DPP-4 inhibitors and their potential role in the management of type 2 diabetes

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SUMMARY
The dipeptidyl peptidase 4 (DPP-4) inhibitors enhance the body’s own ability to control blood glucose by increasing the active levels of incretin hormones in the body. Their mechanism of action is distinct from any existing class of oral glucose-lowering agents. They control elevated blood glucose by triggering pancreatic insulin secretion, suppressing pancreatic glucagon secretion, and signalling the liver to reduce glucose production. The leading DPP-4 inhibitors have shown clinically significant HbA1c reductions up to 1 year of treatment and offer many potential advantages over existing diabetes therapies including a low risk of hypoglycaemia, no effect on body weight, and the potential, based on animal and in vitro studies, for the regeneration and differentiation of pancreatic β-cells. They are efficacious as monotherapy and also in combination with commonly prescribed antidiabetic agents and are suitable for once-daily oral dosing. Consequently, many DPP-4 inhibitors such as vildagliptin (Galvus; LAF-237), sitagliptin (Januvia; MK-0431), and saxagliptin (BMS-477118) have advanced into late-stage human clinical trials.

Search strategy and selection criteria This review was built on a systematic MEDLINE search for publications on the subject with the key words: DPP-4 inhibitor; vildagliptin (LAF-237); sitagliptin (MK-0431); saxagliptin (BMS-477118); and type 2 diabetes; up to August 2006. Meeting abstracts were also searched, as much of the data currently only exists in abstract form.

Take home message for clinician The DPP-4 inhibitors appear to have great potential for the treatment of type 2 diabetes, but time will tell if this will be realized. While they do not lower glucose to a greater extent than existing therapies, they offer many potential advantages, including the ability to achieve sustainable reductions in HbA1c with a well-tolerated agent that has a low risk of hypoglycaemia and no weight gain, and which can be administered as a once-daily oral dose.

Keywords: DPP-4 inhibitor; vildagliptin, sitagliptin, saxagliptin, type 2 diabetes

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INTRODUCTION
In the natural history of type 2 diabetes, the development of insulin resistance, impaired glucose tolerance and finally type 2 diabetes occurs gradually over many years. Pancreatic islet cells are initially able to respond to increased insulin resistance by increasing insulin secretion to maintain normoglycaemia. As the disease develops, however, there is a progressive loss of β-cell function. The resultant hyperglycaemia, if left untreated, can eventually lead to the debilitating vascular complications of type 2 diabetes, including retinopathy, end-stage renal disease, neuropathy and cardiovascular disease.

As type 2 diabetes is a progressive disease, intensification of therapy is normally required over time. While current agents are all generally effective in the short- to medium-term, traditional treatment algorithms often fail to address the progressive nature of the disease. Furthermore, current therapies may also be associated with an increased risk of hypoglycaemia (sulphonylureas and insulin), weight gain (sulphonylureas, thiazolidinediones and insulin), and gastrointestinal intolerance (metformin), which represent major barriers to optimal glycaemic control (1).

Research into the pathophysiology of diabetes has revealed that a complex interplay of hormonal and neural stimuli, not just insulin and glucagon, are involved in the regulation of plasma glucose levels. The development of incretin hormone analogues and compounds that delay their degradation and therefore raise their concentration, and/or compounds that bind to their receptors, may facilitate achievement of optimal glycaemic control. Furthermore, such therapies may target physiological defects not addressed...
by current medications, or may exhibit a mode of action that is additive or synergistic with current therapies. The development of the dipeptidyl peptidase 4 (DPP-4) inhibitors, which potentiate the incretin hormones by inhibiting the enzyme responsible for their degradation, has recently emerged as one such approach that appears promising for the treatment of type 2 diabetes.

**Diabetes and the Incretin Hormones**

The ‘incretin effect’ refers to the amplification of the insulin response to glucose, when delivered orally as opposed to intravenously (2). Incretin hormones are secreted from the gastrointestinal tract during food intake (3). Two incretin hormones, glucose-dependent insulino tropic peptide also called gastric inhibitory polypeptide (GIP), and glucagon-like peptide-1 (GLP-1), have been identified. GLP-1 appears to be responsible for the majority of the incretin effect on pancreatic β-cell function and has become the favoured potential therapeutic target. Secretion of GLP-1 is lower than normal in patients with type 2 diabetes and increasing GLP-1 decreases glycaemia, which suggests that the hormone may contribute to the pathogenesis of the disease (4–6).

The glucoregulatory actions of GLP-1 include: enhancement of glucose-dependent insulin secretion (7); activation of insulin biosynthesis and gene transcription to restore cellular supplies of insulin for subsequent release (8); suppression of inappropriately elevated glucagon secretion (9); slowing of gastric emptying, thereby reducing meal-associated increases in glycaemic excursions (10); suppression of food intake (11,12); and animal data have shown preservation or enhancement of β-cell function as a result of β-cell proliferation and neogenesis and inhibition of apoptosis (13–15). The major therapeutic drawback to using native GLP-1 is its very short half-life of <2 min following exogenous administration, due in part to the protease DPP-4 (16). Thus, while GLP-1 itself cannot be used as a practical therapy the prospect of an agent with multidimensional therapeutic benefits in type 2 diabetes has stimulated the search for therapeutic interventions in the GLP-1 pathway.

There are two current approaches to enhancing endogenous GLP-1 action in vivo: incretin mimetics, such as the GLP-1 analogues and exenatide, and the DPP-4 inhibitors, which potentiate the incretin hormones by inhibiting the enzyme responsible for their degradation (16).

**DPP-4 and DPP-4 Inhibition: Mechanism of Action**

Dipeptidyl peptidase 4, also known as CD 26, is a membrane-associated peptidase of 766 amino acids that is widely distributed in numerous tissues and T-cells, B-cells and natural killer cells. DPP-4 also exists as a soluble circulating form in plasma (17). As a T-cell costimulator, CD 26 is of importance in the immune system. In addition to DPP-4 enzymatic activity, cell surface CD 26 has other signal transferring functions independent of DPP-4, which do not appear to be affected by DPP-4 inhibitors. This may be one reason why the immune-activating component of CD 26 is not affected by DPP-4 inhibitors. DPP-4 exerts its biological effects via two distinct mechanisms of action: as a membrane spanning protein, in which it binds adenosine deaminase and when activated conveys intracellular signals via dimerization and activation of intracellular signalling pathways and as an enzyme (17). The enzymatic activity of DPP-4 is exhibited by both the membrane-spanning and soluble forms of the molecule. DPP-4 preferentially cleaves substrates with a proline residue at the P1 position and accepts most residues at P2 and in prime side positions (18,19). Most inhibitors to date have incorporated a proline or proline mimetic at P1, with either a reversible or an irreversible electrophilic isostere to interact with the active site serine of the enzyme (Figure 1) (14).

![Figure 1: Chemical structures of current DPP-4 inhibitors: vildagliptin, sitagliptin and saxagliptin](image-url)
The DDP-4 inhibitors improve glycaemic control by preventing the rapid degradation of incretin hormones, thereby resulting in postprandial increases in levels of biologically active intact GLP-1 reducing glucose production from the liver by inhibition of glucagon from the α-cells of the pancreas and increasing insulin production. Three DPP-4 inhibitors are in late-stage development: vildagliptin (Galvus; LAF-237 – Novartis), sitagliptin (Januvia; MK-0431 – MSD) and saxagliptin (BMS-477118 – Bristol–Myers Squibb).

Preclinical Studies with DPP-4 Inhibitors

Selectivity

Selective inhibition of DPP-4 is required for an acceptable safety and tolerability profile. At least two human dipeptidyl-peptidases, DPP-8 and DPP-9, whose functions are still unknown, are structurally closely related to DPP-4 and have postproline activity, preferentially cleaving X-proline or X-alanine dipeptides from the N-terminal of polypeptides (20,21). DPP-8 and DPP-9 do not have transmembrane domains and are therefore predicted to be cytosolic proteases, although possibly they are secreted on cellular activation (22). Acute toxicity in animal models was reported for at least one compound with strong DPP-8/DPP-9 inhibitory potency (23). IC$_{50}$ and $K_{i}$ values for DPP-4 have been published for the leading DPP-4 inhibitors (Table 1) (24–28). All have values in the low nanomolar range, with saxagliptin displaying the highest selectivity for DPP-4 (27,28). In contrast, available data show that affinity for DPP-8 and DPP-9 is low (Table 1). It is not known whether in vivo DPP-8 and DPP-9 are inhibited on administration of therapeutic doses of the DPP-4 inhibitors. However, to date no in vivo effects have been reported that point to a pharmacological impact of the inhibition of other peptidases.

Binding

Tight-binding inhibitors are important from a pharmacological point of view, because once bound to their target they inhibit the enzyme function even after the free drug has been cleared from the circulation or the specific site of action, a profile that is important for once-daily dosing. The current DPP-4 inhibitors exhibit slow, tight-binding inhibition kinetics and are reversible competitive inhibitors of DPP-4 (24–28).

Animal models

The DPP-4 inhibitors exhibit excellent oral bioavailability in mice, rats, dogs and monkeys (60 to >90% depending on species), and a halflife ranging from 1 to 5 h (24,27,29). Inhibition of >90% of plasma DPP-4 activity has been demonstrated with vildagliptin, sitagliptin and saxagliptin in rats, mice and monkeys (24,27,29). DPP-4 inhibition has been shown to increase circulating levels of intact GLP-1 and improve glucose tolerance in many animal models of insulin resistance (24,27,30–33). This effect has been attributed to the higher concentrations of intact biologically active GLP-1 arising as a consequence of DPP-4 inhibition (32). Preclinical studies on DPP-4 inhibitors have clearly demonstrated significant potential for their application as therapeutic agents for type 2 diabetes and indicate that glucose tolerance is improved by enhancing many of the biological actions characteristic of GLP-1 receptor agonists [summarized in a recent review by McIntosh et al (34)].

Type 2 diabetes is associated with a progressive decline in β-cell function. Preservation, neogenesis, or restoration of β-cell function is essential to alter or reverse the progression of the insulin secretory defect. Given the observations that GLP-1 can stimulate proliferation and inhibit apoptosis of β-cells in rodents and can promote the differentiation of β-cells from human precursor cells (13,35,36), it seems reasonable to predict that DPP-4 inhibition, leading to increased levels of GLP-1, might also produce beneficial effects on β-cell mass and β-cell survival.

Long-term DPP-4 inhibitor treatment has been shown to both preserve and increase β-cell number through an apparent stimulation of islet neogenesis, and β-cell regeneration (differentiation from precursor cells) and/or enhanced insulin biosynthesis in the rat (35). Histological examination of the pancreas following DPP-4 inhibitor administration in this study demonstrated increased numbers of islets and β-cells (35).

### Pharmacokinetic profile

The DPP-4 inhibitors possess pharmacokinetic properties that support a once-daily dosing regimen (37,38), although they may have a greater glycaemic effect if given twice daily. Studies in healthy volunteers and patients with type 2 diabetes show that these agents are rapidly absorbed ($C_{\text{max}}$ observed in 1–2 h) (37–39) with an absolute oral bioavailability of c. 80–85% (37,40). Moderate hepatic insufficiency has no clinically meaningful effect on the pharmacokinetics.

### Table 1 A comparison of the pharmacokinetic profiles of the DPP-4 inhibitors vildagliptin, sitagliptin and saxagliptin

|          | $IC_{50}$ (nM) | $K_{i}$ (nM) | DPP-4 | DPP-8 | DPP-9 |
|----------|----------------|--------------|-------|-------|-------|
| Vildagliptin (24,25) | 17             | 3.5          | 9     | –     | –     |
| Sitagliptin (26,29)  | 9              | 18           | >50   | >50   | –     |
| Saxagliptin (27,28)  | 0.6            | 26           | –     | –     | –     |
of sitagliptin at a dose of 100 mg/day and no dosage adjustment will be necessary for patients with moderate insufficiency (41).

Renal clearance has been reported as 217 mL/min for vildagliptin (40) and 388 mL/min for sitagliptin (37) and is estimated to account for approximately a third of total body clearance (40). A study of sitagliptin in patients with renal insufficiency has shown that AUC and \( C_{\text{max}} \) values increase with the level of insufficiency (42). Patients with mild renal insufficiency do not require dose adjustment (42,43). However, to obtain an exposure of sitagliptin similar to patients without renal insufficiency, dose reductions may be required in patients with moderate or severe renal insufficiency, or end-stage renal disease (42).

Both \( C_{\text{max}} \) and AUC increase dose proportionally (39). Exposure to vildagliptin (\( C_{\text{max}} \) and AUC) is increased in elderly subjects (\( \geq 70 \) years). As the extent and duration of DPP-4 inhibition are not altered, however, no dosage adjustment is thought to be necessary in the elderly (40). The pharmacokinetics of vildagliptin and sitagliptin are not affected by body mass index (40,44). Available data indicate that the DPP-4 inhibitors in phase 3 clinical trials have a terminal half-life ranging from 8 to 14 h making them suitable for once-daily dosing (44).

Drug interactions

Coadministration of the DPP-4 inhibitors with several other antidiabetic agents and other drugs including metformin (45–47), glyburide (48), pioglitazone (49,50), rosiglitazone (51), simvastatin (52), digoxin (53), and warfarin (54) has not revealed any drug interactions.

Pharmacodynamic Profile

DPP-4 inhibition

Single-dose administration of DPP-4 inhibitors produces long-lasting DPP-4 inhibition in both healthy volunteers (39) and patients with type 2 diabetes (39,44,55) (Figure 2). More than 90% DPP-4 inhibition is achieved with all doses, while the duration of \( > 90\% \) DPP-4 inhibition increases with dose (39,44). The extent and duration of DPP-4 inhibition is not altered by age, gender or body mass index (39,44).

GLP-1

An important function of DPP-4 is to inactivate GLP-1. Administration of the DPP-4 inhibitors to healthy volunteers and patients with type 2 diabetes increases GLP-1 levels by greater than twofold compared with placebo (38,40,44,55,56). Studies with vildagliptin and sitagliptin have shown increased levels of active GLP-1 both at baseline and in response to a meal, suggesting that the effect of DPP-4 inhibitors on glucose tolerance is mediated by the increased active GLP-1 levels (55,57). Only one-third to one-half of the postprandial GLP-1 in the plasma of healthy subjects and patients with type 2 diabetes consists of active GLP-1, the rest being the inactive fragment formed by truncation (58). By raising the proportion of active GLP-1 rather than the total GLP-1 concentration [up to 30 pmol/l after a meal (58)], DPP-4 inhibition results in only modestly elevated plasma levels of GLP-1, supporting the physiological role of GLP-1 without producing GLP-1 concentrations that induce the GLP-1-related side effects.

Insulin and glucagon

Improved metabolic control by DPP-4 inhibition in type 2 diabetes is seen in association with reduced glucagon levels and, despite the lower glycaemia, unaltered insulin levels (45,55). This finding may initially appear surprising in light of the reported effects of GLP-1 to increase insulin secretion in the presence of hyperglycaemia (59). Insulin secretion can improve without changes in circulating insulin levels, however, and when assessing \( \beta \)-cell function it is appropriate to consider insulin levels in the context of the glucose concentration. Thus, unchanged or even decreased insulin levels in the face of decreased glucose could reflect enhanced \( \beta \)-cell responsiveness to glucose,
perhaps with concomitant enhanced insulin sensitivity. Evidence in support of this has been provided by a recent study in which vildagliptin increased insulin secretion at any given glucose level (i.e. improved insulin secretory tone) (60).

β-cell Function

Several studies have demonstrated increased insulin secretion with DPP-4 inhibitors leading the investigators to suggest that DPP-4 inhibitors may be able to improve β-cell function in humans. A phase 2 study in which patients received vildagliptin (100 mg twice daily) vs. placebo for 28 days used a mathematical model to evaluate the effects on β-cell function (60). Vildagliptin significantly increased the insulin secretory rate compared with placebo suggesting that it improves β-cell function (Figure 3). A second phase 2 study explored whether vildagliptin when added to metformin for 1 year could affect β-cell function and insulin sensitivity (61). The study found that meal-related insulin secretion, estimated by determining the C-peptide responses to meal ingestion in relation to the increase in glucose, was increased in the vildagliptin plus metformin vs. placebo plus metformin group for the duration of the 52-week study. The most pronounced effect of vildagliptin was seen during the first 12 weeks of treatment.

The effect of sitagliptin on β-cell function has been assessed by homeostasis model assessment (HOMA-B) in two 24-week studies in which patients were randomized to sitagliptin 100 or 200 mg once daily vs. placebo (46,62). HOMA-B values were significantly increased with sitagliptin relative to placebo suggesting an improvement in β-cell function. To date, the potential effects of saxagliptin on β-cell function have not been reported.

Clinical Studies with DPP-4 Inhibitors

Many DPP-4 inhibitors have entered clinical trials; those in late-stage development include vildagliptin, sitagliptin and saxagliptin. Data are available on the first two in various publications and meeting abstracts, and applications for marketing approval of these two drugs are currently being reviewed by the US Food and Drug Administration. The DPP-4 inhibitors are being evaluated as monotherapy and as combination therapy with current glucose-lowering therapies in patients with type 2 diabetes. To date, 5442 patients have been enrolled in vildagliptin phase 2 and 3 studies and 3549 patients exposed to vildagliptin, 637 for >52 weeks (63). Over 1500 patients have received 100 or 200 mg doses of sitagliptin in phase 3 studies (63).

Glycaemic Control

Vildagliptin monotherapy

Five trials ranging from 4 to 52 weeks duration have evaluated the efficacy of vildagliptin as monotherapy on markers of glycaemic control in drug-naïve patients compared with placebo and in head-to-head trials with commonly prescribed oral antidiabetic agents (55,64–67). In a 4-week study of vildagliptin 100 mg/day vs. placebo (baseline HbA1C 7.2%, fasting plasma glucose 8.8 mmol/l), fasting plasma glucose was reduced by 0.7 mmol/l, 4-h prandial glucose by 1.45 mmol/l and mean 24-h glucose by 0.93 mmol/l compared with placebo (Table 2) (55).

In a 12-week study designed to establish the dose of vildagliptin that was effective in reducing HbA1c levels and was safe and well tolerated in patients with type 2 diabetes (baseline HbA1c 7.6–7.8%, fasting plasma glucose 9.2–9.4 mmol/l for vildagliptin vs. placebo, respectively),
Table 2 A comparison of published phase 2 and phase 3 clinical trial data for the DPP-4 inhibitors vildagliptin and sitagliptin

| Reference     | Study duration (weeks) | Sample | Treatment | Findings between group difference in adjusted mean change |
|---------------|------------------------|--------|-----------|--------------------------------------------------------|
|               |                        |        | Glycaemic control | Hypoglycaemic events | Weight changes |
|               |                        |        | FPG | HbA1c | FPG | None | 0.21 kg vildagliptin | 0.12 kg PCB p = ns |
|               |                        |        | 4-h PPG | 0.7 (p = 0.037) | 1.45 (p < 0.001) |
| Ahren et al. (55) | 4 | Treatment naïve | Vildagliptin 100 mg 1 time/day (n = 18) vs. PCB (n = 19) | |
| Ristic et al. (64) | 12 | Mean age 51–63 years | Vildagliptin 25 mg 2 times/day, 25, 50 or 100 mg 1 time/day, PCB (n = 279) | HbA1c −0.31% (vildagliptin 25 mg 2 times/day) to −0.56% (vildagliptin 50 mg 1 time/day) vs. −0.13% (PCB) | FPG −0.44 (vildagliptin 25 mg 2 times/day) to −0.97 (vildagliptin 50 mg 1 time/day) vs. −0.41 (PCB) | Two cases of symptomatic confirmed hypoglycaemia (vildagliptin 25 mg 2 times/day and 100 mg 1 time/day) | Small changes not significantly different from PCB |
| Pratley et al. (65) | 12 | Treatment naïve | Vildagliptin 25 mg 2 times/day (n = 70) vs. PCB (n = 28) | HbA1c −0.6% (p = 0.0012) | FPG −1.1 (p = 0.0043) | 4-h PPG −1.9 (p < 0.0001) | One episode of symptomatic hypoglycaemia with vildagliptin | Small changes not significantly different from PCB |
| Rosenstock et al. (66) | 24 | Treatment naïve | Vildagliptin 50 mg 2 times/day (n = 459) vs. rosiglitazone 8 mg/day (n = 238) | HbA1c −1.1% (vildagliptin), non-inferior to rosiglitazone | One mild hypoglycaemic event in each group | −0.3 kg vildagliptin +1.6 kg rosiglitazone (p < 0.001) |
| Reference       | Study duration (weeks) | Sample                  | Treatment | Findings between group difference in adjusted mean change |
|-----------------|------------------------|-------------------------|-----------|----------------------------------------------------------|
| DeJager et al. (67) | 52                     | Treatment naïve         | Vildagliptin 50 mg 2 times/day (n = 526) vs. metformin 1000 mg 2 times/day (n = 254) | HbA1c -1.0% (vildagliptin) vs. HbA1c -1.4% (metformin) | Three (0.6%) vildagliptin-treated patients reported one mild event vs. one (0.4%) metformin patient | +0.3 kg vildagliptin -1.9 kg metformin |
| Scott et al. (71)   | 12                     | Prior oral treatment    | Sitagliptin 5, 12.5, 25 or 50 mg 2 times/day; or glipizide 5 mg (up-titrated to 10, 15, and then to 20 mg/ day) vs. PCB | HbA1c* -0.4% (25 mg/day) to -0.8% (50 mg 2 times/day) vs. -1.0% (glipizide) | Twenty-one (17.1%) glipizide patients had ≥1 event compared with two PCB patients and 0, 5, 5 and 2 patients in the sitagliptin 5, 12.5, 25 and 50 mg 2 times/day groups, respectively | No significant weight change for sitagliptin + 1.1 kg glipizide |
| Herman et al. (56) | 12                     | Treatment naïve         | Sitagliptin 25, 50 or 100 mg 1 time/day; sitagliptin 50 mg 2 times/day vs. PCB (n = 552) | HbA1c* -0.4% (25 mg/day) to -0.6% (100 mg 1 time/day) | One event in each sitagliptin group | No mean change in body weight observed |
| Aschner et al. (62) | 24                     | Baseline HbA1c 8.0% (≥7.0 to ≤10.0%) | Sitagliptin 100 mg 1 time/day, 200 mg 1 time/day vs. PCB (n = 741) | HbA1c* -0.79% (100 mg/day) and -0.94% (200 mg/day) FPG* -0.9 (100 mg/ day) and -1.2 (200 mg/day) 2-hr PPG* -2.6 (100 mg/day) and -3.0 (200 mg/day) | Equivalent to PCB | −0.2 kg (100 mg) −0.1 kg (200 mg) −1.1 kg PCB |
| Reference          | Study duration (weeks) | Sample          | Treatment                                                                 | Findings between group difference in adjusted mean change | Glycaemic control | Hypoglycaemic events | Weight changes |
|--------------------|------------------------|-----------------|---------------------------------------------------------------------------|----------------------------------------------------------|------------------|----------------------|-----------------|
| Ahren et al. (45)  | 12 weeks extended to 52 weeks | Mean age 57 years BMI 29.8 kg/m² | Vildagliptin 50 mg 1 time/day (n = 56) vs. PCB (n = 51) added to ongoing metformin 1500–3000 mg/day | HbA1c -0.7% (p < 0.0001) FPG -1.2 (p = 0.0057) 4-h PPG -2.2 (p < 0.0001) | HbA1c -0.7% (p < 0.0001) FPG -1.1 (p = 0.0312) 4-h PPG -2.4 (p = 0.0001) | Two patients experienced one symptomatic event in each group | −0.4 kg (vildagliptin + MET) |
|                   |                        | Baseline HbA1c 7.7% (vildagliptin), 7.8% (PCB) Baseline FPG 9.9 (vildagliptin), 10.3 (PCB) Diabetes duration 5.5 years | 52-week extension Vildagliptin (n = 42) vs. PCB (n = 29) | HbA1c -1.1% (p < 0.0001) FPG -1.1 (p = 0.0312) 4-h PPG -2.4 (p = 0.0001) |                       | No events in extension | −0.2 kg in both groups in extension phase |
| Garber et al. (69) | 24                     | Mean age 56 years BMI 32.8 kg/m² Baseline HbA1c 8.4% (7.5–11%) Diabetes duration 6.2 years | Vildagliptin 50 mg 1 time/day, vildagliptin 50 mg 2 times/day or PCB added to ongoing metformin ≥1500 mg/day (n = 416) | HbA1c -0.7% (p < 0.001) 50 mg/day HbA1c -1.1% (p < 0.001) 50 mg 2 times/day FPG -0.8 (p = 0.003) 50 mg 1 time/day FPG -1.7 (p < 0.001) 50 mg 2 times/day | HbA1c -0.7% (p < 0.001) 50 mg/day HbA1c -1.1% (p < 0.001) 50 mg 2 times/day | One event occurred in each group | No weight gain reported |
| Nathwani et al. (68) | 24                     | Baseline HbA1c 7.5–11% | Vildagliptin 100 mg/day, pioglitazone 30 mg/day, vildagliptin 100 mg/day plus pioglitazone 30 mg/day, vildagliptin 50 mg/day plus pioglitazone 15 mg/day (n = 592) | HbA1c -1.9% (vildagliptin + pioglitazone 100/30 mg/day) vs. −1.4% pioglitazone alone (p < 0.001) | HbA1c -1.9% (vildagliptin + pioglitazone 100/30 mg/day) | Not reported | +0.2 kg vildagliptin 100 mg +1.5 kg pioglitazone 30 mg +2.1 kg vildagliptin 100 mg +pioglitazone 30 mg |

Table 2 (Continued)

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| Reference          | Study duration (weeks) | Sample                                      | Treatment                                      | Findings between group difference in adjusted mean change | Hypoglycaemic events | Weight changes  |
|--------------------|------------------------|---------------------------------------------|-----------------------------------------------|-----------------------------------------------------------|----------------------|-----------------|
| Fonseca et al. (70) | 24                     | Mean age 59 years                           | Vildagliptin 50 mg 2 times/day (n = 125) vs. PCB (n = 131) | HbA1c −0.5% (vildagliptin + insulin) vs. −0.2% (placebo + insulin) (p = 0.022) | Thirty-three patients had 113 events (0 severe) with vildagliptin + insulin 45 patients had 185 events (six severe) with PCB + insulin | Not reported       |
| Brazg et al. (72)   | 4                      | Baseline HbA1c range 6.5–9.6%               | Sitagliptin 50 mg 2 times/day + metformin (≥1500 mg/day for ≥6 weeks) vs. PCB + metformin (n = 28) | FPG* −1.1 (p < 0.001)                                      | No events observed | No weight gain observed |
| Karasik et al. (46) | 24                     | Baseline HbA1c 8.0%                        | Sitagliptin 100 mg 1 time/day + metformin (≥1500 mg/day) vs. PCB + metformin (n = 701) | HbA1c* −0.65% (p < 0.001) FPG −1.4 2-h PPG −2.8 | No increased incidence vs. PCB | −0.7 kg sitagliptin −0.6 kg PCB |
| Rosenstock et al. (50) | 24                     | Mean age 56 years                           | Sitagliptin 100 mg 1 time/day + pioglitazone vs. PCB + pioglitazone (n = 353) | HbA1c* −0.7% (p < 0.001) FPG* −1.0 (p < 0.001) | No increased incidence vs. PCB | No increased incidence vs. PCB |
| Stein et al. (63)   | 52                     | Baseline HbA1c 7.5%                        | Sitagliptin 100 mg 1 time/day plus metformin vs. glipizide (up to 20 mg/day) plus metformin (n = 1172) | HbA1c −0.67% (for both sitagliptin and glipizide vs. baseline, p < 0.001) | Hypoglycaemic events were experienced by 32% patients (glipizide) vs. 4.9% (sitagliptin), p < 0.001 | −1.5 kg sitagliptin +1.1 kg glipizide (p < 0.001) |

*Placebo (PCB) subtracted values. HbA1c values are percent, fasting plasma glucose (FPG) and postprandial glucose (PPG) values are in mmol/l.
patients received one of the following doses: vildagliptin 25 mg twice daily, 25, 50 or 100 mg once daily, or placebo (64). There was a statistically significant reduction in HbA1c levels in the vildagliptin 50 and 100 mg/day groups compared with placebo (Table 2).

A second 12-week study of vildagliptin 25 mg twice daily vs. placebo (baseline HbA1c 8.0–8.1%, fasting plasma glucose 9.4–10.1 mmol/l for vildagliptin vs. placebo, respectively) demonstrated a between-group difference in adjusted mean change in HbA1c from baseline to endpoint of −0.6% for the whole cohort (mean baseline HbA1c of 8.0%) and −1.2% for subjects with a baseline HbA1c of 8.0–9.5% (Table 2). Nearly half of the vildagliptin patients with a baseline HbA1C >7% were able to achieve levels below this target at 12 weeks. Fasting and 4-h mean postprandial glucose were reduced by 1.1 and 1.9 mmol/l, respectively. Subjects with higher baseline HbA1c levels showed a greater response (65).

In a 24-week study of vildagliptin 50 mg twice daily vs. rosiglitazone 8 mg once daily (baseline HbA1c 8.7%) the adjusted mean change in HbA1c from baseline to endpoint in patients receiving vildagliptin was −1.1% and non-inferiority to rosiglitazone was established. In patients with baseline HbA1c >9.0%, the mean change in HbA1c was −1.8% in the vildagliptin group and −1.9% in the rosiglitazone group (66).

A large 52-week study of vildagliptin 50 mg twice daily vs. metformin 1000 mg twice daily (baseline HbA1c 8.7%) demonstrated an adjusted mean change in HbA1c from baseline to endpoint of −1.0% for vildagliptin and −1.4% for metformin. While the between-group difference in HbA1c did not establish non-inferiority of vildagliptin 100 mg/day to metformin 2000 mg/day, a clinically meaningful reduction in HbA1c was sustained throughout 1-year of treatment (Table 2) (67).

A pooled analysis of the vildagliptin monotherapy data from 1300 drug-naïve patients, with the same study entry criteria and who received a dose of vildagliptin 100/mg day has shown an overall reduction in HbA1c of −1.1%. As expected, greater reductions in HbA1c are achieved in patients with higher HbA1c levels at baseline (Figure 4) (68).

**Vildagliptin combination therapy**

Combination treatment with DPP-4 inhibitors and other antihyperglycaemic drugs may be useful as these agents target different pathophysiological processes and would be expected to have added benefit on measures of glycaemic control.

**Combination Metformin – Vildagliptin Therapy.** In a 12-week study extended to 52 weeks patients were randomized to vildagliptin 50 mg once daily vs. placebo added to ongoing metformin treatment (1500–3000 mg/day) (base-

\[ \text{Change from baseline in HbA1c (\%)} \]

|                  | Overall | HbA1c >8% | HbA1c >9% |
|------------------|---------|-----------|-----------|
| **Baseline**     | 1301    | 838       | 440       |
| **HbA1c**        | 8.7     | 9.3       | 9.9       |
| **HbA1c >8%**    | −1.1    | −1.3 *    | −1.7 *    |
| **HbA1c >9%**    |         |           |           |

* p < 0.01 from baseline

line HbA1c 7.7%, 7.8% and fasting plasma glucose 9.9, 10.3 mmol/l for vildagliptin plus metformin versus placebo, respectively) (45). The between-group difference in HbA1c at 12 weeks was −0.7% (Table 2). HbA1c did not change from week 12 to week 52 in vildagliptin-treated patients, but increased in placebo subjects (Figure 5). The between-group difference in HbA1c after 1 year was −1.1%. An endpoint HbA1c of <7.0% was achieved by 41.7% of patients taking vildagliptin plus metformin and by 10.7% of those taking placebo plus metformin. Mean prandial glucose and fasting plasma glucose were significantly reduced in patients receiving vildagliptin vs. placebo by −2.2 and −1.2 mmol/l, respectively.

In a 24-week study in patients randomized to vildagliptin 50 mg once daily, 50 mg twice daily or placebo continuing a previous stable metformin regimen (1500 mg/day) (baseline HbA1c 8.4%) the between-group difference in the adjusted mean change in HbA1c was −0.7% in patients receiving vildagliptin 50 mg once daily and −1.1% in patients receiving 50 mg twice daily (69). Fasting plasma glucose was reduced by −0.8 and −1.7 mmol/l in the two groups, respectively.

**Combination Pioglitazone – Vildagliptin Therapy.** In a 6-month study, 592 patients were randomly assigned to one of four treatment groups: (1) vildagliptin 100 mg/day; (2) pioglitazone 30 mg/day; (3) vildagliptin 100 mg/day plus pioglitazone 30 mg/day; (4) vildagliptin 50 mg/day plus pioglitazone 15 mg/day. Patients randomized to vildagliptin 100 mg plus pioglitazone 30 mg had a statistically significant reduction in HbA1c compared with patients randomized to pioglitazone alone (−1.9% vs. −1.4%; p < 0.001). Among patients with higher baseline HbA1c values (>9%) the combination of vildagliptin and pioglitazone produced a
reduction in HbA1c of −2.8%. Furthermore, two-thirds (65%) of patients on vildagliptin and pioglitazone achieved the American Diabetes Association HbA1c target of ≤7% vs. 42% of those who achieved this goal on monotherapy (vildagliptin 42.5%, pioglitazone 42.9%) (68).

Combination Insulin – Vildagliptin Therapy. The efficacy of vildagliptin in patients with more advanced type 2 diabetes requiring insulin was recently reported in a 24-week study comparing vildagliptin 50 mg twice daily vs. placebo in 256 patients inadequately controlled (baseline HbA1c 8.5%, fasting plasma glucose 9.3 mmol/l) by insulin (>30 U/day). Overall, HbA1c decreased by −0.5% in the vildagliptin plus insulin group and −0.2% in the placebo plus insulin group. However, in patients ≥65 years old HbA1c decreased by −0.7% in the vildagliptin group vs. 0.0% in the placebo group (70). This study showed that adding vildagliptin to insulin was associated with a significant reduction in HbA1c, particularly in older individuals, and despite clinical insulin resistance.

Sitagliptin monotherapy

The sitagliptin clinical programme has followed a design similar to that of vildagliptin. In two 12-week dose-range finding studies, all sitagliptin doses significantly reduced HbA1c compared with baseline (56,71). In treatment-naive patients (baseline HbA1c 7.7%), the largest reduction was observed in the 100 mg once daily group (Table 2). Across the dose range, differences in placebo-subtracted HbA1c ranged from −0.4% (25 mg once daily group) to −0.6% (100 mg once daily group) (56). Observed HbA1c differences from placebo were greater with higher baseline HbA1c. Fasting plasma glucose increased by 0.01 mmol/l in the placebo group, and dose-dependently decreased by −0.6 to −0.9 mmol/l in the other treatment groups. The second dose-ranging study included subjects who had received prior treatment with an oral antidiabetic agent and also randomized patients to glipizide (baseline HbA1c 7.7%) (71). All sitagliptin doses again significantly reduced HbA1c compared with baseline with the largest reductions in the 50 mg twice daily group. Placebo-subtracted differences in HbA1c ranged from −0.4 to −0.8% in a dose-dependent manner for the sitagliptin groups, and −1.0% in the glipizide group. Fasting plasma glucose increased by 0.4 mmol/l in the placebo group, and dose-dependently decreased by −0.04 to −1.0 mmol/l in the sitagliptin groups, and by −1.4 mmol/l in the glipizide group.

In a 24-week study of patients randomized to sitagliptin 100 or 200 mg once daily vs. placebo (baseline HbA1c 8.0%), sitagliptin 100 and 200 mg produced significant reductions in HbA1c (−0.79% and −0.94%, respectively) and fasting plasma glucose (−0.9 and −1.2 mmol/l, respectively). Patients with higher baseline HbA1c (≥9%) had greater reductions in HbA1c than those with baseline HbA1c <8% (62). Sitagliptin 100 and 200 mg also significantly decreased 2-h postprandial glucose compared with placebo (−2.6 and −3.0 mmol/l, respectively). There were no significant differences in HbA1c, fasting plasma glucose, or 2-h postprandial glucose reductions between the sitagliptin doses.

Sitagliptin Combination Therapy

Combination metformin – sitagliptin therapy. Two trials have evaluated the efficacy of sitagliptin in combination with metformin. In a 4-week study, patients with inadequate glycaemic control on metformin monotherapy (on a stable dose of ≥1500 mg/day for ≥6 weeks) were random-
ized to sitagliptin 50 mg twice daily vs. placebo, concomitantly with their current metformin medication (72). Fasting plasma glucose was reduced by −1.3 mmol/l with sitagliptin compared with −0.2 mmol/l on placebo (p < 0.001) (Table 2) (72).

In a 24-week study, the addition of sitagliptin 100 mg once daily to ongoing metformin monotherapy (≥1500 mg/day) (baseline HbA1c 8.0%) led to significant improvements in glycaemic control (46). Placebo-subtracted reductions of −0.65% in HbA1c (Figure 6), −1.4 mmol/l in fasting plasma glucose and −2.8 mmol/l in 2-h postprandial glucose were achieved (Table 2).

**Combination pioglitazone – sitagliptin therapy.** In a 24-week study in patients with inadequate glycaemic control on pioglitazone monotherapy (30 or 45 mg/day) (baseline HbA1c 8.0%, fasting plasma glucose 9.3 mmol/l), the addition of sitagliptin 100 mg once daily vs. placebo led to significant lowering of HbA1c (−0.7%) (Figure 6) and fasting plasma glucose (−1.0 mmol/l) (50). The effects of sitagliptin on glycaemic control were maintained over the 24-week study; endpoint HbA1c was 7.2% and 7.8% for sitagliptin plus pioglitazone vs. pioglitazone alone with 45% and 23% of patients, respectively, reaching the target HbA1c of <7% (p < 0.001).

**Combination glipizide – sitagliptin therapy.** In a 52-week study of adjunctive sitagliptin 100 mg once daily vs. glipizide up to 20 mg/day (maximum titrated dose) in patients with inadequate glycaemic control on metformin monotherapy (baseline HbA1c 7.5%), both groups showed significant reductions in HbA1c of −0.67% compared with baseline. At 52 weeks, sitagliptin achieved the prespecified bounds for non-inferiority vs. glipizide, and similar proportions of patients achieved the HbA1c goal (<7%) in each group (63% for sitagliptin vs. 59% for glipizide (Figure 7) (63).

![Figure 6](image)

**Figure 6** Placebo-subtracted difference in mean change from baseline HbA1c for sitagliptin as add-on to metformin or as add-on to pioglitazone therapy vs. placebo (46,50)

![Figure 7](image)

**Figure 7** Proportion of patients achieving American Diabetes Association HbA1c goal of <7% with sitagliptin vs. glipizide as add-on to metformin therapy at 52 weeks (63)
Ongoing Saxagliptin Trials

A phase 2 study with saxagliptin 10 mg once daily showed a significant reduction in HbA1c from baseline (Figure 8) (73). To date no information on saxagliptin trials is available in either abstract or published form. However, several trials are ongoing with designs similar to those previously described for vildagliptin and sitagliptin including saxagliptin in subjects with type 2 diabetes not controlled with metformin, sulphonylurea or thiazolidinedione monotherapy.

SAFETY

Hypoglycaemia

The insulinotropic action of GLP-1 is glucose dependent, and for GLP-1 to enhance insulin secretion, glucose concentrations must be higher than 5 mmol/l (74). As the glucose-lowering effects of GLP-1 are dependent on elevated blood glucose and subside as glucose levels return to normal, the probability of hypoglycaemia during treatment with a DPP-4 inhibitor is expected to be low. This is an interesting characteristic of incretin mimetics and DPP-4 inhibitors, in contrast to sulphonylureas, which induce insulin secretion irrespective of ambient glucose concentrations.

In monotherapy trials, the overall incidence of hypoglycaemia was similar to placebo for both vildagliptin (55,64,65) and sitagliptin (56,62,75).

In a study in which vildagliptin was added to insulin therapy, hypoglycaemic events were less common and less severe in patients receiving a vildagliptin plus insulin regimen (33 patients, 113 events, 0 severe) compared with those receiving placebo plus insulin (45 patients, 185 events and six severe) (70).

In a head-to-head study, sitagliptin 100 mg once daily lowered the risk of hypoglycaemia by sixfold compared with glipizide, with 32% of the patients using glipizide suffering at least one episode of hypoglycaemia, and 4.9% of sitagliptin patients (p < 0.001) (63).

Weight Gain

In contrast to the results obtained with the GLP-1 analogues, no significant decrease in body weight has been observed with the DPP-4 inhibitors either as monotherapy or as combination therapy (Table 2). The DPP-4 inhibitors appear to be body weight neutral (45,67). An exception to this are the data from a 1-year study of sitagliptin compared with glipizide in patients not adequately controlled on metformin monotherapy. In this study, patients in the sitagliptin 100 mg once daily group experienced significant weight loss (mean −1.5 kg) from baseline at 52 weeks, while patients treated with glipizide experienced significant weight gain (mean + 1.1 kg) from baseline (p < 0.001) (63).

Gastrointestinal Side Effects

Delayed gastric emptying, nausea and vomiting are GLP-1-related side-effects. These are seen with high, non-physiological concentrations (above about 60 pmol/l in human plasma), which are only achieved after exogenous administration of GLP-1. Compared with GLP-1 mimetics, which are administered via injection and lead to pharmacological GLP-1 levels that can produce nausea and vomiting (76,77), vildagliptin and sitagliptin are administered orally and appear to be well tolerated. Interestingly, recently presented data have reported that in patients randomized to vildagliptin 50 mg once daily, vildagliptin 50 mg twice daily or placebo in addition to ongoing metformin therapy (≥1500 mg/day) the number of patients reporting gastrointestinal side effects was significantly lower in the vildagliptin groups compared with placebo.

Other Side Effects

The overall incidence of side effects with vildagliptin and sitagliptin is similar to placebo in monotherapy trials. Overall, the most common side effects seen in the vildagliptin clinical trial programme were cold/flu-like symptoms, headaches and dizziness. The safety and tolerability of sitagliptin at once-daily doses of 100 and 200 mg (twice the proposed registration dose) have been assessed by pooling data from two monotherapy and two add-on studies. The overall incidence of clinical and laboratory adverse experiences was similar between sitagliptin and placebo (78). The most common side effects (≥3% and greater than placebo) reported with sitagliptin were stuffy or runny nose and sore throat; headache; diarrhoea; upper respiratory infection; joint pain; and urinary tract infection (with differences ranging from 0.1 to 1.5% vs. placebo).

Potential Risks Associated with DPP-4 Inhibitors

Dipeptidyl peptidase 4 has effects beyond its proteolytic action, including T-cell activation and proliferation (17).
Although available data indicate that DPP-4 inhibition is a promising treatment for type 2 diabetes, there are theoretical safety concerns associated with long-term DPP-4 inhibitor use in humans. A large number of neuropeptides, growth factors, cytokines and chemokines have been identified as potential DPP-4 substrates (18). To date no evidence of non-specific enzyme inhibition has been found, however, with current DPP-4 inhibitors at clinically relevant doses. Toxicities claimed to be associated with DPP-8 and DPP-9 inhibition in animals (23) have not been observed in clinical trials of vildagliptin or sitagliptin for up to 1 year in duration.

In addition to stabilizing the incretins, DPP-4 inhibitors also prolong the action of the hormones peptide YY and growth hormone-releasing hormone, the neuropeptides neuropeptide Y and substance P, and several chemokines. Potential side-effects resulting from the prolongation of action of these messengers include neurogenic inflammation (substance P, neuropeptide Y), increases in blood pressure (neuropeptide Y), and enhanced general inflammation, and allergic reactions (chemokines). Such side-effects have not been observed in preclinical animal or clinical human studies to date (79).

**Therapeutic Applications of the DPP-4 Inhibitors**

The DPP-4 inhibitors are orally bioavailable and therefore might offer greater benefits compared with injectable agents in terms of patient compliance. Available data indicate that the orally administered DPP-4 inhibitors can sustain reductions in HbA1c to clinically meaningful levels with minimal hypoglycaemic events and no weight gain. As monotherapy, they could compete with traditional oral antidiabetic agents, particularly in view of their weight neutrality and low risk of hypoglycaemia, although because of cost, lack of familiarity, and no endpoint data, likely they will be used mainly in combination treatment in early years after launch.

Combining DPP-4 inhibitors with existing medications with complementary mechanisms of action should be a welcome addition to available agents. They could be particularly useful in combination with metformin or a thiazolidinedione. Their weight neutrality and low risk of hypoglycaemia appears attractive in this context. To become well established as first- or even second-line therapy, long-term studies are required to demonstrate durability of glycemic control (which should in theory be achievable based on the mechanism of action of these agents).

The time course of the pathophysiological processes associated with type 2 diabetes is not yet completely understood. It is generally agreed that these impairments are already present during an early phase of the disease. As DPP-4 inhibition primarily supports the physiological functions of endogenous GLP-1, these inhibitors may be of particular relevance in early forms of type 2 diabetes or even prediabetes, but this still needs to be proven in clinical trials. Protective effects on β-cells if demonstrated would be of great value in these patients and might partly restore their impaired insulin secretion.

**CONCLUSIONS**

The oral DPP-4 inhibitors vildagliptin, sitagliptin and saxagliptin are being evaluated as both monotherapy and in combination with other commonly prescribed antidiabetic agents and are competing to be ‘first in class’ of a new oral treatment modality for type 2 diabetes. At least five phase 2 and six phase 1 DPP-4 inhibitors are closely following and more than 10 further companies are in advanced preclinical research and development. Available data show differences in duration of action and anticipated dosing frequency. While the DPP-4 inhibitors do not lower glucose to a greater extent than existing therapies, they offer many potential advantages. Both vildagliptin and sitagliptin have demonstrated the ability to achieve sustainable reductions in HbA1c with a well-tolerated agent that has a low risk of hypoglycaemia and no weight gain, and which can be administered as a once-daily oral dose.

Traditional treatments for type 2 diabetes do not address the progressive decline in β-cell function and therefore despite therapy patients continue to advance in their disease state. New agents with complementary modes of action and the potential to affect the decline in β-cell function are of great interest. There is a theoretical possibility that the DPP-4 inhibitors could preserve and even reverse the progressive loss of insulin secretory capacity that is the fundamental cause of type 2 diabetes, although long-term studies will be required to demonstrate this. In theory, DPP-4 inhibitor therapy should be started soon after diagnosis of type 2 diabetes, before β-cell function has deteriorated to unacceptable levels. In the first instance, however, DPP-4 inhibitors are likely to be used as part of combination therapy regimens until further data are available. These drugs do appear to have great potential, but time will tell if this will be realized.

**POTENTIAL CONFLICTS OF INTEREST**

Professor Barnett has received fees for lectures and advisory work from Novartis, MSD and Bristol-Myers Squibb all of whom are developing DPP-4 inhibitors.

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