

The Vildagliptin Experience – 25 Years Since the Initiation of the Novartis Glucagon-like Peptide-1 Based Therapy Programme and 10 Years Since the First Vildagliptin Registration

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The discovery of the incretin hormone glucagon like peptide-1 (GLP-1), and its usefulness in the treatment of type 2 diabetes mellitus (T2DM) followed by the finding that dipeptidyl peptidase-4 (DPP-4) inhibition prevents GLP-1 inactivation, led to the discovery of DPP-728. In 1999, studies with DPP-728 established the first proof-of-concept that DPP-4 inhibition improves glycaemic control in patients with T2DM. Further efforts to improve the binding kinetics of DPP-728 resulted in the discovery of vildagliptin (LAF237). In the last 20 years, a plethora of studies conducted by Novartis in collaboration with external investigators has demonstrated the mechanism of action of vildagliptin and its efficacy as monotherapy and as an add-on therapy for patients with T2DM. The studies establish that vildagliptin is a selective DPP-4 inhibitor that blocks GLP-1 and glucose-dependent insulinotropic polypeptide (GIP) inactivation, thereby prolonging their action, resulting in improved glycaemic control. This review aims to discuss the discovery and development of vildagliptin, with an emphasis on mechanism of action and clinical efficacy.

Keywords

Dipeptidyl peptidase-4 (DPP-4) inhibitors, glucagon-like peptide-1, glucose-dependent insulinotropic polypeptide, type 2 diabetes mellitus, vildagliptin

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Prior to the launch of dipeptidyl peptidase-4 (DPP-4) inhibitors 10 years ago, there were no oral anti-hyperglycaemic agents for the treatment of type 2 diabetes mellitus (T2DM) that targeted deficient glucose regulation during both hyperglycaemia and hypoglycaemia.¹ As the Sandoz/Novartis DPP-4 program was central for the development of the DPP-4 inhibitor class, we thought it relevant to share our reminiscences of the discovery, development and clinical profiling of vildagliptin.

In 1990, only 7 years after the discovery of glucagon-like peptide-1 (GLP-1)² and 3 years after the discovery of GLP-1 as a physiological incretin hormone in humans,³ a research group in Sweden showed that GLP-1 infusions were useful in the treatment of T2DM.⁴ At the same time, a drug discovery team led by James E Foley at Sandoz in New Jersey, US had settled on two major therapeutic goals: inhibition of hepatic glucose production (HGP) without the side effects of metformin, and improved insulin secretion without hypoglycaemia associated with sulphonylureas (SUs). The therapeutic goal to improve upon SUs was assigned to Beth Dunning, who had recently joined the Sandoz group from postdoctoral work in Dan Porte's laboratory. It was serendipity that Beth Dunning and Bo Ahrén had shared an office in Seattle in 1984–5. In 1990, at the European Association for the Study of Diabetes in Copenhagen, Dunning, Ahrén and Foley, discussed how GLP-1 could be utilised therapeutically; this marked the beginning of 25 years of collaboration between Bo Ahrén and Sandoz, which became Novartis 20 years ago (personal communication, James E Foley, Copenhagen, 1990).

Discovery

In our early discussions of how to approach a GLP-1-based therapy, the Sandoz discovery team ruled out a peptide approach (to our lasting dismay), despite Sandoz's extensive peptide experience with calcitonin and sandostatin (personal communication, James E Foley, New Jersey, 1991). For almost 2 years, Sandoz chemists and biochemists attempted to make a non-peptide mimetic and then, in 1993, it was reported from Germany that GLP-1 was degraded solely by the enzyme DPP-4.⁵ Our lead chemist at that time, Bob Anderson, then suggested that the physiological rise in GLP-1 levels could be enhanced through inhibiting its inactivation by DPP-4. The five N-terminal amino acids of GLP-1 (the part of the peptide acted on by DPP-4) are identical to those of glucose-dependent insulinotropic polypeptide (GIP), the other known incretin hormone; therefore, the inhibition of DPP-4 was also predicted to enhance post-meal GIP levels even though at the time, most of the interest was in the benefits of GLP-1 (personal communication, James E Foley, New Jersey, 1995).

These findings created a possibility of developing an orally active DPP-4 inhibitor to leverage the increasing usefulness of the incretin hormones as anti-diabetes therapy.

In early 1995, it was reported that the inhibition of DPP-4 raised GLP-1 levels *in vitro*.⁶ Within weeks, Ed Villhauer went through the Sandoz chemical library and identified a molecule called valine pyrrolidide, an orally active DPP-4 inhibitor which had been identified by the Sandoz immunology group. The team then demonstrated that valine pyrrolidide lowered blood glucose levels in rodents (Figure 1A)⁷ and non-human primates (Figure 1B).⁸

Novartis provided valine pyrrolidide to Bo Ahrén and Jens Holst laboratories to further characterise DPP-4 inhibition in animal models. These valine pyrrolidide studies demonstrated that DPP-4 inhibition potentiated the insulinotropic actions of both GLP-1 and GIP in pigs¹⁰ and reduced glycaemia and augmented insulinaemia after oral glucose in mice.¹¹

Thomas Hughes and associates developed assays for DPP-4 as well as for closely related enzymes that were compatible with utilisation of combinatorial chemistry techniques to test more than a thousand substitutions to valine pyrrolidide, resulting in the discovery of DPP-728 in 1996.¹² By 1999, DPP-728 was evaluated in patients, which provided the first human proof-of-concept that a DPP-4 inhibitor could improve glycaemic control in patients with T2DM.¹³

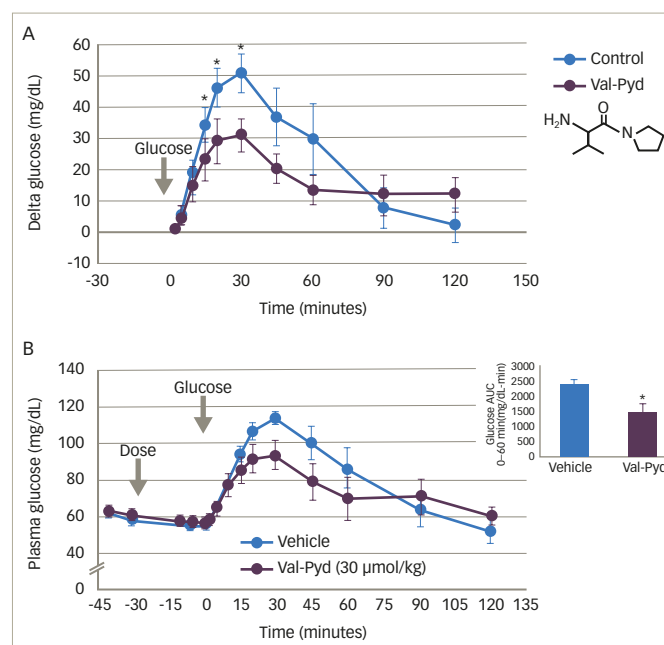
In 1996, kinetic studies revealed that DPP-728 was a substrate for the DPP-4 catalytic site with a slow dissociation rate rather than a simple competitive inhibitor. Engineering of the DPP-728 structure by Ed Villhauer and colleagues to attenuate the dissociation rate further led to the discovery of vildagliptin in 1998. The 'vil' in vildagliptin was in recognition of Ed Villhauer's contribution.^{14,15}

Vildagliptin mechanism

DPP-4 is a large protein with a small catalytic site that inactivates GLP-1 and GIP by cleaving the peptides after the second amino acid from the N-terminal end. Vildagliptin effectively competes with GLP-1 and GIP to enter the catalytic site of DPP-4. Vildagliptin's nitrile group rapidly forms a covalent bond, stabilising vildagliptin in the catalytic site of DPP-4. The dissociation of inactive vildagliptin from the catalytic site occurs slowly, with a half-life of about an hour. While vildagliptin is covalently bound, DPP-4 cannot degrade any other substrate. Following dissociation of inactive vildagliptin, another vildagliptin molecule will compete with GLP-1 and GIP to enter the catalytic site. This results in complete blocking of DPP-4 activity over the entire time that vildagliptin levels are adequate (≥ 50 nM) to effectively compete with GLP-1 and GIP.¹⁶ Therefore, the primary pharmacology of vildagliptin is prolonging meal-induced increases in GLP-1 and GIP. Interestingly, early in the programme, our hypothesis was that the increase in GLP-1 levels at the beginning of a meal is responsible for pancreatic and extra-pancreatic effects, which we characterised as secondary pharmacological actions of DPP-4 inhibitors.¹ However, in collaboration with Ralph DeFronzo's group, further investigation led us to conclude that it was rather the prolongation of meal-induced increases in GLP-1 and GIP that results in these secondary pharmacological actions.^{1,17,18}

The mechanistic studies utilising valine pyrrolidide were reconfirmed with vildagliptin and, in particular, it was shown that vildagliptin improved glycaemia and augmented insulin secretion after oral glucose in obese Zucker rats,¹⁹ as well as in normal and high-fat diet-fed mice.²⁰ A study

Figure 1: Effect of valine pyrrolidide on glucose tolerance in rats (A) and glucose intolerant cynomolgus monkeys (B)



AUC = area under the curve; Val-Pyd = valine pyrrolidide. Sourced with permission from Balkan and Dunning, 1995;⁷ Deems and Dunning, 1995.⁸

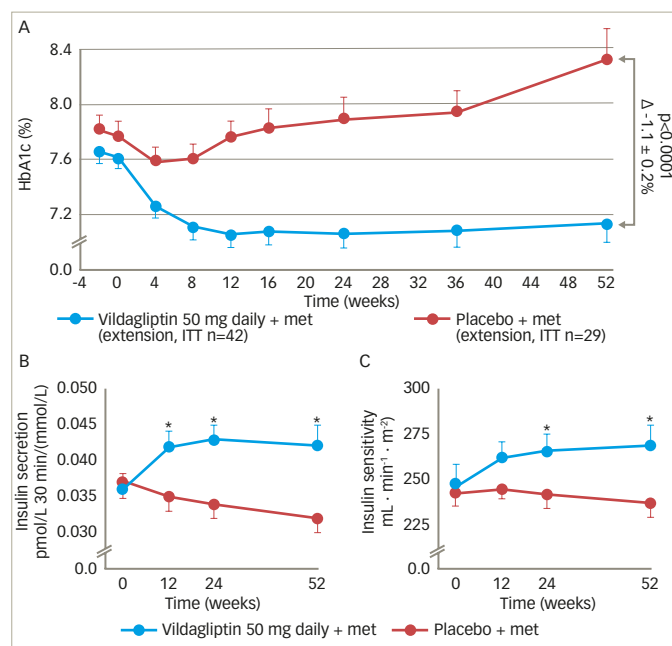
in mice with gene deletions for GLP-1 and GIP receptors showed that vildagliptin had no effect, which supported the hypothesis that the incretin hormones were responsible for improved glycaemia and insulinaemia.²¹ These preclinical studies showed that vildagliptin had the expected effects for a DPP-4 inhibitor on glucose and insulin levels and that these effects were achieved through the incretin hormones.

Over the last 12 years, further clinical profiling studies showed that vildagliptin therapy increases the sensitivity of pancreatic islet α - and β -cells to glucose. These effects result in increased insulin secretion and decreased glucagon secretion, pronounced in hyperglycaemic states, and reduced insulin secretion and increased glucagon secretion during hypoglycaemia.²² Additionally, mobilisation and burning of fat during meals, a decreased gut secretion of apolipoprotein B-48 (apo B-48), a reduction of fasting lipolysis and liver fat and an increase in particle size of low-density lipoprotein are the secondary pharmacological effects of vildagliptin.^{1,16}

These pancreatic and extra-pancreatic effects result in reductions of postprandial plasma glucose (PPG) and fasting plasma glucose (FPG) levels, leading to reduced glycated haemoglobin (HbA1c) levels with no increase in the risk for hypoglycaemia or weight gain.^{1,16} The reductions in FPG associated with vildagliptin include reductions in Cori cycling secondary to decreased PPG levels as well as direct effects on overnight HGP.²³ The glucose-lowering action of vildagliptin is attributable to the effects of GLP-1 and GIP and the effects on α - and β -cells appear to be equally important.^{1,24}

Our original hypothesis was that the absence of an increase in insulin and decrease in glucagon during euglycaemic and hypoglycaemic states explains not just a lack of an increase in hypoglycaemia in the face of reduced glucose levels, but even a reduction in hypoglycaemic events in patients on insulin therapy. We later found that the sensitivity of β -cells to glucose extended into the hypoglycaemic range.²⁵ Furthermore, since GIP was mirroring the extension of meal-induced GLP-1 levels and GIP

Figure 2: Time course of glycosylated haemoglobin levels



* $p < 0.05$ versus placebo. Time course of glycosylated haemoglobin levels (A),³² meal-related insulin secretion (B)³³ and insulin sensitivity (C)³³ during 52-week treatment with vildagliptin 50 mg once daily or placebo added to a stable dose of metformin (1.5–3.0 g/day) in patients with T2DM. Values in the figures are mean (\pm SE). Insulin secretion corrected for glucose (30 minutes AUC of C-peptide divided by 30 minutes AUC of glucose) and insulin sensitivity estimated as the oral glucose insulin sensitivity index measured during standardised breakfast meal tests. AUC = area under the curve; HbA1c = glycosylated haemoglobin; ITT = intent to treat; met = metformin; SE = standard error of the mean; T2DM = type 2 diabetes mellitus. Adapted with permission from Ahrén et al., 2004³² and Ahrén et al., 2004.³³

had been reported to increase the sensitivity of α -cells to glucose in the hypoglycaemic range, we hypothesised that reduced insulin secretion and increased glucagon levels during hypoglycaemia brought about by DPP-4 inhibition with vildagliptin resulted in better counter-regulation, which likely explains the apparent protection against hypoglycaemia observed when vildagliptin is added to insulin therapy.²⁶

Insulin resistance can be a result of glucose toxicity, inappropriately elevated glucagon levels and lipotoxicity. All hypoglycaemic agents, to the extent that they reduce FPG, reduce glucotoxicity, and all GLP-1 based therapies reduce inappropriately elevated glucagon levels. Vildagliptin inhibits fasting lipolysis, which should redistribute fat storage from non-fat tissues to fat cells; observations of 25% reductions in liver fat associated with vildagliptin treatment are consistent with this expected redistribution. Vildagliptin-induced reduction in liver fat is, in turn, consistent with a reduction in lipotoxicity as evidenced by increased glucose utilisation under conditions where lipogenesis is the presumed rate-limiting step.¹

The GLP-1 receptor agonists produce a vital effect by their direct action on the brain stem which delays gastric emptying and promotes satiety, but such an effect is not seen with DPP-4 inhibitors as DPP-4 inhibition do not result in high enough levels of GLP-1 to produce direct action on the brain stem.^{1,16} Vildagliptin did not show significant effect on gastric emptying after a single dose²⁷ or after 8 days of treatment.²⁸ However, a single dose study utilising high-resolution scintigraphy reported a small significant delay in gastric emptying with vildagliptin.²⁹ It is likely that this small effect was not large enough to be detected by techniques precise enough for clinical relevance, but is of scientific interest. Furthermore, the low hypoglycaemic potential of DPP-4 inhibitors prevents the weight gain associated with 'defensive eating' in order to avoid hypoglycaemia.

Unexpectedly, DPP-4 inhibitors do not lead to weight gain despite the caloric penalty related to reduction of glucose levels from above to below the renal threshold. Potential mechanisms that may account for these lost calories are the mobilisation and burning of fat during meals and the reduction in apo B-48 secretion, leading to decreased fat extraction from the gut.^{1,16} In addition, a largely unexplored aspect is how variations in diet may influence the glucose-lowering potential of DPP-4 inhibitors. In a recent study, it was shown that a whey preload can markedly potentiate the glucose-lowering effect of vildagliptin by enhancing endogenous GLP-1 secretion.³⁰

Efficacy

The vildagliptin clinical registration programme began in 2002 and ended in 2006 with new drug application submissions in several countries. David Holmes and Anja Schweizer, among others at Novartis, were instrumental in designing and managing the ongoing studies along with data analysis in collaboration with external investigators. In 2002–3, vildagliptin was tested in patients for the first time by Bo Ahrén and collaborators. In a 4-week study, vildagliptin was effective in lowering HbA1c in drug-naïve patients by 0.4% from a baseline of 7.1–7.2%.³¹ This study also confirmed higher GLP-1 levels and enhanced β -cell function (insulin levels were maintained at lower glucose levels) in humans, which had been previously demonstrated in animals with valine pyrrolidide, DPP-728 and vildagliptin. The study also demonstrated that glucagon levels decreases during meals in humans, a parameter that had not been evaluated in animals with DPP-4 inhibitors.³¹

Bo Ahrén and collaborators then evaluated the efficacy of vildagliptin (50 mg once daily) in patients on metformin with inadequate glycaemic control, showing a between-treatment difference (vildagliptin versus placebo) in the adjusted mean change (AM Δ) in HbA1c of -1.1% after 52 weeks of treatment from a baseline of \sim 7.7% (Figure 2A).³² This improvement in glycaemic control could be ascribed to both enhanced insulin secretion (Figure 2B) and reduced demand for insulin as reflected by increased insulin sensitivity (Figure 2C) demonstrated using the standard meal test.³³

These studies were followed by many larger multicentre studies which included more than 17,000 patients.³⁴ It is not possible to cover all the studies and associated indications; here, we highlight some of the studies of vildagliptin as monotherapy, as an add-on to metformin, and an add-on to insulin, that not only supported registration but also were important in our understanding of its mechanism.

Overall, vildagliptin monotherapy studies provided evidence that treatment with vildagliptin results in consistent and clinically meaningful reductions in HbA1c from baseline levels, without weight gain and with minimal hypoglycaemia.²³ The relationship between baseline HbA1c and the drop from baseline HbA1c along with changes in weight from baseline can be best viewed when the data are pooled: with vildagliptin-treatment, mean Δ HbA1c was -2.1% from a baseline of 10.6%, -1.8% from 9.5%, -1.2% from 8.5%, -0.7% from 7.7% and -0.5% from 6.9%.³⁵

When glucose levels exceed the renal threshold (i.e., the level of glucose above which sodium-glucose cotransporters in the kidneys fail to reabsorb all the available glucose), glucose spills into the urine. Any therapy that reduces glucose levels from above the renal threshold to below it mitigates caloric loss and thus can lead to weight gain.³⁶ However, when vildagliptin monotherapy data were pooled, there was an average \sim 0.5 kg weight loss; weight loss was greatest in patients

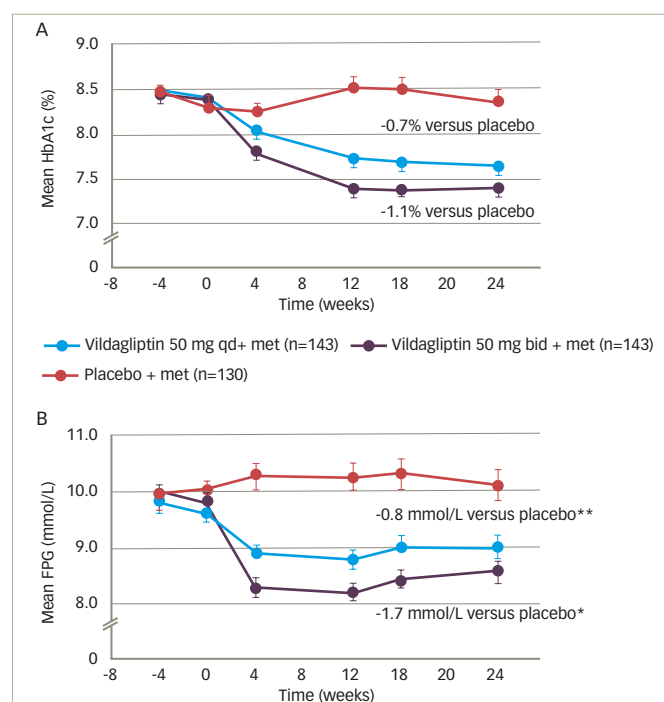
with glycaemic levels below the renal threshold and there was no weight loss at the renal threshold.^{37,38} This modest degree of weight loss was associated with a significant reduction in systolic blood pressure (-2.7 mmHg from a baseline of 132.5 mmHg) and diastolic blood pressure (-1.6 mmHg from a baseline of 81.2 mmHg) and a favourable fasting lipid profile that included a decrease of 0.2 mmol/L from a baseline of 2.0 mmol/L in triglycerides.³⁸

Among the vildagliptin monotherapy studies, the most illuminating was the 1-year, placebo-controlled study involving 306 drug-naïve T2DM patients with mild hyperglycaemia (mean HbA1c of 6.7%). Patients randomised to the group receiving vildagliptin 50 mg once daily plus lifestyle counselling showed a significant reduction in HbA1c (-0.3%) after 52 weeks compared with those receiving placebo along with lifestyle counselling. A 1-year extension (total study duration 2 years) showed continued improvement with vildagliptin compared with placebo, with a placebo-adjusted change in HbA1c of -0.5% from the core study baseline after 2 years. Body weight decreased significantly in vildagliptin-treated patients (-1.1 kg versus -0.3 kg with placebo), and two patients (3.2%) treated with placebo versus none (0.0%) receiving vildagliptin experienced hypoglycaemia. Taken together, 2 years of treatment with vildagliptin mitigated the progressive loss of glycaemic control that was observed in patients with mild hyperglycaemia receiving placebo and lifestyle counselling, without exposing them to hypoglycaemia or weight gain. This appears to result from a corresponding attenuation of the deterioration of β -cell function as assessed by the insulin secretion rate relative to glucose over a period of 2 years.³⁹

There were several very crucial phase III studies examining vildagliptin as add-on therapy in patients inadequately controlled on metformin. In a dose-response study in which baseline HbA1c averaged 8.3%, the between-group difference in HbA1c (vildagliptin versus placebo) was -0.7% and -1.1% in patients receiving vildagliptin 50 mg once daily and twice daily, respectively (Figure 3A). There were also substantial and dose-related decreases in FPG (-0.8 mmol/L and -1.7 mmol/L with vildagliptin 50 mg once daily and twice daily) (Figure 3B). The standard breakfast meal tests at weeks 0 and 24 were performed in a subset of patients which demonstrated a significant reduction in PPG and improved β -cell function (insulin secretion adjusted for glucose, defined as 2-hour glucose area under the curve [AUC_{0-2h}] divided by AUC_{0-2h} for the insulin secretory rate (ISR). There was a lack of dose response on these parameters, as the study drug was administered 30 minutes prior to the breakfast meal tests in both treatment groups. The difference in HbA1c between the two vildagliptin dose regimens may be due to twice the reduction of FPG levels with higher daily dose of vildagliptin.^{17,40}

A 52-week phase III study compared vildagliptin 50 mg twice daily to pioglitazone 30 mg once daily as an add-on therapy in patients inadequately treated with metformin.⁴¹ An interim analysis⁴² performed after 24 weeks of treatment showed that the efficacy of vildagliptin was non-inferior to that of pioglitazone (AM Δ HbA1c=-0.9% versus -1.0%, respectively). Pioglitazone produced a larger decrease in FPG (AM Δ = -2.1 mmol/L) as compared with vildagliptin (AM Δ =-1.4 mmol/L); presumably the PPG control was better in the vildagliptin group. Additionally, there was significant weight gain seen only in the pioglitazone group (AM Δ =+1.9 kg). The 52-week data revealed a modest loss in glycaemic control in both the treatment groups such that the change in HbA1c from baseline (8.4% in both groups) at week 52 was -0.6%, both in patients receiving vildagliptin 50 mg twice daily or pioglitazone 30 mg once daily added to metformin. After 52 weeks of treatment, mean

Figure 3: The time courses of mean glycated haemoglobin



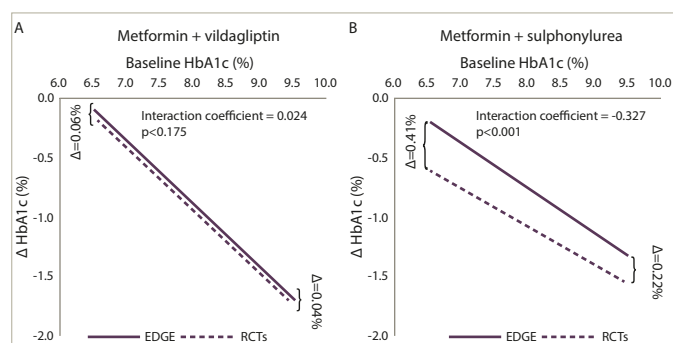
* $p < 0.001$; ** $p = 0.003$ versus placebo. The time courses of mean HbA1c (A) and FPG (B) during 24-week treatment. Figure shows mean (\pm SE) HbA1c levels and FPG levels, with vildagliptin 50 mg once daily, vildagliptin 50 mg twice daily or placebo added to a stable dose of metformin (>1,500 mg/day) in patients with T2DM.⁴⁰ bid = twice daily; FPG = fasting plasma glucose; HbA1c = glycosylated haemoglobin; met = metformin; qd = once daily; SE = standard error of the mean; T2DM = type 2 diabetes mellitus. Source: Adapted with permission from Bosi et al., 2007.⁴⁰

body weight increased significantly in the pioglitazone group (+2.6 kg), but not in the vildagliptin group (+0.2 kg).⁴¹

In a 2-year non-inferiority study comparing vildagliptin (50 mg twice daily) to glimepiride (up to 6 mg/day) in patients with T2DM inadequately controlled with metformin monotherapy, an interim analysis performed after 52 weeks of treatment demonstrated that vildagliptin was non-inferior to glimepiride in patients with low baseline HbA1c (mean=7.3%). The most notable differences between vildagliptin and glimepiride in this study were weight gain with glimepiride (AM Δ =+1.6 kg), vildagliptin (AM Δ =-0.2 kg), and a 10-fold higher number of hypoglycaemic episodes with glimepiride (554 events, 10 severe) than with vildagliptin (39 events, 0 severe).⁴³

Two-year data from this study showed deterioration of glycaemic control for both vildagliptin and glimepiride, even though the initial response was sustained significantly longer with vildagliptin, as reflected by the 'coefficient of failure': from week 24 to week 104, HbA1c increased at a rate of 0.4% per year with vildagliptin versus 0.5% per year with glimepiride ($p=0.008$). This suggests that deterioration of glycaemic control was worse with the sulphonylurea than with vildagliptin, which is consistent with the finding that insulin resistance, as assessed by the homeostatic model assessment of insulin resistance (HOMA-IR), worsened from baseline to week 104 with both treatments, but the increase with glimepiride was significantly greater than with vildagliptin. Interestingly, although the prandial glucose excursion (glucose AUC_{0-2h}) showed a similar decrease in patients receiving vildagliptin as in those receiving glimepiride, prandial insulin levels increased to a greater extent with glimepiride, while prandial glucagon secretion was suppressed with vildagliptin. The differences in body weight between vildagliptin and glimepiride as an add-on to metformin were maintained

Figure 4: Efficacy of vildagliptin versus sulphonylureas as add-on therapy to metformin – comparison of results from randomised controlled trials and observational studies



Δ HbA1c is shown as a function of baseline HbA1c in patients with type 2 diabetes after 24 weeks of treatment with vildagliptin and metformin (A) or SU and metformin (B) during an observational study, EDGE (solid line) or randomised controlled trials (dashed line). EDGE = Effectiveness of Diabetes control with vildaGliptin and vildagliptin/mEtformin; HbA1c = glycated haemoglobin; RCTs = randomised controlled trials. Adapted with permission from Ahrén et al., 2014.⁴⁷

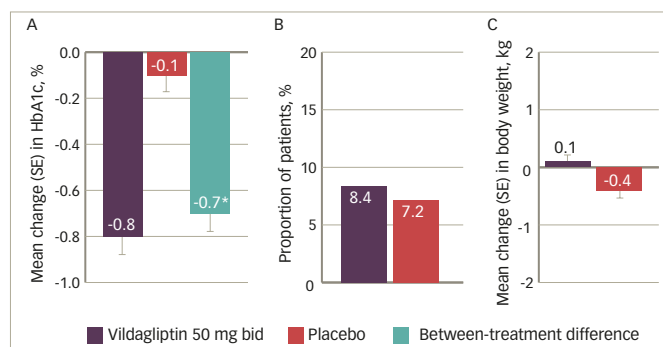
throughout the 2-year study, as were the differences in the frequency and severity of hypoglycaemia.⁴⁴

Higher rates of hypoglycaemia in the glimepiride group were not due to higher doses of glimepiride; hypoglycaemia was more pronounced at 2 mg dose than 6 mg dose, suggesting interesting differences among patients regarding the susceptibility to hypoglycaemia with SUs.⁴⁵ In another non-inferiority trial of vildagliptin versus gliclazide as an add-on to metformin in patients with a higher baseline HbA1c (mean=8.5%), vildagliptin was found to be non-inferior to gliclazide, with respect to reductions in both HbA1c and FPG.⁴⁶ However, there was little difference in weight gain or hypoglycaemia. A study reveals that the decrease in HbA1c from baseline with SU treatment is smaller in real-world setting when compared to randomised controlled trials (RCTs), whereas the decrease in HbA1c with vildagliptin is essentially similar (Figure 4), indicating that the doses of SUs are not adequately increased possibly due to fear of hypoglycaemia and weight gain.⁴⁷

Although previous studies showed that vildagliptin 50 mg twice daily was more efficacious than vildagliptin 50 mg once daily when added to metformin, this was not the case when vildagliptin was added in the same manner to a SU.⁴⁸ Our hypothesis is that the complementary mechanisms of vildagliptin added to metformin therapy could further correct inappropriate overnight HGP while the similar mechanisms of vildagliptin as an add-on to SU therapy could not produce the same effect.

Three different studies demonstrated the effectiveness of vildagliptin in combination with insulin with and without concomitant metformin therapy where vildagliptin decreased HbA1c levels without increasing hypoglycaemia.²⁶ These findings also suggest that vildagliptin is more

Figure 5: Adjusted mean change from baseline to 24-week endpoint in glycated haemoglobin



* $p < 0.001$. Adjusted mean (\pm SE) change from baseline to 24-week endpoint in HbA1c (A) (vildagliptin, $n=221$; placebo, $n=215$), proportion of patients experiencing confirmed hypoglycaemic episodes during 24-week treatment (B) (vildagliptin, $n=227$; placebo, $n=221$) and mean change from baseline to 24-week endpoint in body weight (C) (vildagliptin, $n=222$; placebo, $n=215$) in patients with T2DM receiving 50 mg bid vildagliptin or placebo as an add-on to the ongoing insulin regimen (with or without metformin).²⁶ bid = twice daily; HbA1c = glycated haemoglobin; SE = standard error of the mean; T2DM = type 2 diabetes mellitus. Adapted with permission from Schweizer et al., 2013.²⁶

effective when insulin is used as a basal regimen in contrast to being used to reduce postprandial hyperglycaemia. This is because improvement in insulin secretion likely plays a minor role when relatively high doses of insulin are administered before meals. Data from one of these three studies (Figure 5) show that the reduction in glucose levels was not associated with an increase in hypoglycaemia or an increase in weight secondary to defensive eating.²⁶

Early in the development of incretin-based therapies, was the promise of an increase in β -cell mass. Vildagliptin demonstrated that in young rodents there was increased β -cell mass, but when vildagliptin was studied in a long-term animal study of adult rodents, there was no effect to increase β -cell mass.⁴⁹ To date, there is no evidence that any GLP-1 based therapy is associated with a disease-modifying effect to increase β -cell mass in humans.⁵⁰ However, all data with vildagliptin are consistent with preserving function as well as correcting many of the underlying pathologies associated with T2DM.^{1,16,39} This is consistent with our findings that when all the data are pooled, neither insulin resistance, body mass index, disease duration nor duration of metformin use has an effect on the efficacy of vildagliptin.⁵¹

Concluding statement

Exploring the clinical utility of GLP-1 as a therapeutic approach for treatment of T2DM, marked the beginning of collaboration between Bo Ahrén and Sandoz, 25 years ago. Sandoz later became Novartis; further collaborative studies with investigators from the academic community led to the discovery, development and profiling of vildagliptin. These pioneering activities with vildagliptin over the last 10 years were central to the establishment of DPP-4 inhibitors as a standard of care for the treatment of T2DM. \square

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