Efficacy of saxagliptin as an add-on to oral monotherapy in the phase 3 clinical development program: Predictive factors of the treatment response in type 2 diabetes

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Abstract

Saxagliptin, a dipeptidyl peptidase-4 inhibitor, has been the focus of a large clinical development programme, including Phase 3 randomized vs placebo-controlled clinical trials as add-on therapy in patients with type 2 diabetes (T2D) with inadequate glycemic control using initial monotherapy (metformin, glibenclamide, thiazolidinedione). This clinical programme has shown saxagliptin to be effective in the control of fasting and postprandial glycemic parameters, in addition to a good overall safety profile. The present paper aims at reviewing the overall short-term and long-term efficacy of saxagliptin in its Phase 3 development program and tries to pinpoint some factors that may be more predictive of treatment response in clinical practice. In individual and pooled analyses of the three pivotal add-on to monotherapy trials, saxagliptin (5 mg once daily) led to significant reductions in HbA1c from baseline to 24 weeks. Additional analyses showed that reductions in HbA1c were maintained in the long-term, notably for 102 weeks, in combination with metformin. Data have also shown that the absolute reduction in HbA1c seen with saxagliptine from
baseline to Week 24 was numerically greater with an elevated baseline HbA1c. In these recently published pooled analyses, clinically pertinent reductions in HbA1c were also obtained with saxagliptin across a wide range of subgroups of T2D patients when examined either by specific baseline demographic characteristics or by β-cell function indices such as the HOMA-β.

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1. Introduction

Saxagliptin is a potent selective dipeptidyl peptidase-4 inhibitor, recently approved in the member states of the European Community for the treatment of adult patients with type 2 diabetes (T2D).

The aim of this article is to review the overall efficacy of saxagliptin by assessing its effect on HbA1c reduction in some of the key pivotal add-on to monotherapy trials that were part of the registrational Phase 3 programme of saxagliptin in Europe. This article will also discuss the influence that the baseline HbA1c and other factors might have on the therapeutic response. Individual responses to therapeutic agents both in diabetes therapeutic area as well as outside are heterogeneous. As the absolute reduction from baseline in HbA1c is a key factor for evaluating the efficacy of new diabetes treatments, it is primordial to investigate what factor(s) might be predictors of HbA1c response in clinical practice. The influence of the level of glycemic control at inclusion in the study of T2D patients seems to play a major role in the HbA1c response to antidiabetic treatment [1,2]. Moreover, demographic characteristics of patients such as beta cell function, sensitivity or resistance to insulin and other variables may have an influence as well [3,4].

2. Incretin hormones

The incretin hormones (glucagon-like peptide 1 or GLP-1 and glucose-dependent insulinotropic polypeptide or GIP), which are rapidly secreted by the distal intestine in response to food intake, play a significant physiological role in glucose homeostasis, particularly in the regulation of postprandial hyperglycaemia. GLP-1, which seems to have a more marked effect than GIP, stimulates the early secretion of insulin by the pancreatic beta cells and decreases glucagon secretion by the alpha cells of the islets of Langerhans [5–9]. This results in inhibition of the postprandial hepatic production of glucose and an increase in the peripheral use of glucose through the effect of insulin.

GLP-1 activity is said to be glucose-dependant, meaning that it acts uniquely in presence of elevated blood glucose and in relation to meals [5–7]. It has been shown however that GLP-1 secretion is retained but significantly reduced in patients with T2D compared to healthy subjects [10]. GLP-1 has a very short half-life of around 2 minutes due to very rapid physiological degradation through cleavage by a proteolytic enzyme, the dipeptidyl peptidase-4 (DPP-4) [5–7]. This phenomenon subsequently led to the development of DPP-4-inhibitors, several of which are now available in oral form, for prolonging and potentiating the incretin effect of GLP-1 [11]. These drugs induce an increase in the circulating concentration of GLP-1 in T2D patients, with a glucose-dependant effect. In addition, DPP-4-inhibitors have a specific action on the alteration of alpha cell secretion, which differentiates them from the other classes of available oral antidiabetic agents [11].

3. Saxagliptin: main properties

Saxagliptin is a highly potent (Ki: 1.3 nM), selective, reversible and competitive DPP-4 inhibitor [12–15]. In patients with T2D, the administration of saxagliptin led to the inhibition of DPP-4 enzyme activity for a 24-hour period. After an oral glucose load, the inhibition of DPP-4 resulted in a 2 to 3-fold increase of circulating levels of active incretin hormones (GLP-1 and GIP), a reduction in glucagon concentrations and an increase in glucose-dependent beta cell responsiveness, resulting in higher C peptide and insulin concentrations. The increased secretion of insulin by pancreatic beta cells and the decreased glucagon secretion by pancreatic alpha cells were associated with lower fasting glucose concentrations and a reduction in glucose excursion following an oral glucose load or a meal. Saxagliptin thus improves glycemic control by reducing fasting and postprandial glucose concentrations in patients with T2D [16].

4. Phase 3 clinical trials conducted with saxagliptin

Saxagliptin has been the focus of a large clinical development programme, which includes six randomized, double-blind, placebo-controlled clinical trials comparing safety and efficacy, and which included a total of 4148 patients with T2D, 3021 of whom received saxagliptin [16]. The systematic analysis of events occurring during this clinical trial programme [17] showed the absence of an increased risk of cardiovascular death, myocardial infarction and stroke. This clinical development enabled the marketing authorisation (MA) for saxagliptin (5 mg tablet in a single daily dose) to be granted in the member states of the European Community [16,18], the therapeutic indications being the improvement of glycemic control in adult patients with T2D:

- in combination with metformin, when metformin alone, with diet and exercise, does not provide adequate glycemic control;
- in combination with a sulfonylurea, when the sulfonylurea alone, with diet and exercise, does not provide adequate glycemic control in patients for whom use of metformin is considered inappropriate;
- in combination with a thiazolidinedione, when the thiazolidinedione alone with diet and exercise, does not provide adequate glycemic control in patients for whom use of a thiazolidinedione is considered appropriate.
Among these Phase 3 studies, there were three trials with an initial duration of 24 weeks [19–21] that evaluated saxagliptin in combination therapy after failure of oral monotherapy [18]:

- one trial assessing add-on therapy with metformin in T2D patients with inadequate control with metformin alone at the maximum tolerated dose [19];
- one trial assessing add-on therapy with a sulfonylurea, glibenclamide, in T2D patients with inadequate control with glibenclamide alone [20];
- one trial assessing add-on therapy with a thiazolidinedione (glitazone), pioglitazone or rosiglitazone, in T2D patients with inadequate control with the glitazone alone at the maximum tolerated dose [21].

Details of these trials will not be provided here. Only the results of the saxagliptin group at 5 mg (daily dose selected for the MA) are considered in this article. Table 1 summarizes results of the saxagliptin group at 5 mg (daily dose selected for use by the Marketing Authorisation from the European Medicines Agency) in three Phase 3 24-week clinical trials in patients with type 2 diabetes inadequately controlled with monotherapy.

<table>
<thead>
<tr>
<th>Study/Treatment</th>
<th>n/N</th>
<th>Baseline mean HbA1c (SE)</th>
<th>W24 mean HbA1c (SE)</th>
<th>Adjusted mean change from baseline (SE)</th>
<th>Difference from control (placebo in adjusted mean change from baseline [95% CI])</th>
</tr>
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<tbody>
<tr>
<td>DeFronzo, et al. [19]</td>
<td></td>
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<td></td>
<td></td>
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<tr>
<td>Saxa 5 mg + Met</td>
<td>186/191</td>
<td>8.07 (0.06)</td>
<td>7.37 (0.08)</td>
<td>–0.69 (0.07)</td>
<td>–0.83</td>
</tr>
<tr>
<td>Placebo + Met</td>
<td>175/179</td>
<td>8.06 (0.07)</td>
<td>8.19 (0.09)</td>
<td>+0.13 (0.07)</td>
<td>[–1.02,–0.63]</td>
</tr>
<tr>
<td>Chacra, et al. [20]</td>
<td></td>
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<tr>
<td>Saxa 5 mg + Glib</td>
<td>250/253</td>
<td>8.48 (0.056)</td>
<td>7.83 (0.074)</td>
<td>–0.64 (0.059)</td>
<td>–0.72</td>
</tr>
<tr>
<td>Placebo + Glib</td>
<td>264/267</td>
<td>8.44 (0.055)</td>
<td>8.52 (0.077)</td>
<td>+0.08 (0.057)</td>
<td>[–0.88,–0.56]</td>
</tr>
<tr>
<td>Hollander, et al. [21]</td>
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<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Saxa 5 mg + TZD</td>
<td>183/186</td>
<td>8.35 (0.080)</td>
<td>7.39 (0.086)</td>
<td>–0.94 (0.075)</td>
<td>–0.63</td>
</tr>
<tr>
<td>Placebo + TZD</td>
<td>180/184</td>
<td>8.19 (0.080)</td>
<td>7.91 (0.100)</td>
<td>–0.30 (0.076)</td>
<td>[–0.84,–0.42]</td>
</tr>
</tbody>
</table>

Adapted from [18].

Mean ± standard error (m ± SE) for the whole population of randomized subjects in each study; *P <0.0001; n: number of subjects with HbA1c at baseline and at W24; N: number of subjects randomized; 95% CI: 95% confidence interval.

In this table, only data from the saxagliptin 5 mg od group (dose indicated for use by the Marketing Authorisation from the European Medicines Agency) group and from the comparator group (Met: metformin; Glib: glibenclamide; TZD: thiazolidinediones) are presented. The DeFronzo, et al study also included a saxagliptin 2.5 mg od group and a saxagliptin 10 mg od group; the Chacra et al. study also included a saxagliptin 2.5 mg od group; the Hollander et al. study also included a saxagliptin 2.5 mg od group.

In the three previously cited trials [19–21], the patients that presented at all the scheduled visits over the first 24 weeks of the trial, whether or not they required hyperglycaemia rescue treatment, were eligible for a long-term controlled extension trial of at least 12-month duration. These trial extensions underwent an interim analysis at 76 weeks (cumulative duration of treatment) for the trials studying add-on therapy with sulfonylurea and add-on therapy with a glitazone, and at 102 weeks for the add-on to metformin trial.

At the end of the cumulative duration of treatment in these three studies, the patients that received saxagliptin had better glycemic control than those that received the placebo; the reduction in HbA1c, in the postprandial blood glucose and the fasting blood glucose in patients that had initially been treated with saxagliptin 5 mg were maintained over time [16,18].

In the trials with a treatment duration of 76 weeks (W76), there was a –0.8% variation in HbA1c at W76 between saxagliptin 5 mg + glitazone (n = 82) and the placebo + glitazone combination (n = 53). This difference was –0.7% at W76 between saxagliptin 5 mg + an intermediate fixed dose (7.5 mg) of glibenclamide (n = 56) compared to the titration of glibenclamide (final daily dose of 15 mg in around 92% of patients) + placebo (n = 27) [16,18].

The variation in HbA1c over time for the trial with the longest treatment duration (102 weeks total) is presented in Fig. 1. At Week 102, the mean decrease in HbA1c obtained with the combinations of saxagliptin + metformin vs placebo + metformin was –0.8% [confidence interval of 95% (95% CI): –0.94, –0.50], starting the trials were variable, ranging from around 8.1% with metformin [19] to close to 8.5% with the sulfonylurea [20].

5. Changes in HbA1c during long-term follow-up in type 2 diabetes patients treated with saxagliptin
indicating that the reduction of HbA1c observed at W24 was maintained at W102 (−0.83 (−1.02, −0.63); P < 0.0001) [16,18].

6. Influence of the baseline HbA1c level in the trials on the therapeutic response

Several authors have emphasized the influence of the baseline HbA1c on the therapeutic response to an antidiabetic agent [1,2], particularly when the study includes a large population, covering both recently diagnosed and long-standing T2D. In the Phase 3 clinical trial programmes with saxagliptin, the mean time since diagnosis of the diabetes (mean ± SD) was 6.3–6.7 ± 4.4–5.6 years (n = 743) in the trial of add-on therapy to metformin [19]; 6.8–7.1 ± 5.7–5.9 years (n = 768) in the trial of add-on therapy to glibenclamide [20]; and 5.1–5.3 ± 4.6–5.6 years (n = 565) in the trial of add-on therapy to a glitazone [21]. It was therefore legitimate to perform a specific pooled analysis of these three add-on to monotherapy trials and attempt to dissect the relative impact of baseline HbA1c levels on the HbA1c reduction from baseline.

The data of the three studies of add-on therapy combined with initial monotherapy [19–21] were pooled in order to assess the relationship between the baseline HbA1c and the HbA1c reduction observed at W24 in the T2D patients receiving saxagliptin 5 mg (n = 630) compared to those receiving a placebo as add-on therapy to initial monotherapy (n = 630) [22] (Fig. 2).

The pooled data analysis confirmed that saxagliptin 5 mg added to monotherapy that did not provide adequate glycemic control (HbA1c level at inclusion: 8.3%) resulted in an overall reduction in the HbA1c level at W24 compared to placebo. This reduction in HbA1c however was numerically greater when the HbA1c was higher (Fig. 2).

The analysis of these data also shows that the proportion of patients who attain at W24 the objective recommended by the American Diabetes Association (ADA) [23] of HbA1c less than 7%, without associated symptomatic hypoglycemia events, is consistently greater in those receiving saxagliptin 5 mg compared to those receiving the placebo (Fig. 3). It should be emphasized that out of the patients with an HbA1c close to the objective (< 7.5%) at inclusion, more than half (52%)...
achieved the objective at W24 without having presented with hypoglycaemic events over the 24 weeks.

7. Influence of baseline patient characteristics in the trials on the therapeutic response

The data from the three aforementioned trials evaluating add-on treatment to initial monotherapy [19–21] were pooled in order to assess whether there were differences in the reduction of HbA1c observed at W24 according to the subgroups of baseline demographic characteristics in T2D patients receiving saxagliptin 5 mg (n = 630) compared with those receiving the placebo (n = 630) [24]. The baseline demographic characteristics in T2D patients included in this pooled analysis appear to be well distributed between each treatment group (Table 2). At W24, the mean placebo-corrected HbA1c decreased from −0.42% to −1.00% (Fig. 2). For the main characteristics and defined subgroups [sex: men/women; body mass index (BMI): < 30 kg/m² and ≥ 30 kg/m²; age: < 65 years and ≥ 65 years; renal function, defined by the calculated creatinine clearance: ≤ 80 mL/min and > 80 mL/min], the mean reduction of the HbA1c level vs placebo was similar overall (Fig. 4). A numerically greater reduction of the mean HbA1c from baseline was noted for the subgroup of T2D patients with the longest duration of diabetes (≤ 1.5 years vs ≥ 10 years) and the group with the lowest beta cell function (≤ 58.6 vs > 58.6) as assessed by the Homeostasis Model Assessment-2β (HOMA-2β) Index.

Table 2

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>SAXA 5 mg</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD), years</td>
<td>54.3 (10.1)</td>
<td>54.7 (10.4)</td>
</tr>
<tr>
<td>Gender, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>302 (47.9)</td>
<td>304 (48.3)</td>
</tr>
<tr>
<td>Female</td>
<td>328 (52.1)</td>
<td>326 (51.7)</td>
</tr>
<tr>
<td>Race, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>409 (64.9)</td>
<td>403 (64.0)</td>
</tr>
<tr>
<td>Black</td>
<td>28 (4.4)</td>
<td>21 (3.3)</td>
</tr>
<tr>
<td>Asian</td>
<td>115 (18.3)</td>
<td>118 (18.7)</td>
</tr>
<tr>
<td>Others</td>
<td>78 (12.4)</td>
<td>88 (14.0)</td>
</tr>
<tr>
<td>BMI, mean (SD), kg/m²</td>
<td>30.0 (4.9)</td>
<td>30.0 (5.2)</td>
</tr>
<tr>
<td>Duration of T2D, mean (SD), years</td>
<td>6.2 (5.5)</td>
<td>6.3 (5.6)</td>
</tr>
<tr>
<td>Baseline HbA1c, mean (SD), %</td>
<td>8.3 (0.9)</td>
<td>8.3 (1.0)</td>
</tr>
<tr>
<td>Fasting plasma glucose, mean (SD), mg/dL</td>
<td>172.0 (46.2)</td>
<td>170.9 (44.2)</td>
</tr>
</tbody>
</table>

BMI: body mass index; CI: confidence interval; HbA1c, glycosylated haemoglobin; HOMA-2β, homeostasis model assessment 2 β-cell function; SAXA, saxagliptin; T2D, type 2 diabetes.
8. Discussion

The reduction of HbA1c at 24 weeks that was observed in the clinical trials when saxagliptin (5 mg in one daily administration) was added to initial monotherapy that did not provide adequate glycemc control resulted in a clinically significant reduction of HbA1c for all of the subgroups of T2D patients analysed [24].

Other systematic reviews and analyses found comparable efficacy [29–32], although the reported mean reductions of HbA1c varied according to the tested therapeutic modalities (monotherapy or in combination with various classes of oral antidiabetics). This efficacy of saxagliptin on glycemic control at 24 weeks was maintained over time, with a similar reduction observed at 102 weeks when added as a combination with metformin, and at 76 weeks when combined with a sulfonylurea or a glitazone. These results show that the use of saxagliptin has lasting efficacy on the glycemic control of T2D patients. However, as seen in the pooled analysis of the three trials combining saxagliptin with an initial drug monotherapy, the mean reductions of HbA1c at 24 weeks mask the different response rates according to baseline HbA1c, with the reduction of HbA1c being numerically greater with a higher baseline HbA1c [22]. The relative efficacy of one therapeutic class compared to others or of different drugs within the same class therefore cannot be determined through the simple comparison of the mean reductions of HbA1c in clinical trials; in the absence of direct comparative studies, the baseline HbA1c is therefore a crucial factor to consider when such comparisons are desired. This has already been acknowledged by Bloomgarden et al. who highlighted that an initially low level of glycaemia (fasting glycaemia and HbA1c) was associated with apparent reduced efficacy of oral hypoglycemic treatments. This result was based on 61 clinical studies of oral antidiabetic drugs (sulfonylureas, meglintides, metformin, thiazolidinediones, alpha-glucosidase inhibitors) published before 2004, and which included nearly 9,000 subjects with an overall mean HbA1c of 8.6 ± 1.0%. There was a significant relationship in this study between the mean baseline HbA1c and the mean decrease of HbA1c (R2 = 0.18, F = 21.20, P < 0.0001), and these authors had calculated that the absolute reduction of the HbA1c level vs baseline level was −0.2% for the 6.0–6.9% baseline HbA1c category; −0.1% for the 7.0–7.9% category; −0.6% for the 8.0–8.9% category; −1.0% for the 9.0–9.9% category; and −1.2% for the 10.0–11.8% baseline HbA1c category [1]. Following that, Bloomgarden and Inzucchi resumed this analysis by adding six published comparative clinical trials of two DPP-4 inhibitors, sitagliptin and vildagliptin vs placebo. The addition of these six studies did not modify the significant relationship between the mean baseline HbA1c and the mean decrease of HbA1c [33]. This conclusion was confirmed by DeFronzo et al. who performed a meta-analysis of 59 randomized vs placebo or active comparator trials (8479 patients) lasting 23 to 52 weeks, in which these authors demonstrated a strong positive relationship between the baseline HbA1c and the magnitude of the absolute reduction of HbA1c (R2 = 0.35, P < 0.0001); this relationship was found for the 10 categories of antidiabetic treatment concerned, including injectable and inhaled insulin, irrespective of the class or mode of action [34]. Sherifali et al. recently carried out a systematic review and performed a meta-analysis of 61 trials evaluating the effect of oral antidiabetic agents on the HbA1c level; these trials, describing 103 comparisons, included 26,367 participants, 15,760 of whom were randomized to the intervention drug and 10,607 to the placebo. The majority of the oral antidiabetic agents reduced the HbA1c by 0.5–1.25%. A meta-regression enabled the authors to conclude that a 1%-higher baseline HbA1c predicted an additional 0.5% reduction [95% CI: 0.1–0.9] after 6 months of treatment with oral antidiabetics. They noted however that the duration of diabetes had no apparent effect on the variation in HbA1c [35]. One other recent evaluation compared the effects of antidiabetic drugs acting on the incretin axis to those of other classes of diabetic drugs in combination with metformin alone that did not control diabetes. It concluded that the efficacy of incretin mimetics and DPP-4 inhibitors in controlling glycaemia was comparable to that of conventional antidiabetic drugs when combined with metformin [36]. A similar observation was reported by Phung et al. for the combination of different classes of antidiabetic agents with metformin, with the exception of insulin [4]. This evaluation highlights the fact that although the mean reduction of the HbA1c level observed...
after adding insulin seemed higher, it reflects a much higher mean baseline HbA1c of around 9.6–9.8%: it also shows that although the proportion of patients attaining the objective of HbA1c less than 7% is variable, regardless of the antidiabetic class considered, this is partly dependent on the baseline conditions [36]. Finally, Chapell et al. noticed that the different published trials suggested that there was a greater reduction of HbA1c in T2D patients treated with rosiglitazone or pioglitazone than with sitagliptin; the trials conducted with the thiazolidinediones however tended to include patients with a higher baseline HbA1c. After selecting 23 homogeneous trials (six trials with rosiglitazone at a dose of 4 to 8 mg/day, seven trials with pioglitazone at a dose of 30 to 45 mg/day and 10 trials with sitagliptin at a dose of 100 mg/day), these authors carried out a meta-analysis using a Bayesian model that included an adjustment factor for the differences in baseline HbA1c between trials, with the mean baseline HbA1c in these trials ranging from 6.1% to 10.4%. By using this model, the difference in efficacy between rosiglitazone and sitagliptin was then not significant [0.12 (95% CI: −0.09 to 0.34)]. Similarly, there was no significant difference between the effects of pioglitazone and sitagliptin [0.01 (95% CI: −0.21 to 0.22)] or between those of rosiglitazone and pioglitazone [0.11 (95% CI: −0.37 to 0.146)]; these results enabled the authors to conclude that when the differences of therapeutic effect between trials are adjusted for the baseline HbA1c difference, the analysis suggests that none of the tested treatments has a greater effect than the two others [2]. This analysis technique however did not take into account the baseline HbA1c differences within the same trial, which was the main strength of the pooled analysis done by Maheux et al. on three studies of saxagliptin added to a pre-existing oral antidiabetic drug [22], and which thus clarified and reinforced the initial conclusions of Bloomgarden et al. [1,33].

The therapeutic response may also be influenced by other factors. Cantrell et al. thus did a review of articles published in the last 10 years examining and describing factors associated with the therapeutic response to pharmacological treatments in T2D patients, including insulin [3]. Out of the 43 selected articles, 35 (81%) discussed clinical factors, 31 (72%) described sociodemographic factors and 17 (40%) reported the comorbidities and associated behavioural factors. Although their analysis was limited by the frequent combination of several antidiabetic treatments, by the methods and/or different definitions used in these articles and by the fact that the identification of factors associated with the therapeutic response in T2D patients was generally only a secondary objective of the studies, these authors assessed the role of patient heterogeneity on the therapeutic response and the factors that were likely to alter the interpretation of results on the efficacy of the antidiabetic treatments. They concluded that consideration of the initial level of glycaemia (HbA1c, and fasting blood glucose) was a critical element for interpreting the results in terms of therapeutic efficacy; they particularly emphasized that when a new antidiabetic agent is added to pre-existing treatment, high HbA1c levels are associated with a greater magnitude of HbA1c reduction. They speculated that this apparent difference in efficacy could be related to a more advanced stage of the diabetic disease [3]; the pharmacological treatments represented in the analysed articles however do not include any DPP-4 inhibitors. However, the pooled analysis done on a large population of T2D patients included in three of the saxagliptin Phase 3 add-on trials did not suggest that baseline β-cell function was a true predictor of efficacy as patients with low β-cell function at baseline actually seemed to have greater reduction in HbA1c at W24. These pooled analyses done with saxagliptin therefore suggest that this DPP-4 inhibitor results in a clinically pertinent reduction in HbA1c, regardless of the categories and subgroups established according to the initial characteristics of the patients.

Genetic characteristics could nevertheless be involved in the interindividual variability of response to antidiabetic treatments. The role of a genetic polymorphism coding for TCF7L2 (transcription factor 7-like 2), as a major risk factor of T2D, has been suggested for many years in many studies, but this polymorphism is also associated with an altered capability of GLP-1 (and GIP) to stimulate insulin secretion [37,38], and TCF7L2 seems to be necessary for GLP-1 expression in the pancreatic beta cells [39]. Similarly, recent genome-wide association studies have identified a series of novel T2D risk genes and variants, the majority of them, such as the transmembrane factor GIP-R, WFS1 (Wolfram syndrome 1, or wolframin) and KCNQ1 (KQT-like subfamily, member 1), in addition to TCF7L2, being determinants of an impaired beta cell secretory function and/or associated with an alteration in glucose-stimulated insulin secretion, proinsulin conversion to insulin and incretin signals, likely to affect the secretion, sensitivity or action of incretin hormones (review in [40]). The discovery of these genetic variants and their influence on the incretin hormones suggests that they could constitute a factor of variability in the therapeutic response and raises the question as to whether certain T2D patients are more sensitive than others to drugs acting on the incretin hormone axis, indicating the possibility, in the future, to use molecular approaches to determine the therapeutic response of drug acting on this axis [8].

9. Conclusion

Saxagliptin, a DPP-4 inhibitor, is an effective and durable therapeutic alternative for managing type 2 diabetes in combination with other oral antidiabetic agents. Saxagliptin has a good safety profile, associated with a low risk of hypoglycaemia and a neutral body weight effect.

Pooled subgroup analysis showed that HbA1c reductions were greatest in those patients with higher baseline HbA1c values, reinforcing the potential role of saxagliptin as an early add-on therapeutic option; HbA1c lowering from baseline was also greater than placebo across diverse demographic and diabetes subgroups. It supports the use of saxagliptin 5 mg once daily, as an add-on therapy, in a broad range of type 2 diabetic patients.

Disclosure of interest

J.-F. G.
References


