Short Report: Treatment

Long-term 4-year safety of saxagliptin in drug-naive and metformin-treated patients with Type 2 diabetes

J. Rosenstock1, J. L. Gross2, C. Aguilar-Salinas3, M. Hissa4, N. Berglind5*, S. Ravichandran5 and D. Fleming5

1Dallas Diabetes and Endocrine Center at Medical City, Dallas, TX, USA, 2Centro De Pesquisa Em Diabetes, Porto Alegre, Rio Grande Do Sul, Brazil, 3Instituto Nacional de Ciencias Medicas y Nutricion, Mexico City, Mexico, 4Hospital Universitario Walter Cantidio, Fortaleza, Ceará, Brazil and 5Bristol-Myers Squibb, Princeton, NJ, USA

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Abstract

Aims To evaluate the safety of saxagliptin ± metformin over 4 years in patients with Type 2 diabetes mellitus.

Methods Drug-naive (n = 401; study 11) or metformin-treated (n = 743; study 14) adults with HbA1c of 53–86 mmol/mol (7.0–10%) were enrolled in two randomized, placebo-controlled, double-blind trials of saxagliptin 2.5, 5 or 10 mg/day. Patients rescued during or completing 24 weeks of treatment could continue in a 42-month long-term blinded phase, for which the primary goal was assessment of safety and tolerability. Between-group efficacy was not evaluated in the long-term phase of study 11. Time to rescue or discontinuation because of inadequate glycaemic control, change from baseline in HbA1c and percentages of patients achieving HbA1c < 53 mmol/mol (< 7.0%) were assessed in study 14.

Results No new safety findings were noted during the long-term phase. Most adverse events were mild or moderate, with slightly greater frequency of upper respiratory infections with saxagliptin. Hypoglycaemic event rates were similar with saxagliptin and placebo. In study 14, time to rescue or discontinuation because of inadequate glycaemic control was longer with saxagliptin plus metformin than for placebo plus metformin. From baseline to week 154, HbA1c decreased with saxagliptin but increased with placebo.

Conclusion Saxagliptin monotherapy or add-on to metformin is generally safe and well tolerated, with no increased risk of hypoglycaemia, for up to 4 years.

What’s new?

- This report evaluated the safety of saxagliptin ± metformin in patients with Type 2 diabetes over 4 years of treatment; this is the first report of any dipeptidyl peptidase-4 (DPP-4) inhibitor over this time frame.
- The results show that saxagliptin, with or without metformin, is generally safe and well tolerated, with no increased risk of hypoglycaemia, for up to 4 years of treatment.
- Because Type 2 diabetes is a chronic, progressive disease, limiting hyperglycaemic exposure over time requires intensification of treatment.

Patients requiring rescue in study 11 continued taking blinded study medication (saxagliptin or metformin 500 mg/day plus placebo) but also received open-label metformin up to 2000 mg/day. In study 14, rescued patients received blinded study medication (saxagliptin or placebo) plus pioglitazone up to 30 or 45 mg/day (study site dependent). Rescue criteria were fasting plasma glucose > 13.3 mmol/l at weeks 4 and 6; > 12.3 mmol/l at week 8; and > 11.2 mmol/l at weeks 12–24; HbA1c > 64 mmol/mol (8.0%) at weeks 30–50; > 58 mmol/mol (7.5%) at weeks 63–76; and > 53 mmol/mol (7.0%) at weeks 89–193. Patients with persistent hyperglycaemia after 12 weeks on maximum dosages of rescue medication were discontinued from the study.

Endpoints

Safety and tolerability endpoints included adverse events, serious adverse events and hypoglycaemia (reported episodes and episodes confirmed by finger-stick glucose concentration ≤ 2.8 mmol/l), discontinuations as a result of adverse events, and clinically relevant changes in laboratory assessments, electrocardiograms, body weight or vital signs.

The main efficacy endpoint during the long-term phase was time to rescue or study discontinuation as a result of inadequate glycaemic control. Other outcomes included change from baseline in HbA1c and percentages of patients achieving HbA1c < 53 mmol/mol (< 7.0%). There was no analysis of long-term efficacy in study 11 because patients who received placebo and completed 24 weeks of treatment without rescue received metformin 500 mg/day added to blinded study medication during the 4-year treatment period (hereafter, this group is referred to as ‘placebo/metformin’).

Statistical analyses

The safety population included all patients who received ≥ 1 dose of double-blind study medication. In study 14, time to rescue or discontinuation because of inadequate glycaemic control was estimated by Kaplan–Meier analysis. For analyses of change from baseline in HbA1c and HbA1c < 53 mmol/mol (< 7.0%) (assessed using last observation carried forward), only data prior to rescue and at timepoints for which ≥ 10% of patients had observed data were included.

Results

Patients

Patient demographics and baseline disease characteristics were previously reported for both studies [6,7]. In study 11, the proportions of patients who discontinued from the study were similar across treatment groups (Table 1). In study 14, discontinuations were higher in the placebo group compared with the saxagliptin groups. The most common reason for discontinuation was inadequate glycaemic control.

Safety

Most adverse events were of mild to moderate intensity, and no new safety findings were noted during the long-term phase (Table 1). The most common adverse events were infections and infestations in both study 11 (55.9% of all saxagliptin-treated patients and 49.5% of placebo-treated patients) and study 14 (60.3% with saxagliptin and 57.5% with placebo). Serious adverse event incidence was low across treatment groups. No dose-related trends in adverse events were observed. No specific type of adverse event was predominant leading to study discontinuation. In sensitivity analyses of data collected before rescue medication, the distribution of adverse events was similar.

Study 11

The proportion of patients reporting any adverse event was higher with saxagliptin (all groups combined, 88.2%) than with placebo/metformin (81.1%), but the proportion with treatment-related adverse events was lower with saxagliptin (23.9%) than with placebo/metformin (26.3%) (Table 1). The proportions of patients with ≥ 1 serious adverse event were similar for saxagliptin (12.4%) and placebo/metformin (11.6%). Discontinuations related to adverse events were more frequent with saxagliptin (9.5%) than with placebo/metformin (5.3%).

Reported hypoglycaemia was similar across treatment groups (Table 1). Two cases of confirmed hypoglycaemia with saxagliptin were of moderate intensity; neither required medical intervention or third-party assistance.

No consistent or clinically relevant changes in body weight, body mass index or waist circumference occurred during the study. Two saxagliptin-treated patients (one each in the saxagliptin 5- and 10-mg groups) developed pancreatitis (one of moderate intensity and unrelated to treatment, the other of mild intensity and possibly related to treatment); both cases resolved after study medication discontinuation.
Mean absolute lymphocyte counts remained within the normal range in all treatment groups throughout the study.

During the short-term phase, one patient receiving saxagliptin 5 mg developed supraventricular tachycardia, considered possibly treatment related. An elderly woman in the placebo/metformin group died of cerebral haemorrhage 8 days after a myocardial infarction; this death was not considered treatment related.

**Study 14**

The proportion of patients reporting any adverse event was higher with saxagliptin plus metformin (all groups combined, 87.4%) than with placebo plus metformin (79.3%), but the proportion with treatment-related adverse events was similar between treatments (31.0 vs 31.3%) (Table 1). The proportions of patients reporting serious adverse events were higher in all saxagliptin groups combined (12.8%) than in the placebo group (8.4%). Compared with placebo plus metformin, saxagliptin plus metformin was associated with higher rates of discontinuation related to adverse events (7.4 vs 5.0%) and serious adverse events (2.8 vs 0.0%).

Reported hypoglycaemic episodes were similar across treatment groups (Table 1). Confirmed hypoglycaemia, reported in eight patients receiving saxagliptin (1.4%) and
one patient receiving placebo (0.6%), was mild to moderate in intensity and did not require medical intervention or third-party assistance.

Mean body weight decreased in all treatment groups. No pancreatitis was reported. Mean lymphocyte counts remained within the normal range in all groups throughout the 4-year treatment period.

Treatment-related serious adverse events were reported in four patients receiving saxagliptin plus metformin and in one patient receiving placebo plus metformin (Table 1). Two patients receiving saxagliptin plus metformin and two patients receiving placebo plus metformin died; none were considered treatment related.

Efficacy

In study 14, time to discontinuation or rescue for inadequate glycaemic control was longer with saxagliptin plus metformin than with placebo plus metformin (Fig. 1), with a mean (SD) duration of study medication exposure of 70.4 (56.9) weeks, 71.8 (61.6) weeks and 78.2 (63.5) weeks in the saxagliptin 2.5, 5 and 10 mg plus metformin groups, respectively, compared with 45.4 (46.2) weeks in the placebo group.

From baseline to week 154, HbA1c decreased in patients receiving saxagliptin 2.5, 5 and 10 mg plus metformin [−4 mmol/mol (−0.4%), −5 mmol/mol (−0.4%) and −2 mmol/mol (−0.2%), respectively] but increased in patients receiving placebo plus metformin [1 mmol/mol (0.1%)]. At week 154, the proportions of patients who achieved HbA1c < 53 mmol/mol (< 7.0%) were 19, 24 and 28% with saxagliptin 2.5, 5 and 10 mg plus metformin, respectively, and 13% with placebo plus metformin (last observation carried forward).

Discussion

No dose-related trends in adverse events or meaningful differences in short-term (24-week) vs. long-term safety were noted with saxagliptin treatment of up to 4 years. The most frequent adverse events with both saxagliptin and placebo were infections. Saxagliptin did not appear to increase the risk of hypoglycaemia when used as monotherapy, with or without metformin rescue (study 11), or in combination with metformin, with or without pioglitazone rescue (study 14). In these trials, neither saxagliptin nor placebo was associated with increased body weight.

The progressive loss of data over the 4 years, in part attributable to the increasingly stringent rescue criteria, limited the ability to draw definitive conclusions about the long-term efficacy of saxagliptin. However, given the progressive nature of Type 2 diabetes and the mean baseline HbA1c of 64 mmol/mol (8.0%) [7], relatively few patients could be expected to maintain HbA1c < 53 mmol/mol (< 7.0%) for 4 years. Nevertheless, in study 14, time to discontinuation or rescue for inadequate glycaemic control was numerically longer and overall rates of discontinuation and rescue were numerically lower for saxagliptin vs. placebo over the long term, with a greater proportion of patients sustaining target HbA1c up to 4 years.

Despite limitations on efficacy evaluation, these long-term studies demonstrate that treatment with saxagliptin, with or without metformin, is generally safe and well tolerated, with no increased risk of hypoglycaemia, for up to 4 years, the longest-duration safety data set so far of any DPP-4 inhibitor ever reported. However, the results suggest that DPP-4 inhibitors alone may not alter the natural history of Type 2 diabetes over the long term. As Type 2 diabetes is a chronic,
progressive disease, the need to limit hyperglycaemic exposure over time requires progressive escalation of treatment.

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**Competing interests**

JR has served on scientific advisory boards and received honorarium or consulting fees from Pfizer, Roche, Sanofi, Novo Nordisk, Eli Lilly, MannKind, GlaxoSmithKline, Takeda, Daiichi Sankyo, Johnson & Johnson, Novartis and Boehringer Ingelheim, and has received grants/research support from Merck, Pfizer, Sanofi, Novo Nordisk, Roche, Bristol-Myers Squibb, Eli Lilly, Forest, GlaxoSmithKline, Takeda, Novartis, AstraZeneca, Amylin, Johnson & Johnson, Daiichi Sankyo, MannKind, and Boehringer Ingelheim. JLG has served on scientific advisory boards for Pfizer, Bristol-Myers Squibb, Eli Lilly, Novo Nordisk and has received grants/research support from Pfizer, Bristol-Myers Squibb, Eli Lilly, Novo Nordisk, Takeda. CA-S has received research support from Bristol-Myers Squibb and Sanofi-Aventis. MH has received grant/research support from Bristol-Myers Squibb, Eli Lilly, and Sanofi-Aventis. SR and DF are employees of and hold stock in Bristol-Myers Squibb. NB is an employee of AstraZeneca, was an employee of Bristol-Myers Squibb at the time this study was conducted, and holds stock in Bristol-Myers Squibb.

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**References**


