Vildagliptin: novel pharmacological approach to treat Type 2 diabetes

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Vildagliptin is an orally active inhibitor of the enzyme dipeptidyl peptidase-4. It prevents the inactivation of the gut hormone glucagon-like peptide-1, which results in increased endogenous levels of the hormone. This stimulates insulin secretion and inhibits glucagon secretion by increasing the glucose sensitivity of the pancreatic α- and β-cells. A large body of evidence shows that vildagliptin improves glycemic control in subjects with Type 2 diabetes. Thus, vildagliptin reduces hemoglobin (Hb)-A_{1c} by 0.8–1.1% from baseline levels of 7.7–8.5% as monotherapy in Type 2 diabetes. Furthermore, vildagliptin reduces HbA_{1c} when used in combination therapy with metformin, a thiazolidinedione, a sulfonylurea or insulin. Moreover, vildagliptin is well tolerated, the risk of hypoglycemia is low and body weight is not increased during the treatment. Therefore, vildagliptin represents a novel pharmacological therapy for Type 2 diabetes. Its main potential is as an add-on therapy to metformin in patients with insufficient glycemic control, as an add-on to sulfonylurea and as a first-line treatment as monotherapy in patients who are intolerant to or have contraindications for metformin.

Type 2 diabetes has developed into an increasingly serious global health burden owing to a dramatic increase in the prevalence. It has been estimated that the prevalence of diabetes for all age groups worldwide will increase from 2.8% in 2000 to 4.4% in 2030 [1]. This corresponds to an increase in the total number of people with diabetes from 171 million in 2000 to 366 million in 2030. Furthermore, the present-day treatment does not sufficiently prevent the development of secondary complications to the disease. Complications to the disease are therefore seen at an increasing rate, including mortality from cardiovascular diseases. A critical factor underlying secondary complications is hyperglycemia, and therefore treatment to improve glycemic control is of major importance [2]. The basis for treatment is lifestyle changes with increased physical activity and dietary modifications. When this is insufficient, addition of pharmacological treatment is necessary. Until recently, pharmacological interventions included biguanides, thiazolidinediones, sulfonylureas, meglitinides, α-glucosidase inhibitors and insulin [3,4]. Recent development has also added the amylin analog pramlintide, the glucagon-like peptide (GLP)-1 mimetic exenatide and the dipeptidyl peptidase (DPP)-4 inhibitor sitagliptin to the therapeutic arsenal [5,6]. Current guidelines recommend the biguanide metformin as first-line treatment, with subsequent addition of sulfonylureas and/or thiazolidinediones [7].

One problem is that, even with aggressive therapy, glycemic control deteriorates [8]. This is partially explained by failure of the current therapy to target all defects associated with Type 2 diabetes. A main metabolic defect is insulin resistance, that is, failure of insulin to increase glucose disposal sufficiently or inhibit hepatic glucose production. However, insulin resistance is not sufficient to cause Type 2 diabetes since, under normal conditions, it is compensated by adaptive changes in islet function. These adaptive changes include increase in insulin secretion, reduction in glucagon secretion and increase in β-cell mass [9–14]. However, in subjects with islet dysfunction, these adaptive changes are inadequate, which may result in impaired glucose tolerance and Type 2 diabetes [10]. Therefore, in relation to the requirement, patients with Type 2 diabetes exhibit low insulin and high glucagon secretion. The most commonly used current therapy only partially addresses these defects: biguanides and thiazolidinediones improve insulin sensitivity and sulfonylureas improve insulin secretion [15–17]. The treatments do not, however, address high glucagon and low β-cell mass. In addition, current therapy is often associated with adverse events, such as hypoglycemia with sulfonylureas and insulin, gastrointestinal discomfort with biguanides and increase in body weight, edema and cardiac insufficiency with thiazolidinediones [15–18]. There is thus a need to develop novel therapy, which should target the

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main defects of the disease. An ideal diabetes therapy should also show glycemic durability, present a favorable safety profile with low risk of adverse events including hypoglycemia, and should be cost-effective.

GLP-1 as a target for treatment of Type 2 diabetes

A current novel therapy and a therapy in development is based on the gut hormone GLP-1 [19–21]. GLP-1 is the main incretin hormone, that is, an intestinal hormone augmenting glucose-stimulated insulin secretion after oral glucose or meal ingestion [22]. The history of GLP-1-based therapy for Type 2 diabetes goes back to the early 1990s, when it was demonstrated that intravenous infusion of GLP-1 reduced insulin requirement to a meal intake in both Type 1 and Type 2 diabetes [23]. The antidiabetic action of GLP-1 was later confirmed in a number of studies and ultimately demonstrated in a 6-week study using continuous subcutaneous infusion of GLP-1 in subjects with Type 2 diabetes [24]. Several different actions of GLP-1 contribute to the antidiabetic action: the hormone stimulates insulin secretion in a glucose-dependent manner [25], it inhibits glucagon secretion [11], delays gastric emptying [26] and induces satiety [27]. In addition, rodent studies have shown that GLP-1 has the potential to stimulate insulin biosynthesis and insulin gene transcription and to increase β-cell mass by stimulating β-cell neogenesis and proliferation and inhibiting apoptosis [12,28]. Therefore, GLP-1 affects several of the important targets for treatment of diabetes, although it should be emphasized that it is unknown whether GLP-1 indeed increases β-cell mass in humans.

One problem in the development of GLP-1 as a novel therapy for Type 2 diabetes has been that the hormone is rapidly inactivated, resulting in a half-life of native GLP-1 of less than 3 min. The inactivation is due to the enzyme DPP-4 [29]. To overcome this problem, two strategies have been explored. One strategy is the use of GLP-1 receptor agonists, which are resistant to DPP-4 (GLP-1 mimetics). Several GLP-1 mimetics have been developed; most of them are variants or modifications of the GLP-1 molecule. A GLP-1 mimetic that has been introduced in the market is exenatide (Byetta®, Amylin and Eli Lilly) [30]. Exenatide is an injectable compound that is administered twice daily and has been shown to improve glycemic control and to reduce body weight in subjects with Type 2 diabetes [30]. Except for nausea and vomiting, which are seen in 20–30% of patients, exenatide is safe and well tolerated [30,31]. Other GLP-1 mimetics are in development, such as liraglutide (Novo Nordisk) [21] and, recently, small-molecule GLP-1 receptor agonists were also presented [32]. Furthermore, long-acting GLP-1 agonists are also under development.

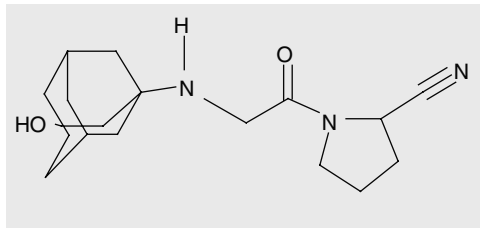
DPP-4 inhibition as a strategy to treat diabetes

Another approach for GLP-1-based therapy is to inhibit the enzyme DPP-4, which prevents the inactivation of GLP-1 and thereby enhances and prolongs the action of the endogenous incretin hormone [20–22]. DPP-4 belongs to a family of enzymes that also includes DPP-8 and DPP-9. DPP-4 cleaves bioactive peptides with alanine or proline as the second amino acid from the N-terminal end by removing the N-terminal dipeptide [29,33]. GLP-1 (alanine as the second amino acid) is a substrate for DPP-4; the cleavage process yields GLP-1 [9–36], which is largely inactive in reducing glucose. The prevention of the inactivation of GLP-1 by DPP-4 enhances and prolongs the action of the endogenously released GLP-1 [34]. Several animal studies have supported this idea by presenting data that genetic deletion of DPP-4 [35] or pharmacological inhibition of DPP-4 improves glucose tolerance and insulin secretion in various models [36–39]. A proof-of-concept study on this strategy in subjects with Type 2 diabetes was published in 2002; it showed improved metabolic control with reduced fasting and prandial glucose levels and reduction of hemoglobin (Hb)-A_{1c} after 4 weeks of treatment with the DPP-4 inhibitor NVP-DPP728 [40]. Several DPP-4 inhibitors are now in different stages of clinical development [38]. Besides vildagliptin (LAF237, Galvus®; Novartis), the most clinical experience exists for sitagliptin (MK-0431, Januvia®; Merck). Both these compounds are orally active and they efficiently inhibit DPP-4 [6,41].

Vildagliptin chemistry

The full name of vildagliptin is 1[[(3-hydroxy-1-adamantyl)amino-]acetyl]-2-cyano-(s)-pyrrolidine; **Figure 1** shows the chemical structure. It has a molecular weight of 303.41 g and belongs to a group of compounds with an N-substituted glycyl-2-cyanopyrrolidines [41,42]. This group of compounds follows a common design with an L-amino acid with a protonable N-terminal primary amine at the P-2 site, mimicking

Figure 1. Chemical structure of vildagliptin.



the N-terminal dipeptide of the natural substrates [43]. The adamantyl group adjacent to the amine of the structure of vildagliptin is essential for biological activity by providing steric bulk [42]. Vildagliptin exhibits high affinity to DPP-4 [43] and inhibits the enzyme in a two-step reversible, competitive manner [44]. Vildagliptin shows a much higher affinity to DPP-4 than to the other enzymes within this enzyme family, such as DPP-8 or DPP-9 [44]. This has been thought to be important, since a compound inhibiting DPP-8 and DPP-9 is associated with toxicity in rodents [45]. However, whether this toxicity is due to DPP8/9 inhibition or related to the specific compound is not known, and such toxicity has not been observed for vildagliptin or any of the other DPP-4 inhibitors in development. This adverse event is therefore not a concern for vildagliptin or other DPP-4 inhibitors in development.

Pharmacokinetics & metabolism of vildagliptin

Vildagliptin is active after oral intake and has been demonstrated to exhibit an oral bioavailability of 85% in subjects with Type 2 diabetes [46]. The mean elimination half-life has been shown to be 2.1 h. Protein binding in plasma is low (~9%) and distribution volume at steady state is approximately 70 l. Total systemic clearance rate is 13 l/h and the main elimination mechanism is metabolism, although approximately 20% of vildagliptin is cleared unmetabolized through renal elimination [46]. The main metabolic pathway of vildagliptin is hydrolysis for formation of a carboxylic acid, known as LAY151, which is renally secreted. One study has examined whether the pharmacokinetics of vildagliptin is altered in subjects with hepatic impairment. In that study, subjects with mild, moderate or severe hepatic impairment were given 100 mg vildagliptin. There was no significant difference in the pharmacokinetics of vildagliptin in these patients [47].

Figure 2 shows the effect of vildagliptin at different doses on plasma DPP-4 activity in subjects with Type 2 diabetes, as reported by He and colleagues [48]. It is seen that whereas plasma DPP-4 activity through a 24-h study period was unchanged after placebo administration, vildagliptin markedly and rapidly inhibited the enzyme activity. This was seen already at the lowest tested dose of 10 mg, which inhibited DPP-4 activity by almost 100% over a 4-h period. By increasing the dose, the duration of inhibition of DPP-4 activity was prolonged, and at doses that have been used in the clinical studies (50 and 100 mg), marked inhibition of DPP-4 activity lasts for 12–16 h. Since the inhibition is not complete over a 24 h period, it could be discussed whether vildagliptin should be given in the morning or evening. However, a recent 4-week study in subjects with Type 2 diabetes reported that there was no significant difference regarding improved glycemic control by giving 100 mg as a single dose before the breakfast meal in the morning versus before the dinner meal in the evening [49].

Mechanisms of antidiabetic action of vildagliptin

Several studies have been directed to understand the mechanism of action of the antidiabetic effect of vildagliptin. These studies are summarized in the following sections.

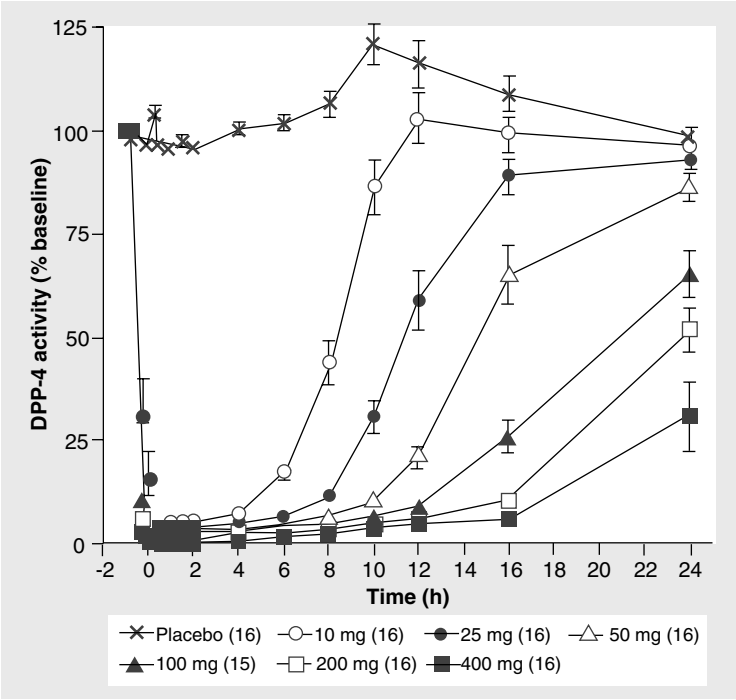
Incretin hormones

The antidiabetic action of vildagliptin relies on the incretin hormones. This is evident from animal studies, where the effects of vildagliptin are lost in mice lacking the GLP-1 and glucose-dependent insulinotropic polypeptide (GIP) receptors [50]. In humans, vildagliptin increases the overall daily concentration of active concentrations of both GLP-1 and the other incretin hormone, GIP [51]. The active GLP-1 and GIP concentrations after meal ingestion are augmented by two- to three-fold by vildagliptin. It should be emphasized that the sustained diurnal pattern of the incretin hormones persists after vildagliptin treatment, with peaks after each meal, and also that the fasting, not only the prandial levels, of the incretin hormones are elevated by the treatment.

Islet function

Since a main effect of GLP-1 is to augment glucose-stimulated insulin secretion, it is also expected that vildagliptin stimulates insulin

Figure 2. Plasma DPP-4 activity expressed as a percentage of baseline following single oral doses of vildagliptin or placebo in patients with Type 2 diabetes.



Means ± SEM, are shown; numbers within parenthesis refer to number of subjects. Reproduced with permission from [48].

secretion. This has been shown in animal studies [52–54]. In subjects with Type 2 diabetes, following meal ingestion there is a sustained insulin level after treatment with vildagliptin in spite of lower glycemia, a sign of stimulation of insulin secretion [55]. Furthermore, mathematical modeling of insulin and glucose data or estimation of the insulin secretory rate, as calculated by C-peptide deconvolution, have demonstrated a stimulated insulin secretion by vildagliptin in Type 2 diabetes [51,56–59]. Similarly, following oral glucose tolerance test (OGTT), vildagliptin increases the absolute insulin levels in the presence of lower glycemia [48]. It has also been shown that the increased insulin secretion by vildagliptin is sustained through a 52-week study period [56,57]. However, after a 4-week washout, insulin secretion is no longer augmented [57]. In addition, the proinsulin levels are reduced by vildagliptin [59], which is a sign of improved β-cell function. GLP-1 also reduces glucagon secretion [11], and this has similarly been demonstrated after vildagliptin [54,60]. In fact, the reduction in glucagon levels after vildagliptin is associated with reduced glucose production in the liver, which may explain the robust reduction in fasting glucose with this strategy [60]. Therefore, these mechanistic studies have shown that vildagliptin, as does GLP-1, stimulates insulin secretion and inhibits glucagon secretion, that is, it affects two of the most important targets for treatment. By contrast, no studies exist on the potential effect of vildagliptin on β-cell mass in humans. The results that vildagliptin does not induce a permanent enhancement of insulin secretion after 52 weeks of treatment, but instead that the effect vanishes after a 4-week washout, argue against an action of vildagliptin on β-cell mass in humans [57].

Insulin sensitivity

Although no direct increase in insulin sensitivity is seen during acute administration of GLP-1 in subjects with Type 2 diabetes, as evident from euglycemic, hyperinsulinemic clamp studies [61], a long-term effect has shown an increased insulin sensitivity [24]. In addition, after treatment with vildagliptin, an increased insulin sensitivity has been shown. One study showed increased insulin sensitivity during meal ingestion after 12-week treatment in combination with metformin in subjects with Type 2 diabetes using an indirect method with surrogate markers for assessment of insulin sensitivity [56]. Another study demonstrated increased insulin sensitivity during an intravenous glucose tolerance test after 6 weeks' treatment of subjects with impaired fasting glucose [62]. The mechanism underlying the improved insulin sensitivity after vildagliptin treatment remains to be established. Hypothetically, improved insulin sensitivity may be due to the improved glycemic control, to the reduction in circulating glucagon and/or to a direct action to improve insulin action. It should be emphasized that only indirect markers for assessing insulin sensitivity have been used in these studies. Recently, however, a study has reported that vildagliptin following a 6-week course increases insulin sensitivity in subjects with Type 2 diabetes, when measured by the hyperinsulinemic clamp technique [63].

Gastric emptying

GLP-1 is known to inhibit gastric emptying [27]. However, by contrast, vildagliptin has been shown not to exert any clinically important effect on gastric emptying. Thus, one study examining the time for gastric content to be reduced by 50% after meal ingestion showed that this time period was not altered significantly by vildagliptin [64]. Hence, it is unlikely that vildagliptin exerts any clinically important effect

on gastric emptying. The difference between the actions of GLP-1 and vildagliptin on gastric emptying is most likely explained by the lower GLP-1 levels, which are achieved during DPP-4 inhibition, than by following exogenous administration of GLP-1.

Preclinical studies of vildagliptin

As previously reviewed, vildagliptin improves glucose tolerance in Zucker rats, ob/ob mice, C57BL/6J mice fed a high-fat diet and in high-fat diet-fed rats with insulin resistance [41,52]. Recent studies have also demonstrated a potent long-term action of vildagliptin in animals. Thus, an 8-week administration of vildagliptin to normal mice resulted in augmented glucose disposal and glucose-stimulated insulin secretion in association with augmented glucose-stimulated insulin secretion from isolated islets [53]. Moreover, vildagliptin also improves glucose tolerance in mice with overexpression of the human islet amyloid polypeptide in β-cells [54]. Hence, experimental data show that vildagliptin augments glucose tolerance and that this is associated with increased insulin secretion. Regarding the potential influence on β-cell mass, daily administration of vildagliptin to neonatal rats for 21 days increased β-cell mass [65]. However, it should be emphasized that no evidence that vildagliptin increases β-cell mass in humans has been demonstrated.

Clinical studies with vildagliptin as monotherapy

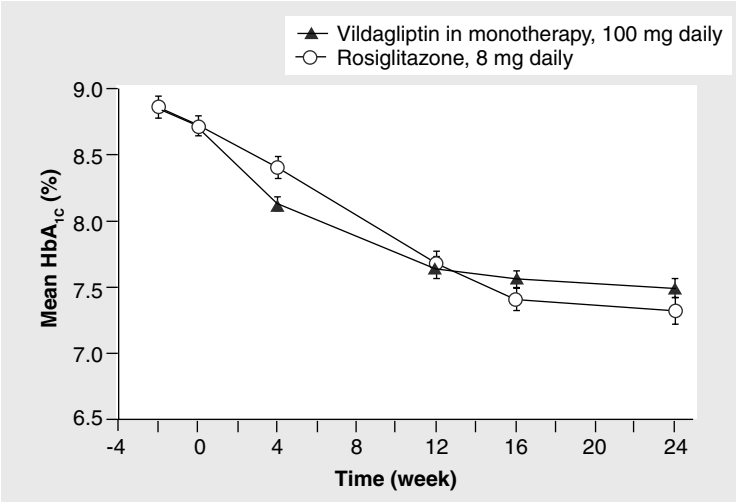
In monotherapy, vildagliptin reduces fasting and prandial glucose as well as HbA_{1c} in studies from 4 up to 52 weeks in subjects with Type 2 diabetes. The first study examined the 4-week effect of vildagliptin at 100 mg once daily to 18 drug-naive patients in comparison with 19 patients given placebo [55]. Baseline HbA_{1c} levels were 7.2% and baseline fasting glucose was 9.0 mmol/l. The results showed that vildagliptin, in comparison with placebo, reduced fasting glucose by 0.7 mmol/l and the 24-h mean glucose by 0.93 mmol/l and, even though the study persisted only for 4 weeks, HbA_{1c} was significantly reduced, by 0.53% versus only 0.15% in the placebo group. Furthermore, vildagliptin was safe and well tolerated with no hypoglycemia, and body weight did not change.

A subsequent 12-week study examined four different doses of vildagliptin in monotherapy in patients with Type 2 diabetes [66]. A total of 279 patients were studied and they were given 25 mg twice daily (n = 51), 25 mg once daily (n = 54), 50 mg once daily (n = 53), 100 mg once daily (n = 63) or placebo (n = 58). Baseline HbA_{1c} in this study was 7.7%. It was found that after 12-week treatment, HbA_{1c} was reduced by 0.46% by vildagliptin at 50 mg once daily and by 0.40% at 100 mg once daily compared with an increase in HbA_{1c} in the placebo group by 0.13%. Also in this study, vildagliptin was well tolerated. Another 12 week study examined vildagliptin as monotherapy at 25 mg twice daily (n = 70) versus placebo (n = 27) in patients with a mean baseline HbA_{1c} of 8.0% [67]. It was found that the placebo-adjusted reduction in HbA_{1c} by vildagliptin was 0.6%.

Furthermore, a large 24-week study comprising 519 drug-naive patients with Type 2 diabetes showed that vildagliptin (50 mg twice daily) reduced HbA_{1c} by 1.1% from a baseline of 8.7% (**Figure 3**) [68]. This study also showed that vildagliptin was noninferior to rosiglitazone given at 8 mg once daily. Vildagliptin (50 mg twice daily; n = 526) has also been compared with treatment with metformin 1 g twice daily (n = 254) in subjects with Type 2 diabetes [69]. It was found that vildagliptin reduced HbA_{1c} by 1.0% from a baseline of 8.7%. Metformin reduced HbA_{1c} by 1.4%; hence, although noninferiority versus metformin was not reached, vildagliptin also showed a clinically meaningful reduction of HbA_{1c} in this study. Furthermore, a 24-week study examined the effects of vildagliptin (50 mg once daily, 50 mg twice daily or 100 mg once daily) versus placebo in a total of 632 subjects with Type 2 diabetes having a mean baseline HbA_{1c} of 8.4% [70]. It was found that vildagliptin reduced HbA_{1c} by 0.8–0.9% in the three groups, with nonsignificant difference between the groups. In the placebo group, HbA_{1c} was reduced by only 0.3%.

The studies reported so far included patients with HbA_{1c} levels exceeding 7.5%. To study whether vildagliptin was active also in subjects with more mild derangement of the glycemic control, one study comprising 306 patients evaluated the influence of monotherapy of vildagliptin at 50 mg once daily for 52 weeks in diabetic patients with a HbA_{1c} of 6.2–7.5% [71]. The results showed that, when adjusted for the effect of placebo, vildagliptin reduced HbA_{1c} in these mildly diabetic patients by 0.3%. Furthermore, vildagliptin (50 mg once daily) has also been given for 12 weeks in 90 subjects with impaired glucose tolerance compared with placebo administration to 89 subjects [72]. The results showed that, in this study population, vildagliptin

Figure 3. Time course in HbA_{1c} during a 24-week trial in patients with Type 2 diabetes treated with vildagliptin in monotherapy (100 mg daily; n = 434) or rosiglitazone (8 mg daily; n = 221).



Means ± SEM are shown. HbA_{1c}: Hemoglobin A_{1c}.
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improved glycemia, as evident by a significant reduction in peak glucose excursion after a 2-h oral glucose tolerance test.

Vildagliptin has thus been shown to improve glycemic control as monotherapy in several different studies up to 52 weeks. A recent meta-analysis of five Phase III studies with vildagliptin as monotherapy, at either 50 mg twice daily or 100 mg once daily (total 1682 patients), showed that HbA_{1c} was reduced by 1.0% from a mean of 8.6% [73]. Furthermore, fasting glucose was reduced by 1.1 mmol/l from a baseline of 10.3 mmol/l. All studies showed that vildagliptin is safe and well tolerated. Hypoglycemia was seen in 0.4% of the subjects and mean body weight was reduced by 0.3 kg from a baseline of 91 kg. Moreover, the data obtained from the Phase III studies have also been divided in subjects below versus those above 65 years of age. This subdivision has revealed that, in the elderly, vildagliptin is safe and well tolerated and reduces HbA_{1c} [74]. Finally, when analyzing the efficacy, safety and tolerability of vildagliptin as monotherapy in the Phase III studies based on ethnicity, no ethnic difference was observed [75].

Clinical studies with vildagliptin in combination therapy

Studies have reported the experience of treatment with vildagliptin in combination with metformin, a thiazolidinedione, a sulfonylurea or insulin (**Table 1**).

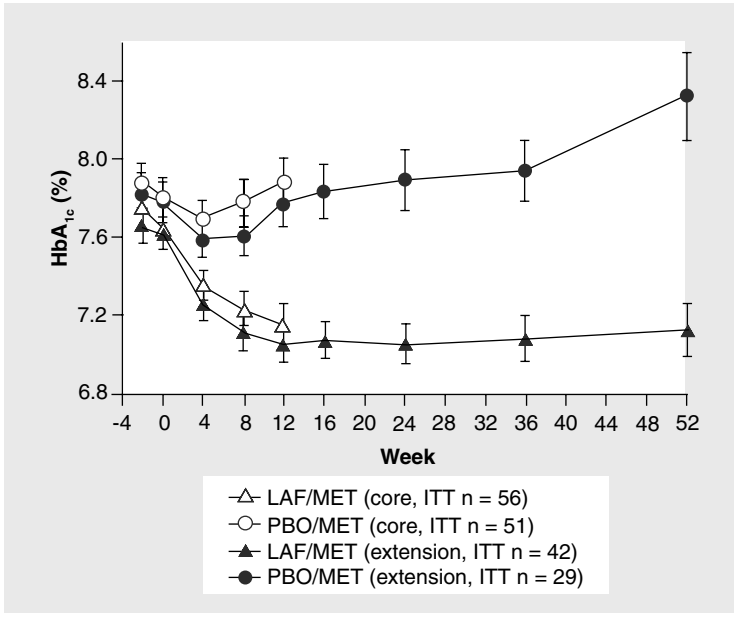
Metformin

The first study combining vildagliptin with other pharmacological treatment was a 52-week trial, in which vildagliptin (50 mg daily) was added to ongoing treatment with metformin in a total of 107 patients with a mean baseline HbA_{1c} of 7.8% [76]. The study comprised an initial core study for 12 weeks, which was followed by a 40-week extension period. During the initial 12-week study period, vildagliptin plus metformin reduced HbA_{1c} levels by 0.7% compared with metformin alone. Furthermore, the placebo-adjusted reduction in HbA_{1c} by vildagliptin in combination with metformin after 52 weeks was 1.1% (**Figure 4**). In this study, body weight was not significantly different between the two groups. Adverse events were similar in the two groups in the core study, whereas in the extension study, 69% of patients had an adverse events in the group receiving vildagliptin and metformin versus 58% in the group given metformin alone [76]. This study was followed by a larger study comprising 416 patients, in which vildagliptin (50 mg once or twice daily) was added to ongoing treatment with metformin in patients with a mean baseline HbA_{1c} of 8.4% [77]. The placebo-adjusted reduction in HbA_{1c} by vildagliptin in combination with metformin was 1.1% at the dose of 50 mg twice daily after 24 weeks. In these studies, the add-on of vildagliptin to other treatments was safe and well tolerated. Adverse events were similar in the groups, except that gastrointestinal adverse events were less common in subjects treated with vildagliptin and metformin in combination versus those given metformin alone. Furthermore, relative to the placebo group, body weight was unchanged in patients receiving vildagliptin at 50 mg in combination with metformin, whereas a slight increase (by 1.0 kg) was seen in patients receiving vildagliptin at 100 mg in combination with metformin [77].

Thiazolidinedione

In a 6-month study involving 463 patients with a mean baseline HbA_{1c} of 8.7%, vildagliptin was given at 50 or 100 mg daily as an add-on to pioglitazone (45 mg daily) [78]. It was found that HbA_{1c} was reduced by 0.8 and 1.0% by the two doses of vildagliptin, respectively. Total number of adverse events was not significantly different between the three study groups and, in general, the adverse events were considered mild and unrelated to study medication. However, peripheral edema occurred more frequently in patients

Figure 4. Time course in HbA_{1c} levels during a 52-week trial in patients with Type 2 diabetes treated with metformin with addition of vildagliptin (50 mg daily) or placebo.



The study consisted of a core study and an extension phase. In the core study, the intent-to-treat populations consisted of 56 patients in the vildagliptin plus metformin group (LAF/MET) (50 mg once daily) and 51 patients in the placebo plus metformin group (PBO/MET). A total of 42 patients receiving vildagliptin plus metformin (LAF/MET) participated in the extension and 29 patients receiving placebo plus metformin (PBO/MET) participated in the extension. Data are means ± SEM. Reproduced with permission from [76].

receiving vildagliptin (7.5%) than in those receiving placebo added to pioglitazone (2.5%). The reason for this is not known. Patients receiving placebo had an increased body weight of 1.4 kg during the course of the study and no additional body weight increase was observed when vildagliptin was added at 50 mg. At 100 mg vildagliptin, however, body weight increased by another 1.3 kg [78].

sulfonylurea

In a 24-week trial involving 276 patients with a mean HbA_{1c} level of 8.5%, vildagliptin (50 mg once or twice daily) was added to ongoing treatment with the sulfonylurea compound glimperide (4 mg daily). It was found that vildagliptin (in both groups) reduced HbA_{1c} levels by 0.7% in combination with glimepiride versus glimepiride alone [79]. Adverse events were similar in the study groups – hypoglycemia was seen in 0.6% of patients receiving glimepiride alone versus 1.2% in patients receiving glimepiride and vildagliptin 50 mg daily and 3.6% in patients receiving glimepiride and vildagliptin at 100 mg daily.

Insulin

Vildagliptin has also been added to insulin in subjects with more advanced Type 2 diabetes in a 24-week study in 296 patients with a mean baseline HbA_{1c} of 8.4% [80]. Subjects in the study had a daily insulin dose exceeding 30 U with a mean daily dose of 82 U/day. Approximately a third of the patients were using insulin glargine and almost half were using short-acting insulin as part of their daily regimen; the remainders were using combinations of NPH and regular insulin [80]. The results showed that HbA_{1c} was reduced by 0.5% versus baseline in the group given vildagliptin with insulin versus 0.2% in the group given insulin alone, resulting in an adjusted mean difference between vildagliptin and placebo of 0.3%. The effect was more pronounced in elderly subjects. During the treatment period, the insulin dose had to be increased by 1.2 U/day in the vildagliptin group for achievement of glycemic control, versus 4.1 U/day in the group given insulin alone. This was seen in association with fewer incidences of hypoglycemia in the group given vildagliptin.

Thus, the studies with vildagliptin as an add-on therapy to metformin, a thiazolidinedione, a sulfonylurea and insulin in patients with inadequate glycemic control show good efficacy (**Table 1**). Mean HbA_{1c} levels are reduced by 0.7–1.1%; in combination with insulin by 0.3%. All studies showed that the highest reduction was seen in subjects with highest baseline HbA_{1c} levels. In all these combination studies, vildagliptin was safe and well tolerated, with a similar adverse events profile to placebo. Incidences of hypoglycemia were low during treatment with vildagliptin and vildagliptin was body weight neutral.

Body weight, adverse events & other effects in studies with vildagliptin

Body weight

GLP-1 is known to induce satiety, which results in reduced food intake and reduced body weight [27]. However, as has been shown in several of the studies, vildagliptin does not affect body weight [65–70,76–78].

Adverse events

Vildagliptin has been shown to be safe and well tolerated. In four monotherapy studies, 750 patients were treated with vildagliptin in a total of 449 months and any adverse event was reported in 68% of the patients [41,55,66–68]. The most common adverse events were headache (9.3%), nasopharyngitis (9.1%), dizziness

Table 1. Reduction in HbA_{1c} by vildagliptin when used in combination therapy when compared with monotherapy with metformin, sulfonylurea, thiazolidinedione or insulin alone.

Combination	Baseline HbA_{1c} (%)	Duration (weeks)	Placebo-adjusted reduction in HbA_{1c} (%)	Ref.
Metformin	7.8	52	1.1	[76]
	8.4	24	1.1	[77]
Thiazolidinedione	8.7	24	1.0	[78]
Sulfonylurea	8.5	24	0.7	[79]
Insulin	8.4	24	0.3	[80]

(4.7%), diarrhea (4.1%), back pain (3.6%), upper respiratory tract infection (3.6%), nausea (1.1%), peripheral edema (1.0%) and cough (0.8%). These figures were not significantly different from those reported in the placebo groups. One episode of hypoglycemia (<3.1 mmol/l) occurred in 0.8% of the patients. In the combination studies, in which vildagliptin was given together with metformin, sulfonylurea, thiazolidinedione or insulin, the number of adverse events was not higher than in the groups given metformin, sulfonylurea, thiazolidinedione or insulin alone, except in the study in which vildagliptin at 100 mg was combined with pioglitazone [76–80]. The most common adverse events in these studies were dizziness (6.3%), asthenia (5.6%), tremor (5.2%), headache (5.1%), upper respiratory tract infection (4.8%) and nasopharyngitis (4.7%). Hypoglycemia was observed in 5.2% of the patients treated with vildagliptin versus 7.0% of patients given placebo; these patients were mainly seen in the study combining vildagliptin with insulin versus insulin alone [80]. It should be emphasized, however, that these studies are of 52-week duration at most; hence, long-term safety and tolerability remain to be established.

Laboratory toxicity tests have not shown significantly different results between subjects treated with vildagliptin versus other compounds or placebo in the published clinical trials. However, a recent analysis by Novartis A/S of pooled clinical trial data involving more than 8000 patients treated with vildagliptin has shown an imbalance in liver enzyme levels during treatment. Thus, an elevation of aspartate aminotransferase and alanine aminotransferase to levels greater than three times the upper limit of normal has been seen in 0.86% of patients receiving vildalgliptin at 100 mg once daily, in 0.34% of patients receiving vildagliptin at 50 mg twice daily and in 0.21% of patients receiving vildagliptin at 50 mg once daily [101]. The corresponding figure in placebo groups was 0.4% and in groups treated with a comparator, 0.2%. Hence, according to this analysis, a dose of 100 mg of vildagliptin, but not of 50 mg once daily or 50 mg twice daily, increases levels of these liver enzymes. The reason for this discrepancy needs to be explored.

Other effects

Clinically important measures in diabetes treatment are lipids, blood pressure and cardiovascular markers. However, so far very few studies have examined these processes in detail following treatment with vildagliptin. In general, the clinical studies have reported no significant effects on fasting lipids, blood pressure or potential changes in electrocardiography. However, one study reported an interesting and significant improvement of prandial lipemia after vildagliptin, in that the compound induced a reduction in prandial lipemia following ingestion of a fat-rich meal [81]. Furthermore, by pooling blood pressure data from Phase III studies, a slight reduction in systolic and diastolic blood pressure by vildagliptin (by 8 and 4 mmHg, respectively), was observed, which requires further study [82].

Regulatory affairs

Vildagliptin has been approved in Mexico and Brazil to be used at both 50 and 100 mg daily doses. In Europe, a positive opinion has been received recommending vildagliptin to be used at 50 mg once daily in combination with sulfonylurea, or at 50 mg twice daily for use in combination with metformin or a thiazolidinedione [102]. In the USA, Novartis received an approvable letter for vildagliptin from the FDA in February, 2007, but was asked to perform a study in subjects with severe renal impairment.

Conclusion & future perspective

DPP-4-inhibition is an interesting novel therapy for Type 2 diabetes that shows clinically meaningful reductions in HbA_{1c}, both in monotherapy and in combination therapy with existing treatments. [83]. DPP-4 inhibition targets impaired islet function, is orally active and is safe

and well tolerated with low risk of hypoglycemia. DPP-4 inhibition is body weight neutral and therefore does not increase body weight.

Vildagliptin is an efficient representative of this class of DPP-4 inhibitory compounds. It shows all the benefits that may be expected from a DPP-4 inhibitor. Further studies should aim at comparing the effects of vildagliptin versus sitagliptin and comparing the effects of vildagliptin versus a GLP-1 mimetic in head-to-head-studies. Furthermore, add-on therapy with vildagliptin in combination with insulin should be studied in more detail. Studies are also required to establish the long-term durability with metabolic and cardiovascular outcome. Finally, potential adverse events in long-term studies are also important to study.

A concern for DPP-4 inhibitors has been that several bioactive peptides are substrates for DPP-4 and, therefore, that long-term complications may occur due to prevention of inactivation of these other peptides. Such bioactive peptides include IGF-1, chemokines and various neuropeptides [29], although whether DPP-4 is of physiological importance for inactivation of these peptides in humans is not known. However, even though vildagliptin and other DPP-4 inhibitors have a clean adverse events profile, long-term follow-up is important from this perspective.

Since vildagliptin is efficient and safe both as monotherapy and in combination therapy, its place in future treatment would be as a first-line treatment or as an add-on to existing treatment in subjects with inadequate metabolic control. Since metformin is accepted as a first-line treatment in many countries and also has a low cost, it is expected that vildagliptin will have its first introduction as an add-on to metformin when this treatment alone is insufficient. Initial combination between metformin and vildagliptin would also be a possibility. In subjects who are intolerant to metformin, with contraindications for or adverse events with metformin, vildagliptin would be a first-line treatment – this may apply to elderly patients. There is also the possibility that vildagliptin may be added to sulfonylurea and to thiazolidinediones in subjects with insufficient glycemic control with these agents alone. In the future, vildagliptin may also be used in combination with insulin to reduce the dose of insulin for avoidance of hypoglycemia and body weight increase.

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Executive summary

- Vildagliptin is an orally active inhibitor of dipeptidyl peptidase-4 and raises endogenous levels of active glucagon-like peptide-1.
- Vildagliptin has been shown to improve glycemic control in Type 2 diabetes, both when used in monotherapy and when used in combination with metformin, sulfonylurea, thiazolidinedione and insulin.
- Vildagliptin is well tolerated with very few adverse events reported and a low risk of hypoglycemia.
- Vildagliptin represents a novel treatment of Type 2 diabetes that may be used in combination with metformin, sulfonylurea or thiazolidinedione, and as monotherapy in subjects who are intolerant to metformin.
- Vildagliptin will probably have its most important value as an add-on therapy to metformin in patients with insufficient glycemic control when treated with this agent alone.

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