.4 % in the glimepiride group). The second and third most common reasons for not completing the double-blind treatment period were voluntary discontinuation (4.7 % in the saxagliptin group and 5.3 % for the glimepiride group) and AE (4.2 % in the saxagliptin group and 1.9 % in the glimepiride group).

No patient in the saxagliptin group and 7 patients in the glimepiride group were discontinued for major and/or frequent hypoglycaemic events. A total of 27 patients (7.5 %) in the saxagliptin group and 18 patients (5.0 %) in the glimepiride group discontinued the study due to lack of efficacy.

The mean age was 72.6 years; 60.1% of patients were <75 years old, and 39.9% were ≥75 years old. The majority of patients were white (98.2%) consistent with the regions represented in the study, which included Central Europe (38.1%), Latin countries (including Southern European countries, 18.9%), and Nordic countries (43.1%). There was a higher proportion of males (61.8%) compared to females (38.2%) in the study. The majority of patients were overweight or obese (39.4% with body mass index [BMI] ≥25 to <30 kg/m^2 and 44% with BMI ≥30 kg/m^2), and the mean BMI was 29.6 kg/m^2.

In general, the treatment groups were balanced with respect to demographic and baseline characteristics.

Summary of efficacy results

- Superiority of saxagliptin compared to glimepiride was not demonstrated for the primary endpoint of proportion of patients with HbA1c <7% at Week 52 without confirmed or severe hypoglycaemia. Similar proportions of patients in the saxagliptin (37.9%) and glimepiride (38.2%) treatment groups achieved the primary endpoint (OR 0.99, two-sided 95% CI 0.73, 1.34, p=0.9415).

- A significant treatment-by-subgroup interaction was detected for the primary endpoint for age stratum (p=0.0389). Results numerically favoured saxagliptin in patients aged <75 years (39.2% in the saxagliptin group and 33.3% in the glimepiride group, OR 1.29, 95% CI 0.87, 1.91), and numerically favoured glimepiride in patients aged ≥75 years (35.9% in the saxagliptin group and 45.5% in the glimepiride group, OR 0.67, 95% CI 0.42, 1.08).

- A lower proportion of patients in the saxagliptin group (1.1%) compared to the glimepitide group (15.3%), experienced a confirmed or severe hypoglycaemic event over 52 weeks (OR 0.06, 95% CI 0.02, 0.17).

- A lower proportion of patients in the saxagliptin group (44.7%) compared to the glimepiride group (54.7%) achieved an HbA1c target of <7.0% at Week 52 (LOCF) (OR 0.67, 95% CI 0.50, 0.90).

- A lower proportion of patients in the saxagliptin group (18.5%) compared to the glimepiride group (30.9%) achieved an HbA1c target of ≤6.5% at Week 52 (LOCF) (OR 0.51, 95% CI 0.36, 0.72).

- Reductions in adjusted mean HbA1c were smaller in the saxagliptin group (-0.44%) compared to the glimepiride group (-0.64%) at Week 52 (LOCF) (difference 0.20%, 95% CI 0.10, 0.30).

- Reductions in adjusted mean FPG were smaller in the saxagliptin group (-0.73 mmol/L) compared to the glimepiride group (1.29 mmol/L) at Week 52 (LOCF) (difference 0.56 mmol/L, 95% CI 0.34, 0.78 mmol/L).

- Reductions in adjusted mean fasting insulin level were observed in both treatment groups at Week 52 (LOCF) (–2.0 μU/mL in the saxagliptin group and –0.6 μU/mL in the glimepiride group, difference -1.5 μU/mL, 95% CI –3.0, 0.0 μU/mL).

- Adjusted mean HOMA-β increased to a lesser extent in the saxagliptin group (3.83%) compared to the glimepiride group (16.22%) at Week 52 (LOCF) (difference -12.38%, 95% CI –16.58%, –8.19%).

Summary of safety results

- The proportion of patients experiencing at least one AE excluding hypoglycaemia was similar in both treatment groups (213 patients, 59.3% in both groups); the proportion of patients experiencing at least one AE or hypoglycaemic event was lower in the saxagliptin group (220 patients, 61.3%) than in the glimepiride group (252 patients, 70.2%).

- A higher proportion of patients in the saxagliptin group (41 patients, 11.4%) experienced serious adverse events (SAEs) compared to the glimepiride group (32 patients, 8.9%). A higher proportion of patients discontinued due to an AE in the saxagliptin group (16, 4.5%) compared to the glimepiride group (11, 3.1%). One patient in each patient group died during the double-blind treatment period.

- The proportion of patients experiencing at least one hypoglycaemic event (any event) was lower in the saxagliptin group (21 patients, 5.8%) compared to the glimepiride group (125 patients, 34.8%).

- Neoplasms were reported in 10 patients (2.8%) in the saxagliptin group and in 3 patients (0.8%) in the glimepiride group. Events of neoplasm in the saxagliptin group were distributed across multiple organ systems, and most events occurred in

patients with risk factors for cancer who had a short exposure time to saxagliptin (≤6 months in 8/10 cases).

- A higher proportion of patients reported an AE of fracture in the saxagliptin group (9 patients, 2.5%) compared to the glimepiride group (4, 1.1%). Events of fracture in the saxagliptin group were associated with a short exposure time to study medication (≤7 months in 7 cases, ≤9 months in all cases). All patients had either prior risk factors for osteoporosis or pre-existing osteoporosis, no patient had a hypoglycemic event associated with fracture, and no event was considered by the investigator to be related to saxagliptin therapy.

- There were no meaningful differences between the two groups in AEs of special interest: infection, opportunistic infection, skin lesion, localised edema, or adjudicated cardiovascular (CV) events. One patient in the saxagliptin group experienced a hypersensitivity reaction (anaphylactic shock) that was attributed to diclofenac and was considered unrelated to study therapy. No patient in either treatment group had an AE of lymphocytopenia, thrombocytopenia, or pancreatitis.

- Small decreases in creatinine clearance compared to baseline were observed at Week 52 in both treatment groups (-2.7 mL/min/1.73 m^2 in the saxagliptin group and -3.8 mL/min/1.73 m^2 in the glimepiride group). There were few patients with marked laboratory abnormalities in either treatment group.

- There were no clinically meaningful changes in systolic blood pressure, diastolic blood pressure, or heart rate in either treatment group.

- Patients in the saxagliptin group showed a mean reduction in body weight, whereas patients in the glimepiride group showed a mean increase in body weight compared to baseline at Week 52 (-0.8 kg, 95% CI -1.2, -0.4 versus 1.0 kg, 95% CI 0.6, 1.3, respectively).