

# Vildagliptin: a DPP-4 inhibitor for the treatment of Type 2 diabetes

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### Practice Points

- Vildagliptin is an orally active DPP-4 inhibitor that prevents the inactivation of GLP-1 and improves islet function.
- Vildagliptin efficiently lowers HbA<sub>1c</sub> in subjects with Type 2 diabetes when used both in monotherapy and add-on to ongoing therapy with metformin, sulfonylurea, thiazolidinedione or insulin.
- The clinically recommended dose of vildagliptin is 50 mg twice daily, except when combined with sulfonylurea or in subjects with renal impairment, when the recommended dose is 50 mg once daily.
- Vildagliptin is a safe therapy with adverse events similar to placebo groups in clinical trials. Of special interest is that hypoglycemia is rarely seen and that there is no weight gain.
- Vildagliptin is active as a therapy of Type 2 diabetes across all ages and degrees of obesity, and is also efficient in patients with renal impairment.

**SUMMARY** The key defect in Type 2 diabetes is islet dysfunction, which includes impaired insulin secretion, augmented glucagon secretion and reduced  $\beta$ -cell mass. The incretin hormone GLP-1 targets this islet dysfunction. GLP-1 is inactivated by DPP-4 and, consequently, DPP-4 inhibition has evolved as an efficient treatment of hyperglycemia in Type 2 diabetes since it increases the concentrations of intact GLP-1. Several DPP-4 inhibitors have been developed and all of them have been shown to be efficient in improving glycemia with a low risk for adverse events. This article reviews basic and clinical studies on one of the DPP-4 inhibitors, vildagliptin. It is a specific inhibitor of DPP-4 and improves glycemia both when used in monotherapy and when used as an add-on to metformin, sulfonylurea, thiazolidinedione or insulin in subjects with Type 2 diabetes. Clinical studies have shown that vildagliptin reduces HbA<sub>1c</sub> in association with a low risk of adverse events, including hypoglycemia, and no weight gain. Vildagliptin is also efficient in elderly patients and in patients with renal impairment. Its main place in therapy is as add-on to ongoing therapy with metformin in patients in whom metformin alone is insufficient for reaching the glycemic target. Vildagliptin may also be used as monotherapy in patients in whom metformin cannot be used and as an add-on to sulfonylurea or thiazolidinedione. In the future, it may also be used as an add-on to insulin therapy. There is, at present, an extensive experience with the use of vildagliptin for at least 5 years in many countries. However, long-term surveillance of its effects and safety is still of importance.

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Type 2 diabetes is a global disease, which is increasingly diagnosed, with glucose and lipid abnormalities resulting in micro- and macro-vascular complications. Reducing the burden of the disease and its complications by prevention and treatment is one of the most important health challenges of our time. For this, there is a need of well-organized healthcare systems and tools for improving metabolic abnormalities.

Of key importance in the management of Type 2 diabetes is targeting the hyperglycemia, since elevated glucose is a risk factor both for acute symptoms of the disease and for the increased risk for retinopathy, nephropathy and neuropathy [1]. Improving glycemia is also of importance for reducing the high cardiovascular risk in Type 2 diabetes [2]. Of importance in this management is targeting the key factor underlying hyperglycemia, which is islet dysfunction, involving impaired insulin secretion [3], defective suppression of glucagon secretion [4] and reduced  $\beta$ -cell mass [5]. Glucose-lowering treatment guidelines from various bodies suggest metformin as the first-line pharmacologic agent when dietary and lifestyle changes are not sufficient, followed by addition of sulfonylurea, thiazolidinediones,  $\alpha$ -glucosidase inhibitors and/or insulin as pharmacological agents when metformin alone is insufficient [6]. However, only up to 50% of the patients reach the target for glycemic control when using these therapies. Therefore, there is great hope for novel therapies. During recent years, dipeptidyl peptidase-4 (DPP-4) inhibitors and glucagon-like peptide-1 (GLP-1) receptor agonists have emerged as new classes of therapeutic agents [7].

#### DPP-4 inhibition

The rationale behind the use of the DPP-4 inhibitors in therapy of Type 2 diabetes is that they inhibit the catalytic site of the widely distributed enzyme DPP-4 which inactivates the gut incretin hormones GLP-1 and glucose-dependent insulinotropic polypeptide (GIP) [8]. Therefore, DPP-4 inhibition prevents the inactivation of these hormones which results in increased prandial endogenous levels of intact GLP-1 and GIP by approximately two- to three-fold. The consequence of this is that insulin secretion is stimulated and glucagon secretion is inhibited, and these effects occur in a glucose-dependent manner. DPP-4 inhibition therefore targets the key pathophysiological factors of Type 2 diabetes.

In the 1990s, it was already suggested that inhibition of DPP-4 is a target to treat Type 2

diabetes [9]. Initial animal studies supported this assumption and paved the way for the first clinical proof-of-concept for DPP-4 inhibitors in subjects with Type 2 diabetes, which was published in 2002 [10]. Several DPP-4 inhibitors have subsequently been developed and at present five different DPP-4 inhibitors are approved for clinical use in various countries (vildagliptin, sitagliptin, saxagliptin, linagliptin and alogliptin). These DPP-4 inhibitors are all small molecules that are oral agents and potent inhibitors of the enzyme. They differ in chemical structure, in mode of inhibiting the catalytic site of the enzyme, in specificity towards inhibition of other enzymes and in pharmacokinetics, as recently reviewed [11,12]. In terms of clinical efficacy and safety, they have not been examined in long-term head-to-head studies. However, they are all efficacious when used both in monotherapy and in combination therapy with other treatments and by comparing the many studies involving each of them, it seems as they similarly reduce  $HbA_{1c}$  with a similarly good tolerability and a low risk for adverse events [8]. This article is focused on vildagliptin.

#### Vildagliptin: chemical & pharmacokinetic characteristics

Vildagliptin is a small molecule with a cyanopyrrolidine structure with a nitrile group which specifically binds to and inhibits the catalytic site of DPP-4 [13]. The binding is long-lasting, which enables vildagliptin to inhibit DPP-4 over a longer period of time than would be expected from its circulating half-life. Thus, it has been shown that the circulating half-life of vildagliptin is only approximately 2 h [14], whereas the inhibition of DPP-4 activity after a single dose (of 50 mg) lasts for approximately 12 h [15].

Following oral administration, vildagliptin is rapidly absorbed with a bioavailability of approximately 85% [16]. Vildagliptin is extensively metabolized, which is primarily a hydrolysis process in many tissues, including the liver. Only approximately 22% of administered vildagliptin is eliminated as the parent compound. As demonstrated by He and collaborators, there are four metabolic pathways resulting in one major and four minor metabolites, which are all devoid of DPP-4 inhibitory activity [14]. The major metabolite (M20.7) accounts for approximately 55% of metabolism of vildagliptin and is produced through hydrolysis of the cyano-group. This metabolism is independent from

the CYP450 complex, indicating no important interactions with drugs eliminated by this route. Interestingly, the DPP-4 enzyme itself is responsible for approximately 20% of vildagliptin metabolism by hydrolyzing the cyano group. Vildagliptin and its metabolites are all primarily eliminated through the kidney, with only approximately 5% eliminated in the feces. The renal clearance of vildagliptin and its metabolites is higher than the glomerular filtration rate, suggesting both passive filtration and active renal transportation as mechanisms for the elimination.

Since vildagliptin is cleared through kidney, its plasma levels are elevated in kidney insufficiency [14]. Therefore, when vildagliptin is used in patients with moderate (glomerular filtration rate [GFR] 30–50 ml/min) or severe (GFR <30 ml/min) renal impairment, the administered dose is reduced to 50 mg once daily (q.d.), whereas in subjects with normal kidney function or mild renal impairment (GFR >50 ml/min), the dose is 50 mg twice daily (b.i.d.). Furthermore, although vildagliptin is metabolized in the liver, no increase in vildagliptin concentration is seen in subjects with mild or moderate hepatic insufficiency compared with subjects with normal liver function, whereas in subjects with severe hepatic insufficiency, there is an increased vildagliptin exposure after administration [17]. **Table 1** summarizes the pharmacokinetic characteristics of vildagliptin.

### Vildagliptin: pharmacodynamics characteristics

Vildagliptin augments the increase in levels of intact GLP-1 and GIP after oral glucose [18] and mixed meal [19,20]. Postprandial levels of intact GLP-1 are raised to approximately 15–20 pmol/l after vildagliptin versus approximately 5–10 pmol/l after placebo [19,20] and postprandial intact GIP levels are raised to approximately

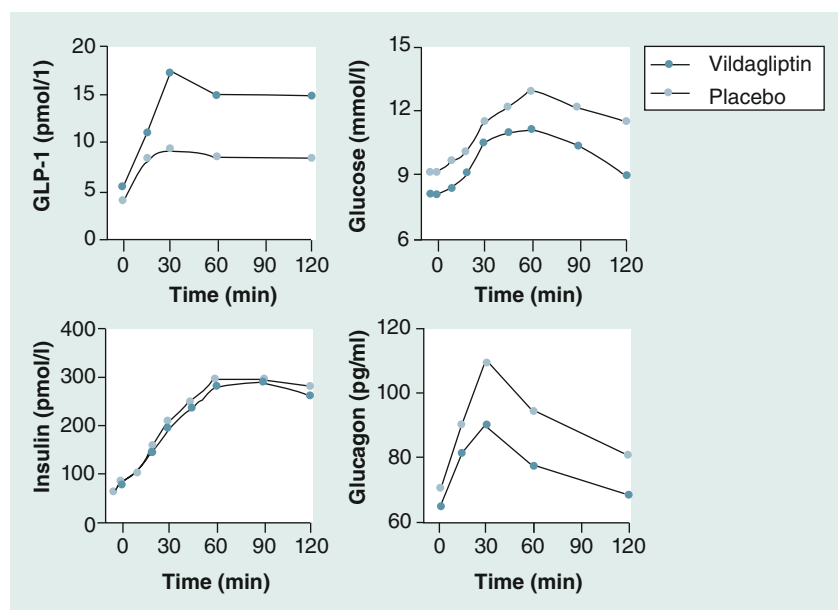
100 pmol/l after vildagliptin versus approximately 50 pmol/l after placebo [18]. Also fasting GLP-1 and GIP levels are increased during treatment with vildagliptin, from approximately 3–5 pmol/l to approximately 5–10 pmol/l (GLP-1) and from approximately 20 pmol/l to approximately 40 pmol/l (GIP) [20]. These results show that there is increased exposure to the incretin hormones throughout the entire 24 h period. As a consequence, vildagliptin stimulates insulin secretion in a glucose-dependent manner [21]. **Figure 1** shows the effects of vildagliptin on intact GLP-1, insulin and glucose after meal ingestion. The stimulation of insulin secretion by vildagliptin is long-standing and also evident after at least 1 year of treatment [22]. Vildagliptin also reduces proinsulin, which is another sign of improved  $\beta$ -cell function [23].

Vildagliptin also suppresses glucagon secretion, as shown after oral glucose and meal ingestion as seen in **Figure 1** [18,19]. This suppresses hepatic glucose production [24]. The reduction in glucagon levels by vildagliptin correlates with the improved glycemia, as shown after a 4-week study period in drug-naïve patients [19].

It has recently been demonstrated that in contrast to the inhibition by vildagliptin of glucagon secretion during hyperglycemia, glucagon levels are not suppressed by vildagliptin at low glucose levels [25]. Hence, the effect of vildagliptin on glucagon secretion is glucose-dependent. The mechanism of the sustained glucagon secretion during hypoglycemia by vildagliptin is not known but may be explained by GIP, which has been shown to stimulate glucagon secretion during hypoglycemia [26]. It may also be explained by a reduction in insulin secretion during the hypoglycemia and/or by increased autonomic activity [25]. In any case, the sustainment of glucagon secretion during hypoglycemia by vildagliptin is an important mechanism to prevent hypoglycemia during

**Table 1.** The pharmacokinetic characteristics of vildagliptin as reported in references.

Process	Characteristics of vildagliptin
Absorption	Rapid after oral administration (bioavailability approximately 85%)
Distribution	Extensive distribution; does not cross membranes
Protein binding	Low protein binding (<10%)
Metabolism	Extensive metabolism (cyano group hydrolysis → M20.7; amide bond hydrolysis → M15.3; glucuronidation → M20.2; pyrrolidine oxidation → M20.9 and M21.6); 22% unmetabolized
Circulating half-life	Approximately 2 h
Elimination	Mainly (90%) through kidney (glomerular filtration and active transport)
Data taken from [14–17].	



**Figure 1. Active GLP-1, glucose, insulin and glucagon levels before and after intake of breakfast (performed at time 0) after 4 weeks of treatment with placebo (n = 19) or vildagliptin (100 mg once daily) in subjects with Type 2 diabetes (n = 18). Means ( $\pm$  standard error) are shown.**

Reproduced from [19] with permission from The Endocrine Society.

treatment with vildagliptin, particularly when used in combination with insulin.

Vildagliptin increases  $\beta$ -cell mass in streptozotocin-injected neonatal rats [27] and also improves the islet topography in diabetic mice [28]. Whether such an effect occurs in humans is not known. One study showed that 1-year treatment with vildagliptin increased the  $\beta$ -cell secretory effect, but after a 12-week washout, this effect had disappeared, suggesting that no disease-modifying effect on  $\beta$ -cell mass or function is evident after 1-year of therapy [29]. On the other hand, a 2-year study in patients with Type 2 diabetes who have mild hyperglycemia may indicate that such an effect may occur [30]. Thus, during the first year of treatment, the increased insulin secretion by vildagliptin declined following a 4-week washout period, whereas after the second year of treatment, insulin secretion was higher after treatment with vildagliptin than in the placebo group, also after four week washout [30]. This needs, however, to be verified in long-term studies.

Vildagliptin has also been shown to reduce fasting lipolysis, which may be a direct adipocyte action of the incretin hormones [21]. At the same time, vildagliptin also increases postprandial lipolysis in adipose tissue (probably through increased noradrenaline levels) in association

with increased postprandial muscle fat oxidation [31]. These two actions together suggest that fat accumulated in adipocytes during fasting may be mobilized and burned in muscle in the fed state during vildagliptin treatment. Furthermore, it has also been demonstrated that postprandial triglyceride-rich lipoprotein levels are reduced by vildagliptin after a fat-rich meal in patients with Type 2 diabetes, mainly through reduction in Apo B-48 [32]. The mechanism explaining the reduced postprandial lipemia after vildagliptin has not been established. It is possible that the effect is mediated by GLP-1, since, interestingly, it has been reported that GLP-1 inhibits triglyceride absorption in rats [33]. Furthermore, DPP-4 inhibition (sitagliptin) and GLP-1 receptor activation (exendin-4) have been shown to reduce intestinal secretion of triglycerides and Apo B-48 in mice, and conversely, this intestinal secretion is enhanced in mice with genetic deletion of the GLP-1 receptor [34].

Vildagliptin has also been demonstrated to increase glucose disposal during hyperinsulinemic, euglycemic clamp by an effect independent from changes in insulin levels [35]. This may be explained by reduced glucose and/or lipotoxicity and by reduction in fatty acid oxidation. By contrast, vildagliptin does not seem to affect gastric emptying, gastric volume and satiety [36]. **Table 2** summarizes the islet and extra-islet effects of vildagliptin.

### Differences & similarities to other DPP-4 inhibitors

**Tables 1 & 2** show the well-documented characteristics of vildagliptin. Since there are several other DPP-4 inhibitors available for the treatment of Type 2 diabetes, it is of interest to compare them. Although there is a shortage of studies directly comparing the various DPP-4 inhibitors, some similarities and differences can be concluded from the literature. With regard to the pharmacokinetic characteristics, comparisons between the DPP-4 inhibitors have been performed in detail [11,12,37]. In short, all available DPP-4 inhibitors are rapidly absorbed after oral intake and they are extensively distributed in the body without crossing the cell membranes. A difference between the DPP-4 inhibitors is the degree of protein binding: the low protein binding of vildagliptin is similar to that of most other DPP-4 inhibitors with an exception of linagliptin, which binds extensively to proteins. Moreover, all DPP-4

inhibitors effectively prevent the inactivation of the incretin hormones by DPP-4 due to binding to the catalytic site of DPP-4 by either covalent (vildagliptin and saxagliptin) or non-covalent (sitagliptin, alogliptin, linagliptin) binding. The duration of DPP-4 inhibition is dose-dependent for the DPP-4 inhibitors, and in the clinically used doses, vildagliptin inhibits DPP-4 for approximately 12–16 h, whereas the inhibition of the other four DPP-4 inhibitors is approximately 24 h [11]. Therefore, vildagliptin is dosed b.i.d., whereas the others are dosed q.d.. Furthermore, under *in vitro* conditions, high doses of vildagliptin and saxagliptin also inhibit the DPP-4 like enzymes DPP-8 and DPP-9 (the function of which are unknown), whereas this does not occur for the other DPP-4 inhibitors. This is, however, probably of no importance under *in vivo* conditions, since these enzymes, in contrast to DPP-4, are strictly intracellular enzymes, and the DPP-4 inhibitors do not cross the plasma membranes. Furthermore, the degree of metabolism also differs between the DPP-4 inhibitors and, like vildagliptin, saxagliptin is also extensively metabolized, whereas sitagliptin, linagliptin and alogliptin are not appreciably metabolized [11]. Circulating half-life also differs between the DPP-4 inhibitors, from the short half-life of vildagliptin and saxagliptin, to the medium half-life (approximately 10–24 h) for sitagliptin and alogliptin, to the long half-life (up to 40 h) for linagliptin. In terms of elimination, linagliptin is mainly eliminated through the biliary route, whereas the others, like vildagliptin, are cleared renally.

Since the DPP-4 inhibitors are all effective inhibitors of the catalytic site of DPP-4, they all prevent the inactivation of GLP-1, which increases the circulating level of the intact form of incretin, stimulates insulin secretion and inhibits glucagon secretion with improvement in glycemia. This is also what has been seen in studies, as reviewed in this article for vildagliptin, although the various DPP-4 inhibitors have been examined in different studies and also with different emphases to characterize their mechanistic actions. Finally, all DPP-4 inhibitors improve glycemia under different conditions in patients with Type 2 diabetes and they are safe with very low risk for adverse events, including hypoglycemia. Presently, there do not seem to be differences in glycemic effect, safety or tolerability, when meta-analyses are performed [38]. However, head-to-head studies are required to compare the DPP-4 inhibitors in more detail.

### Vildagliptin: clinical experience in monotherapy

The first clinical study with vildagliptin in patients with Type 2 diabetes was a 4-week trial in which vildagliptin was administered as monotherapy to previously drug-naïve patients [19]. The patients had a baseline HbA<sub>1c</sub> of 7.2% and this was reduced by 0.53% by vildagliptin within the 4-week study period. At the end of the trial, a standard meal was served and it was found that vildagliptin reduced glucose excursion and at the same time reduced glucagon levels but sustained insulin levels. This study therefore showed improved islet function in association

**Table 2. Pharmacodynamic effects of vildagliptin.**

Process	Effect	Ref.
Postprandial intact GLP-1 levels	Increased	[18,19]
Fasting intact GLP-1 levels	Increased	[20]
Insulin secretion	Stimulation	[21,22]
Glucagon secretion after meal	Inhibition	[18,19]
Glucagon secretion at hypoglycemia	Sustained or increased	[25]
Hepatic glucose production	Inhibition	[24]
β-cell mass increased in animal models	Increased	[27]
Islet dystopography in animal model of diabetes	Improved	[28]
Fasting lipolysis	Reduced	[21]
Postprandial lipolysis	Increased	[31]
Muscle–fat oxidation	Increased	[31]
Postprandial lipid levels	Reduced	[32]
Glucose disposal during clamp	Increased	[35]
Gastric emptying and gastric volume	Not affected	[36]
Satiety	Not affected	[36]



with improved glycemia by vildagliptin. Several more studies followed vildagliptin as monotherapy in patients with Type 2 diabetes lasting 12–24 weeks with a larger number of patients (Table 3) [39–48]. One study also examined vildagliptin in monotherapy [50-mg q.d.] for 12 weeks in subjects with impaired glucose tolerance ( $\text{HbA}_{1c}$  5.9%) [43]. Vildagliptin reduced prandial glucose by 32% in these subjects. Together these studies also show that the risk for adverse events is very low with vildagliptin. Thus, the number of adverse events reported during treatment with vildagliptin is not higher than during treatment with placebo. Of particular importance from a clinical perspective is the very low degree of hypoglycemia (<1%) and that no weight gain was observed with vildagliptin.

Vildagliptin has also been examined as monotherapy in head-to-head comparisons with other therapies. One study compared treatment with vildagliptin versus metformin in subjects with

a mean baseline  $\text{HbA}_{1c}$  8.7% [44]. During the 1-year study period,  $\text{HbA}_{1c}$  was reduced by 1.0% by vildagliptin and by 1.4% by metformin, which was not noninferior by vildagliptin compared with metformin. Body weight was unchanged by vildagliptin (+0.3 kg) and reduced by metformin (-1.9 kg). The total number of adverse events was similar in the two groups, but patients treated with vildagliptin experienced lower rates of gastrointestinal adverse events than in the group treated with metformin (a three- to four-fold higher incidence of diarrhea, nausea and abdominal pain in that group); hypoglycemia was rare in both groups.

Another study compared the long-term (2-year) effect of vildagliptin with rosiglitazone when given as monotherapy to patients with inadequate glycemic control when treated with diet and exercise alone (mean  $\text{HbA}_{1c}$  8.6%) [45]. It was found that  $\text{HbA}_{1c}$  was reduced by 0.8% by vildagliptin and by 1.4% by rosiglitazone, that body

**Table 3. Summary of clinical trials when vildagliptin has been examined in subjects with Type 2 diabetes either as monotherapy, as an add-on to ongoing therapy with metformin, glimepiride, pioglitazone or insulin, or as initial combination therapy with metformin.**

Treatment	Duration (weeks)	Baseline $\text{HbA}_{1c}$ (%)	Change in $\text{HbA}_{1c}$ by vildagliptin (%)	n	Ref.
Monotherapy (100 mg q.d.)	4	7.2	-0.53	18	[19]
Monotherapy (100 mg q.d.)	12	7.6	-0.53	63	[39]
Monotherapy (25 mg b.i.d.)	12	8.0	-0.26	70	[40]
Monotherapy	24	8.4	-0.7	83	[41]
Monotherapy (50 mg q.d.)	24	8.4	-0.8	163	[42]
Monotherapy	24	8.4	-0.8	152	[42]
Monotherapy (100 mg q.d.)	24	8.4	-0.9	157	[42]
Monotherapy	52	8.7	-1.0	526	[44]
Monotherapy	104	8.6	-0.82	396	[45]
Monotherapy	12	7.6	-0.95	188	[46]
Monotherapy	24	8.6	-1.4	441	[47]
Monotherapy	24	8.6	-1.1	300	[50]
Metformin	52	7.7	-0.6	56	[49]
Metformin	24	7.5	-1.1	185	[50]
Initial metformin (500 mg b.i.d.)	24	8.6	-1.6	290	[50]
Initial metformin (1000 mg b.i.d.)	24	8.7	-1.8	295	[50]
Metformin	52	7.3	-0.44	1396	[51]
Metformin	52	8.4	-0.9	295	[53]
Glimepiride (50 mg q.d.)	24	8.5	-0.58	132	[54]
Glimepiride	24	8.6	-0.63	132	[54]
Glimepiride	12	7.9	-1.0	102	[55]
Pioglitazone (50 mg q.d.)	24	8.6	-0.8	147	[56]
Pioglitazone	24	8.7	-1.0	158	[56]
Insulin	24	8.4	-0.5	144	[57]

Dosage of vildagliptin is 50 mg b.i.d. unless otherwise stated. Duration of therapy, baseline  $\text{HbA}_{1c}$ , change in  $\text{HbA}_{1c}$  from baseline by vildagliptin and number of patients in the vildagliptin arm of the various trials are shown.  
b.i.d.: Twice daily; n: Number of patients; q.d.: Once daily.

weight did not change with vildagliptin but was increased by 4.7 kg in the rosiglitazone-treated group, and that the number of patients with peripheral edema was lower with vildagliptin.

Two studies have compared vildagliptin with  $\alpha$ -glucosidase inhibitors as monotherapy; one study with voglibose in Japanese patients [46] and one study with acarbose in Chinese subjects [47]. The 12-week study in comparison with voglibose showed that vildagliptin reduced HbA<sub>1c</sub> by 0.95% and voglibose by 0.38% (baseline HbA<sub>1c</sub> 7.6%), and the 24-week study with acarbose showed that vildagliptin reduced HbA<sub>1c</sub> by 1.4% and acarbose by 1.3% (baseline HbA<sub>1c</sub> 8.6%). Both studies showed that patients on vildagliptin had fewer gastrointestinal adverse events than patients on  $\alpha$ -glucosidase inhibitors.

#### **Vildagliptin: clinical experience in combination with metformin**

There is extensive experience of vildagliptin as an add-on therapy to metformin in patients with Type 2 diabetes who are insufficiently controlled with metformin alone, and also when used in initial combination with metformin. The conclusion from these studies is that vildagliptin is efficient in improving glycemia in association with a low risk for adverse events, including hypoglycemia, and with weight neutrality (Table 3) [48–53]. The first study examining vildagliptin as an add-on to metformin was a 12-week study that was followed by a 40-week extension period in patients with a baseline HbA<sub>1c</sub> of 7.8% [49]. The results showed a placebo-adjusted reduction in HbA<sub>1c</sub> of 0.7% during the initial 12 weeks and of 1.1% after the entire 52-week study period. Furthermore, in a larger 24-week study, vildagliptin reduced HbA<sub>1c</sub> by 1.1% from a baseline of 7.5% when added to metformin [50], and an initial combination with vildagliptin plus metformin reduced HbA<sub>1c</sub> by 1.6–1.7% (depending on metformin dose) from a baseline of 8.6% after 24 weeks [48]. Therefore these studies show potent efficacy of the combination of vildagliptin and metformin.

One long-term (52-week) study compared the add-on to metformin of vildagliptin versus glimepiride [52]. The main results of this study are shown in Figure 2. The study showed that the two compounds similarly reduced HbA<sub>1c</sub> (by 0.4 and 0.5%, respectively, from a baseline of 7.3%), whereas adverse events were markedly different in the groups in favor of vildagliptin [51]. The difference in degree of hypoglycemia and body weight between vildagliptin and glimepiride persisted

throughout a second year extension of this study [52]. Another study compared vildagliptin with pioglitazone as an add-on to metformin in patients with a mean HbA<sub>1c</sub> 8.4% and showed reduction in HbA<sub>1c</sub> of 0.9% with vildagliptin and of 1.0% with pioglitazone [53]. There was no difference in the overall number of adverse events between the two groups but body weight increased with pioglitazone (by 2.6 kg) but not with vildagliptin (+0.2 kg).

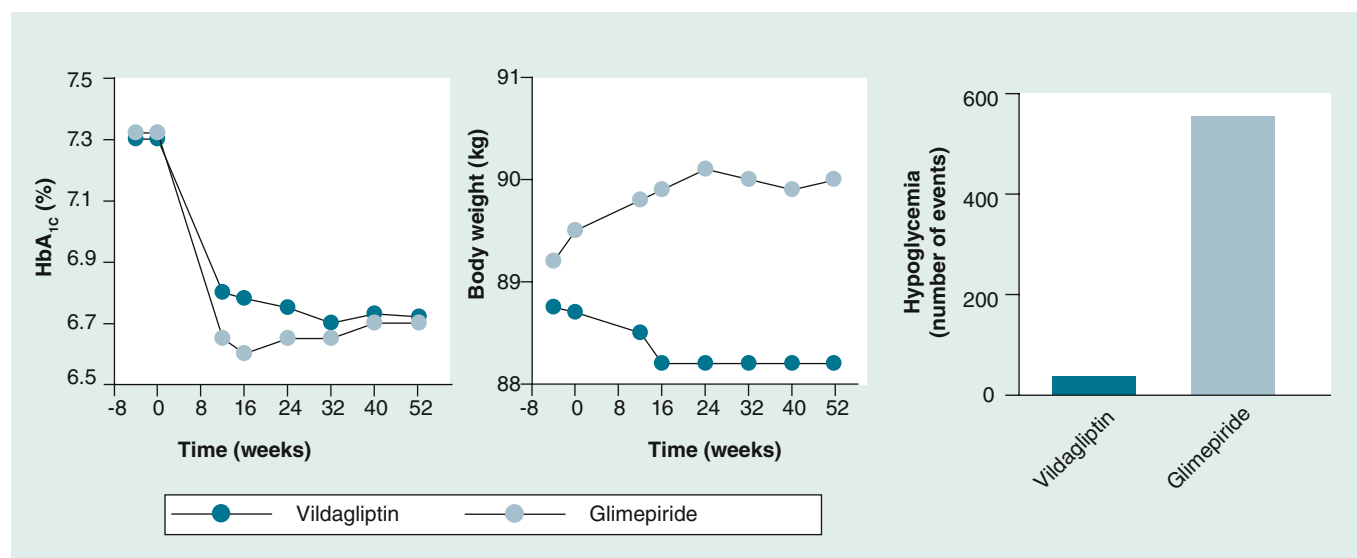
#### **Vildagliptin: clinical experience in combination with sulfonylurea, thiazolidinedione or insulin**

Vildagliptin improves glycemia when added to ongoing therapy with sulfonylurea. Thus, when vildagliptin was added to ongoing therapy with glimepiride, HbA<sub>1c</sub> was reduced after 24 weeks by 0.6% with vildagliptin at the dose of 50 mg q.d. and by 0.76% at the dose of 50 mg b.i.d. [54]. Another study investigated the effects and tolerability of vildagliptin when added to ongoing therapy with glimepiride in Japanese patients with Type 2 diabetes having a mean HbA<sub>1c</sub> of 7.9% [55]. During the 12-week study period, vildagliptin reduced HbA<sub>1c</sub> by 1.0% with no significant change in HbA<sub>1c</sub> (–0.1%) in the placebo-treated group, which continued with glimepiride therapy. There was no difference in adverse events between the two treatment arms; hypoglycemia was observed in only three of the 202 patients: two in the vildagliptin group and one in the placebo group.

Vildagliptin also improved glycemia when added to ongoing therapy with pioglitazone in a 6-month study in patients with a mean baseline HbA<sub>1c</sub> of 8.6% [56]. Vildagliptin reduced HbA<sub>1c</sub> by 1.1% (50 mg b.i.d.) versus 0.3% in the placebo group given pioglitazone alone. One study has evaluated the add-on of vildagliptin to insulin in subjects with Type 2 diabetes with a mean baseline HbA<sub>1c</sub> 8.9% over 24 weeks [57]. HbA<sub>1c</sub> was reduced by vildagliptin by 0.5% versus 0.2% in the group given insulin alone. This was associated with a reduced risk for hypoglycemia.

#### **Vildagliptin: clinical experience in very elderly patients & in patients with renal impairment**

A recent publication undertook a meta-analysis of patients treated with vildagliptin in seven monotherapy studies (baseline HbA<sub>1c</sub> 8.3%) and in three studies on add-on to metformin (baseline HbA<sub>1c</sub> 8.5%) in patients >75 years old (mean



**Figure 2.** Glycated hemoglobin levels, body weight and number of hypoglycemic episodes during 52-week treatment with vildagliptin 50 mg twice daily ( $n = 992$  at week 52 per protocol population) or glimepiride up to 6 mg/day ( $n = 976$  at week 52 per protocol population) added to metformin ( $\geq 1500$  mg/day). Means ( $\pm$  standard error) are shown.

HbA<sub>1c</sub>: Glycated hemoglobin.

Adapted with permission from [51].

age 77 years) to report efficacy and safety of the treatment in this patient group [58]. The results showed that vildagliptin reduces HbA<sub>1c</sub> by 0.9% in monotherapy and by 1.1% when used as an add-on to metformin. This was associated with a small reduction in body weight (by 0.9 kg) in the monotherapy studies, with no change in body weight when studied as an add-on to metformin. No hypoglycemia occurred in the studies and adverse events were reported to be the same in vildagliptin-treated patients and controls. It was therefore concluded that vildagliptin is also safe and efficacious in very elderly patients with Type 2 diabetes.

One study examined the 24-week safety, tolerability and efficacy of vildagliptin when used in patients with Type 2 diabetes who have moderate ( $n = 165$ ; baseline HbA<sub>1c</sub> 7.9%; GFR 30–50 ml/min) or severe ( $n = 97$ ; baseline HbA<sub>1c</sub> 7.7%; GFR <30 ml/min) renal impairment [59]. The patients continued with their background antidiabetic medication (in most cases insulin), and vildagliptin (50 mg q.d.) or placebo was added. Compared with placebo, vildagliptin reduced HbA<sub>1c</sub> by 0.5–0.6% without any increased risk of adverse events or worsening of renal impairment. Hence, vildagliptin may be an option for the antihyperglycemic management of patients with Type 2 diabetes and renal impairment, and because vildagliptin is eliminated by

the kidney [14], it has been approved for use in patients with GFR <50 ml/min at the dose of 50 mg q.d.

### Vildagliptin: experience on safety & tolerability

As evident from the large number of clinical trials, vildagliptin is well tolerated, and the number of adverse effects is low and, in fact, no different from the numbers of adverse events seen in placebo groups [60]. These relates to all types of reported adverse events, such as urinary tract or respiratory infections or headache. Furthermore, retrospective analyses of clinical trials have not shown any increased risk for fractures, cancer or cardiovascular events during treatment with vildagliptin or other DPP-4 inhibitors [61–63]. A large meta-analysis has also been undertaken to examine the cardiovascular safety of vildagliptin in relation to other therapies. The study was a pooled analysis of 25 Phase III studies using vildagliptin as monotherapy or combination therapy for more than 12 weeks and the study comprised more than 6000 patients. A subgroup analysis also examined the cardiovascular safety in patients who have a higher risk, mainly in those with a preceding cardiovascular event. It was found that the relative risk for a major acute cardiovascular event for vildagliptin (50 mg b.i.d.) compared with other comparators was 0.84% with a



confidence interval of 0.62–1.14 – that is, no significantly increased risk compared with comparators [64]. The cardiovascular safety of vildagliptin is also reinforced by a study on effects of vildagliptin on cardiac repolarization and conduction in 101 healthy volunteers given vildagliptin consecutively for 5 days [65]. The study showed that vildagliptin did not prolong the QT interval on ECG or affect cardiac conductivity, showing no deleterious effects on cardiac repolarization and conductivity in healthy subjects.

It has been discussed whether incretin-based therapies increase the risk of pancreatitis, since pancreatitis has occurred during this treatment [66]. There are also clinical reports of acute pancreatitis in patients treated with vildagliptin [67]. However, there does not seem to be any increased risk for acute pancreatitis in patients treated with vildagliptin when compared with the generally increased risk for pancreatitis in Type 2 diabetes, as shown in pooled analyses [60]. This pooled analyses of more than 7000 subject-years of exposure to vildagliptin and 6500 subject-years of exposure to comparators showed that the odds ratio for pancreatitis with vildagliptin compared with comparators was 0.70 with a confidence interval of 0.26–1.88, that is, no significant difference. A meta-analysis of all clinical trials with all DPP-4 inhibitors arrived at the same conclusion [63]. Nevertheless, it is important to have longer follow-up periods and postmarketing surveillance with regard to long-term safety, but the experience of today suggests a high tolerability with no additional risk for adverse events with vildagliptin or the other DPP-4 inhibitors.

In an earlier meta-analysis of clinical trials, it was found that when vildagliptin was administered at 100 mg q.d., a small increase in liver transaminases occurred when compared with the clinically recommended dosing of 50 mg b.i.d., although this was not related to any increased risk for hepatic adverse events [60]. Liver function tests are therefore recommended before and regularly during treatment with vildagliptin.

### **Vildagliptin & potential effects on diabetes complications**

It has been demonstrated that GLP-1 receptors are widely expressed and therefore that there is a potential that GLP-1 affects a number of different organs in the body, such as the heart, bones, kidney and the nervous system [68].

It is therefore possible that DPP-4 inhibitors also have extrapancreatic effects which may be beneficial for patients treated with these agents. In recent years, potential cardiovascular benefits of incretin-based therapy have been discussed. Both the heart and endothelial cells express GLP-1 receptors, and administration of GLP-1 has been shown to be cardioprotective and to improve endothelial function in different conditions [69]. Improvement of cardiovascular morbidity is therefore a possibility in long-term treatment with incretin-based therapy [70]. Several long-term cardiovascular outcome studies have therefore been initiated; results from these are expected from the year 2014 and onwards. Presently, therefore, no evidence for this has been presented in controlled clinical studies. However, a meta-analysis of clinical trials has examined the risk of major cardiovascular events during treatment with any of several different DPP-4 inhibitors in 40 different clinical trials. This analysis showed a trend for each of the DPP-4 inhibitors (sitagliptin, vildagliptin, saxagliptin and alogliptin) towards a lower cardiovascular risk compared with comparators [63]. This trend did not, however, reach significance for any of the individual DPP-4 inhibitors; however, if all 40 studies were analyzed together, there was a significantly reduced risk of major acute cardiovascular diseases during clinical trials in patients treated with DPP-4 inhibitors than with comparators. The widespread expression of GLP-1 receptors in vascular cells also may suggest that incretin-based therapy may improve microvascular complications, which have not yet been studied in detail [71].

### **Vildagliptin: clinical positioning**

Since vildagliptin improves islet function and therefore targets the key pathophysiologic defects in Type 2 diabetes, it may be used in both early and late stages of the disease. A preferential use of vildagliptin is as an add-on to metformin, sulfonylurea or thiazolidinediones in subjects with inadequate glycemic control on these therapies alone. Vildagliptin also holds promise as a monotherapy in whom metformin is contraindicated or unsuitable, and as an add-on to insulin therapy in subjects to improve glycemia and at the same time reduce the risk for hypoglycemia and/or weight gain. It should also be emphasized that vildagliptin is efficient across all age groups and in patients with low and high BMI, as well as in patients with renal

impairment. Vildagliptin will therefore be of particular importance in the treatment of elderly patients and of patients with renal impairment, where several of the other therapies are undesirable. Finally, the low risk of hypoglycemia with vildagliptin also suggests that it may be used in patients in whom hypoglycemia is undesirable. Vildagliptin, together with the other DPP-4 inhibitors, therefore offers a well documented glucose-lowering option in the treatment of Type 2 diabetes.

### Future perspective

Vildagliptin has been characterized in detail with regard to chemistry and binding characteristics, pharmacokinetics, pharmacodynamics and clinical effects and possibilities. What is now important to study is long-term durability and effects on long-term end points for more than 2 years, which is the time period for the longest studies so far. Furthermore, for exact clinical positioning in relation to other therapies, it will also be important to undertake head-to-head comparisons with other DPP-4 inhibitors, to allow guidelines to be more specific. Comparisons between DPP-4 inhibitors and GLP-1 receptor agonists are also of interest; two previously reported comparisons have

shown that GLP-1 receptor agonists (liraglutide or exenatide) have better effects on HbA<sub>1c</sub> and lowering of body weight compared with DPP-4 inhibition (sitagliptin) and this is supported by meta-analysis [38,72,73]. Widening the indication to include Type 1 diabetes is another future possibility for DPP-4 inhibitors, as was recently suggested for vildagliptin based on results of a 4 week study period [74]. Finally, there are also interesting future perspectives for the incretin therapy field as a whole, including the development of novel approaches, such as combining DPP-4 inhibitors with GLP-1 secretagogues [75].

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