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Vildagliptin

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Contents

Abstract

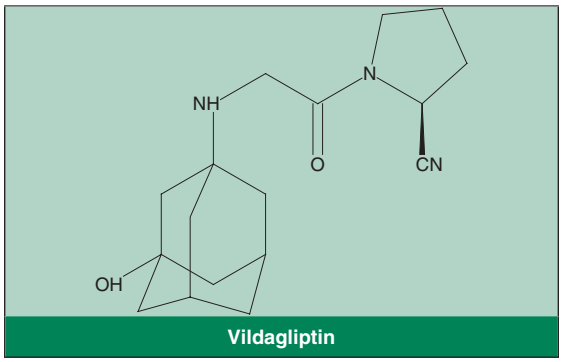
▲ Vildagliptin is a dipeptidyl peptidase-4 (DPP-4) inhibitor that is being evaluated in the treatment of patients with type 2 diabetes mellitus. It improves glycaemic control by inhibiting DPP-4 from inactivating the incretin hormones glucagon-like peptide-1 and glucose-dependent insulinotropic polypeptide, prolonging incretin activity in response to ingestion of nutrients. This allows for increased insulin sensitivity, decreased glucagon secretion and improved β-cell function in a glucose-dependent manner.

▲ Glycaemic control with vildagliptin 50 or 100 mg/day, measured by a change from baseline in mean glycosylated haemoglobin (HbA_{1c}) at study endpoint, was improved relative to placebo in several well designed clinical trials of vildagliptin monotherapy in patients with type 2 diabetes. In randomised active comparator studies, noninferiority of vildagliptin in reducing HbA_{1c} levels from baseline was established to rosiglitazone, but not to metformin.

▲ Vildagliptin also showed efficacy in reducing HbA_{1c} levels in patients with type 2 diabetes when used in combination with metformin, pioglitazone or insulin.

▲ Vildagliptin was generally well tolerated when administered alone or in combination with additional antidiabetic treatment. Gastrointestinal adverse events were mild to moderate in intensity, and occurred less frequently than with metformin. Hypoglycaemic events were rare and occurred at a similar incidence to that with placebo.

Features and properties of vildagliptin (Galvus®)	
Indication	
Control of hyperglycaemia in adult patients with type 2 diabetes mellitus	
Mechanism of action	
Inhibits the enzyme dipeptidyl peptidase-4 from inactivating the incretin hormones glucagon-like peptide-1 and glucose-dependent insulinotropic polypeptide, prolonging incretin activity in response to ingestion of nutrients	
Dosage and administration in phase III clinical trials	
Dosage	50–100 mg/day
Route of administration	Oral
Frequency of administration	Once or twice daily
Pharmacokinetic profile at steady state (results of two studies in healthy volunteers receiving 100mg once daily)	
Maximum plasma concentration	467 and 531 ng/mL
Area under the plasma concentration-time curve from zero to 24 hours	1960 and 2189 ng • h/mL
Plasma elimination half-life	1.68h
Most common adverse events	
Nasopharyngitis, headache, dizziness	



Vildagliptin

Diabetes mellitus is characterised by chronic hyperglycaemia which, if left unchecked, results in long-term damage, dysfunction and eventual failure of organs such as the eyes, kidneys and heart.[1] Type 2 diabetes accounts for 90–95% of patients with diabetes,[1] and results from a progressive defect in insulin secretion on an insulin-resistant background.[2] Insulin resistance in type 2 diabetic patients may improve with lifestyle changes (reduction in weight through changes in diet and exercise) and/or pharmacological intervention, but rarely is it restored to normal levels using these methods.[1] The severity of hyperglycaemia has the potential to change over time in these patients, reflecting the extent and progression of the underlying disease.[1]

Recent research in type 2 diabetes has focused on the incretins, glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1), which are gastrointestinal (GI) hormones that stimulate insulin secretion after ingestion of nutrients.[3,4] Postprandial GLP-1 is decreased in type 2 diabetic patients, despite the insulinotropic response to GLP-1 remaining intact.[4] Insulinotropic response to GIP is greatly impaired and may be absent in patients with type 2 diabetes.[4]

In addition to its glucose-dependent effects on insulin secretion, GLP-1 also acts to decrease glucagon secretion in a glucose-dependent manner[3] and to increase β-cell mass and improve β-cell function.[3] It also delays gastric emptying, reducing postprandial hyperglycaemia.[5] The biological activity of GLP-1 is extremely short lived; the half-life of the circulating protein is approximately 1–2 minutes,[5] due to rapid inactivation by the enzyme dipeptidyl peptidase-4 (DPP-4) [section 1].[3,5-8] Efforts to circumvent this have had limited success. For instance, DPP-4-resistant GLP-1 analogues, GLP-1-like peptide agonists or GLP-1 fusion proteins can increase the duration of action of GLP-1 by increasing its metabolic stability. However, these agents must be administered either intravenously or subcutaneously, as their oral bioavailability is limited or non-existent.[7] Targeting the GLP-1 receptor using non-peptidergic small molecule agonists has also not been successful.[7]

An alternative approach to targeting GLP-1 is to increase the proportion of active GLP-1 in the circulation of type 2 diabetics by inhibiting its inactivation by DPP-4.[3-8] Consequently, low molecular weight, orally active DPP-4 inhibitors, such as vildagliptin (Galvus®)[1], have been developed. This profile examines the pharmacological properties of vildagliptin and its clinical use in patients with type 2 diabetes.

1. Pharmacodynamic Profile

This section provides a summary of the pharmacodynamic data obtained from studies in patients with type 2 diabetes receiving oral vildagliptin. Apart from four large, well designed studies (n = 71–697),[9-13] studies were small (n = 9–37)[14-23] and several results were only reported in abstracts.[19-23]

Mechanism of Action

- Vildagliptin belongs to a class of DPP-4 inhibitors that transiently modify the enzyme via covalent bonding.[6] Despite the presence of structurally related enzymes (DPP-8 and DPP-9), there was no evidence of an interaction between these enzymes and vildagliptin in animal studies.[24] The affinity of vildagliptin for DPP-4 was 32–250 times greater than its affinity for DPP-8 and DPP-9.[24]
- DPP-4 enzymatic activity is found throughout the body,[5,6] and is also a component of the immune

1 The use of trade names is for identification purposes only and does not imply endorsement.

system, DPP-4 being also known as the T-cell marker CD26.[8] The effects of inhibition of DPP-4 on the immune system and other systems involving substrates of DPP-4 have not been fully elucidated.[7,8]

- Vildagliptin is a potent, reversible, competitive inhibitor of DPP-4 that binds in the S1- and S2-catalytic sites of the protein to inhibit its activity via a two-step mechanism.[25,26]

- *In vitro* studies show that the binding of vildagliptin to DPP-4 exhibits slow binding inhibition kinetics,[25,26] with a time- and concentration-dependent steady-state approach.[26] This class of slow-binding inhibitor displays an initial phase of rapid binding followed by a slow phase of very tight binding,[27] which allows for an extended period of DPP-4 inhibition.

- Vildagliptin also effectively inhibits DPP-4 activity in humans.[14,17,18] For example, after 4 weeks' treatment with oral vildagliptin 100mg once daily in a randomised, placebo-controlled trial in patients with type 2 diabetes (n = 37), mean DPP-4 activity was significantly reduced to 1.9% of baseline at 45 minutes after administration ($p < 0.001$), and to 60.0% of baseline at 24 hours ($p < 0.001$).[18] Throughout the study, DPP-4 activity was unchanged in placebo recipients.[18]

- Two other randomised, placebo-controlled studies in patients with type 2 diabetes also showed >90% inhibition of DPP-4 activity after administration of vildagliptin 10–100mg twice daily for 28 days,[14,17] with the duration of >90% inhibition increasing with dose.[14]

- Previously untreated patients with type 2 diabetes receiving vildagliptin had increased plasma levels of GLP-1 and GIP in response to food.[16,18] In two studies (n = 37[18] and 20[16]), recipients of vildagliptin 100mg once[18] or twice[16] daily achieved significantly higher mean plasma GLP-1 levels versus baseline at 30 minutes after breakfast following 4 weeks' treatment ($p < 0.01$)[18] and significantly higher mean plasma GLP-1 and GIP levels versus placebo at the 13.5 hour assessment during standardised meals tests on days 1 ($p \leq 0.01$ and $p < 0.001$) and 28 (both $p < 0.001$).[16]

- Fasting plasma levels of GLP-1 and GIP were also affected by vildagliptin treatment in patients with type 2 diabetes.[18,23] In two 4-week studies in which patients (n = 37[18] and 9[23]) received vildagliptin 100mg once[18] or twice[23] daily, fasting plasma GLP-1[18,23] and GIP[23] levels were significantly increased from baseline at week 4 (all $p < 0.05$).

Effect on Glucose Homeostasis

Data in this section are from small (n = 12–37) phase II trials that were either single-dose studies[21] or of 28 days duration.[14,16,18] For data on glucose homeostasis in phase III trials, see section 3.

- Glucose-related parameters were consistently improved with vildagliptin treatment in patients with type 2 diabetes.[14,16,18,21] Mean fasting plasma glucose (FPG) levels were significantly decreased compared with placebo at study end after treatment with vildagliptin 100mg once[18] or twice[16] daily in two 4-week studies (both $p < 0.05$). Compared with placebo, vildagliptin treatment also reduced 24-hour mean glucose levels on both day 1 ($p = 0.022$)[16] and at study end ($p \leq 0.01$).[16,18]

- Mean postprandial glucose excursions in type 2 diabetic patients were decreased by 1.0 mmol/L in the vildagliptin 100mg once-daily group compared with the placebo group ($p = 0.005$ vs placebo);[18] mean 4-hour postprandial glucose was also significantly reduced ($p < 0.001$ vs placebo).[18]

- Patients with type 2 diabetes receiving vildagliptin 25 or 100mg twice daily in a third study had a reduction in mean glucose levels of 10% and 19% (both $p < 0.05$ vs placebo).[14] Endogenous glucose production during a 6-hour meal test was significantly ($p = 0.004$) suppressed compared with placebo after a single 100mg dose of vildagliptin in 16 patients with type 2 diabetes.[21]

- Mean postprandial glucagon levels were reduced in patients with type 2 diabetes receiving vildagliptin.[16,18,21] Mean plasma levels of glucagon at 0.5[18] and 3.5[16] hours after food were significantly reduced in vildagliptin recipients (100mg once[18] or twice[16] daily) compared with placebo recipients on day 1 in one study ($p = 0.03$),[16] and with baseline in another study ($p = 0.005$).[18] A single 100mg dose

of vildagliptin reduced mean postprandial plasma glucagon levels by 93% compared with placebo ($p < 0.01$).[21]

Effect on β-Cell Function

- Insulin secretion rates were taken as a marker of β-cell function in most studies where this parameter was examined;[11,16] in one study where β-cell function was calculated separately as a function of fasting insulin and fasting glucose,[13] only patients taking vildagliptin 100mg once daily showed significant ($p = 0.007$) improvements versus placebo.
- Insulin secretion was variable in vildagliptin recipients.[11,16,21] Insulin secretion rates determined experimentally were significantly increased compared with placebo in patients receiving vildagliptin 50mg once daily for 52 weeks ($p = 0.018$)[11] and in patients receiving a single 100mg dose of vildagliptin (increased by 21%; $p = 0.003$),[21] but not in patients receiving vildagliptin 100mg twice daily for 4 weeks.[16] However, a model-derived mean insulin secretion rate in patients receiving vildagliptin in this study was determined to be significantly different from that with placebo (between group difference at 7 mmol/L glucose: 101 pmol/min/m^2; $p < 0.005$).[16]
- The rate of insulin secretion can also be estimated using C-peptide levels. The effect of vildagliptin treatment on C-peptide levels was mixed; significant increases from placebo in both postprandial (4-hour mean levels; $p = 0.003$)[12] and fasting ($p = 0.005$)[13] levels of C-peptide were seen in patients receiving vildagliptin 25mg twice daily for 12 weeks in two studies,[12,13] whereas postprandial C-peptide levels in patients receiving vildagliptin 100mg once[22] or twice[16,17] daily were not different from baseline.[16,17,22]
- The area under the time-concentration curve (AUC) for mean C-peptide in patients receiving vildagliptin 50mg plus metformin 1500–3000 mg/day for 1 year was significantly ($p = 0.019$) increased compared with placebo (change from baseline to study end, vildagliptin vs placebo: +10.8 vs −19.4 pmol/L 240 min).[11]
- Several parameters related to insulin secretion were improved in vildagliptin recipients. The insulinogenic index was significantly improved in two placebo-controlled studies of patients with type 2 diabetes.[9,21] After 1 year of vildagliptin treatment, the between-group difference in insulinogenic index (change in insulin at peak glucose divided by the change in glucose at peak) was 0.17 ($p = 0.016$ vs placebo).[9]
- A single 100mg dose of vildagliptin resulted in an increase in insulinogenic index (change in insulin secretion rate divided by the change in plasma glucose during a 6-hour meal tolerance test) of 29% in a second study ($n = 16$; $p = 0.01$ vs placebo).[21] The adaptation index (insulin secretion multiplied by insulin sensitivity) increased significantly in recipients of vildagliptin 50mg plus a stable dosage of metformin (1500–3000 mg/day), both from baseline ($p = 0.003$) and from placebo ($p = 0.04$) after 1 year.[11]
- Vildagliptin treatment also improved postprandial insulin response.[12,13] Four-hour mean insulin response corrected for peak glucose[12] and mean insulin levels[13] were significantly improved in patients receiving vildagliptin 25mg twice daily ($p < 0.05$)[12] and 100mg once daily ($p = 0.022$)[13] compared with placebo.
- Vildagliptin treatment significantly improved insulin sensitivity in patients with type 2 diabetes.[11,16,19] After 52 weeks of treatment, mean insulin sensitivity in a group of 57 patients (estimated from a model of glucose clearance, which provides a measure of oral glucose insulin sensitivity [OGIS]) was significantly increased from baseline in vildagliptin 50mg once daily plus metformin recipients ($p = 0.012$).[11]
- Placebo plus metformin recipients in this study did not show an increase from baseline, resulting in a significant ($p = 0.036$) between-group difference in OGIS of 27 mL/min/m^2 favouring vildagliptin.[11] The between-group difference in mean adaptation index (insulin secretion × insulin sensitivity) was also significantly improved ($p = 0.04$ vs placebo plus metformin).[11]

• Smaller studies (n = 12–20) of 4–12 weeks' duration[16,19,20] also showed that insulin sensitivity was significantly improved with vildagliptin 50[19,20] or 100mg[16] twice daily versus baseline ($p = 0.016$)[19] or placebo (3-hour OGIS; $p \leq 0.015$).[16,20] A two-step insulin clamp study showed that vildagliptin improved insulin resistance by approximately 15% compared with placebo.[20]

• Recipients of vildagliptin and metformin also had improvements in some other insulin-related endpoints compared with patients receiving placebo plus metformin in clinical studies.[9,11] Plasma insulin levels did not change significantly with the addition of vildagliptin to metformin after 12 weeks of treatment in one phase II study (n = 107);[9] however, after a 40-week extension study (52-week assessment; n = 71), significant between-group differences in insulin AUC from 0 to 4 hours, adjusted mean change in 4-hour mean reactive insulin levels and insulin secretion rates in favour of vildagliptin plus metformin were evident (all $p < 0.05$ vs placebo plus metformin).[11]

Effects on Plasma Lipids

• The effect of vildagliptin treatment on plasma lipids was variable in both small, short-term pharmacodynamic studies[15] and larger, longer phase II[9,12,13] and phase III[10] clinical studies. Fasting levels of total triglycerides, total cholesterol and serum apolipoprotein B were not significantly changed in recipients of vildagliptin 50mg twice daily compared with placebo after 4 weeks of treatment in a small study of 30 patients.[15]

• In response to a fat-rich meal test, vildagliptin recipients in the same study had significant decreases in the mean incremental AUC, compared with placebo recipients, for total triglycerides (−2.0 vs +1.0 mmol/L • h; $p = 0.011$), chylomicron triglycerides (−1.0 vs +0.5 mmol/L • h; $p < 0.001$) and chylomicron cholesterol (−0.1 vs +0.03 mmol/L • h; $p = 0.020$).[15]

• Plasma lipids (triglycerides and high-density lipoprotein [HDL]-, low-density lipoprotein [LDL]- and very-low-density lipoprotein [VLDL]-cholesterol), were generally unchanged in vildagliptin treatment groups compared with placebo groups in 12-week clinical monotherapy studies.[12,13] However, vildagliptin 100mg recipients had a small but significant ($p = 0.004$) reduction in HDL-cholesterol levels compared with placebo.[13]

• In a comparison with rosiglitazone, vildagliptin recipients had statistically significant improvements in triglycerides and total-, LDL-, non-HDL- and VLDL-cholesterol levels (all $p \leq 0.01$ vs rosiglitazone).[10] Patients receiving vildagliptin had a smaller increase in HDL-cholesterol than rosiglitazone recipients ($p = 0.003$ vs rosiglitazone) after 24 weeks of treatment.[10]

• In patients on a stable metformin regimen, total cholesterol was the only lipid parameter that significantly improved with vildagliptin treatment compared with placebo (between-group difference at 52 weeks of −0.3 mmol/L; $p = 0.034$).[9] There were no significant changes in triglyceride, or HDL- or LDL-cholesterol levels after 12 or 52 weeks of treatment.[9]

2. Pharmacokinetic Profile

Data in this section are generally from pharmacokinetic studies (n = 12–40) of oral vildagliptin in healthy volunteers,[28-30] patients with hepatic impairment[28] or patients with type 2 diabetes[14,31-33] that were either single-dose[28-30] or of 5–28 days' duration.[14,31-33] Some studies were randomised,[14,29] placebo-controlled,[14,31,32] or had a crossover design.[29,31,32] Additional pharmacokinetic data was taken from a conference presentation.[34]

• Vildagliptin is rapidly absorbed, with the maximum plasma concentration (C_{max}) achieved within 1–2 hours of administration.[14] C_{max} increased dose proportionally when oral vildagliptin 10, 25 or 100mg was administered twice daily in patients with type 2 diabetes (quantitative data not reported).[14] In three studies, steady-state vildagliptin C_{max} values were 467[33] and 531[32] ng/mL in patients receiving oral vildagliptin 100mg once daily, and 666 ng/mL in patients receiving oral vildagliptin 100mg twice daily.[31]

- The AUC for vildagliptin increased in a dose-proportional manner with increasing doses in the dose-ranging study (quantitative data not reported).[14] At steady-state, AUC from time zero to 24 hours for vildagliptin 100mg once daily was 1960[33] and 2189[32] ng • h/mL; the AUC from time zero to infinity was 2455 ng • h/mL for vildagliptin 100mg twice daily.[31]

- The absolute oral bioavailability of vildagliptin in healthy volunteers was 85%, and the volume of distribution at steady-state was 70.5L.[29]

- Metabolism of vildagliptin occurs via hydrolysis, and the major metabolite, LAY151, is pharmacologically inactive.[28,34] Vildagliptin does not inhibit or induce cytochrome P450. Excretion of vildagliptin occurs mainly via the urine (85%), with 15% excreted in the faeces.[34]

- The mean terminal elimination half-life ($t_{1/2}$) was 1.68 hours with a dosage of vildagliptin 100mg once daily[33] and 2.54 hours with a 100mg twice-daily dosage;[31] despite the short $t_{1/2}$, vildagliptin has a long duration of action because of slow-binding inhibition kinetics (section 1). Total body and renal clearance values of vildagliptin were 40.6 and 13.0 L/hour.[29] Hepatic excretion does not contribute significantly to elimination of the drug.[29]

- The pharmacokinetics of vildagliptin were not affected by age, gender or body mass index (BMI).[30]

- Exposure to vildagliptin in individuals with hepatic impairment was increased compared with that of healthy volunteers after a single 100mg dose, but the level of exposure did not correlate with the severity of liver disease and was not considered clinically relevant.[28] Vildagliptin $t_{1/2}$ values were not affected by hepatic impairment.[28] No studies in patients with renal impairment have been reported to date.

- No clinically relevant pharmacokinetic interactions requiring dose adjustment were observed during coadministration of vildagliptin and pioglitazone,[32] metformin[33] or glibenclamide (glyburide).[31]

3. Therapeutic Efficacy

Oral vildagliptin has been investigated as monotherapy[10,12,13,35-37] or in combination with metformin,[9,38] pioglitazone[39] or insulin[40] in the treatment of type 2 diabetes. Trials included two phase II dose-finding studies[13,35] (one in Japanese patients[35]) of vildagliptin 10–50mg twice daily,[35] or vildagliptin 25–100mg once daily or 25mg twice daily,[13] and several fixed-dose studies: two phase II studies[9,12] investigating the efficacy of vildagliptin 25mg twice daily or 50mg once daily, and seven phase III studies, investigating the efficacy of vildagliptin 50mg once or twice daily, or vildagliptin 100mg once daily (one abstract[39] reported the results of two studies).[10,36-40] A pooled analysis of the phase III trial data has also been performed.[34] The trials were randomised, double-blind, placebo or active comparator controlled, multicentre studies in patients with type 2 diabetes (n = 71–780).[9-13,34-40] The active comparators in monotherapy trials were rosiglitazone and metformin. Treatment periods ranged from 4 to 52 weeks; one study consisted of a 12-week core treatment period and a 40-week extension.[9,11] Where specified, four studies had a 4-week placebo[9,12,13] or pioglitazone[39] run-in period. Twice-daily dosages, where stated, were administered at breakfast and dinner,[13] whereas a once-daily dosage was administered before breakfast.[13]

The mean age of the patients was 53–59 years. Mean duration of diabetes, where stated, was 2.0–4.7 years in the monotherapy trials, and 4.6–6.2 years in the combination studies, except for one combination therapy trial in patients receiving insulin therapy where it was 14.6 years.[40] Mean baseline glycosylated haemoglobin (HbA_{1c}) was 7.6–8.8%. FPG baseline means were 8.8–10.3 mmol/L in all studies. Patients were treatment naive in several studies.[10,12,35-37,39] In those studies including previously treated patients, drug therapy regimens included metformin,[36,38] pioglitazone[39] or insulin.[40] Where stated in fully published phase II studies, exclusion criteria included patients with significant complications from diabetes, clinically significant metabolic or cardiovascular disorders,

liver disease, asthma, major skin allergies or previous GI surgery.[9,11,13]

The primary efficacy endpoint for all trials was change in HbA_{1c} levels. Other endpoints included FPG, postprandial glucose, bodyweight and blood lipids. Intent-to-treat (ITT) analysis was used for some analyses,[9,12] while per-protocol analysis was used for other results.[11,13] The type of analysis was not reported in several studies.[10,35-40] Three of the studies were fully published,[9,12,13] while the others were available as abstracts[10,35-40] and conference presentations.[34] Some information regarding the trials was taken from the manufacturer's clinical trials website.[41] Additional clinical data were obtained from the manufacturer, and are cited as data on file.[42]

Monotherapy

Data in this section relates to therapeutic efficacy endpoints from large (n > 100) phase IIb and phase III trials. For results in smaller studies and other glucose parameters, see section 1.

- Vildagliptin improved glycaemic control, as assessed by HbA_{1c}, in randomised, placebo-controlled trials in patients with type 2 diabetes.[12,13,35] In two phase II studies (n = 279[13] and 98[12]), a significantly greater reduction in HbA_{1c} levels from baseline was generally seen with vildagliptin 50mg (between-group difference −0.43%[13] and −0.6%[12]) or 100mg (−0.4%[13]) daily compared with placebo (all $p \leq 0.004$) after 12 weeks' treatment.[12,13] However, in the dose-finding study, the between-group difference was not significant for patients receiving vildagliptin 25mg once or twice daily versus placebo (figure 1).[13]
- In the dose-finding study in Japanese patients (n = 291), 12 weeks of vildagliptin treatment resulted in significant decreases in mean HbA_{1c} levels from baseline (7.4%) of 0.53%, 0.67% and 0.92% in patients receiving vildagliptin 10, 25 or 50mg twice daily ($p < 0.001$ vs placebo).[35] Similarly, plasma FPG and 2-hour postprandial glucose levels were significantly reduced with all vildagliptin dosages compared with placebo (all $p < 0.001$ vs placebo).[35]

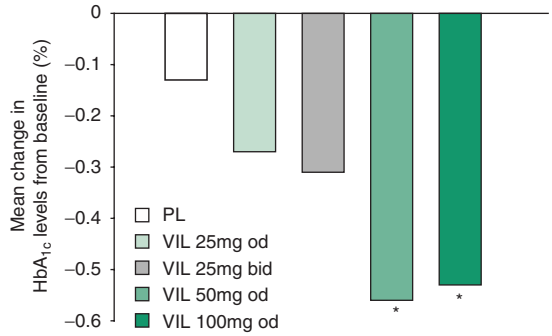


Fig. 1. Effect of vildagliptin (VIL) monotherapy on glycosylated haemoglobin (HbA_{1c}) levels in patients with type 2 diabetes mellitus. Results of a randomised, double-blind, placebo (PL)-controlled, dose-finding study of 12 weeks' duration.[13] Patients (n = 279)[13] received VIL 25, 50 or 100mg once daily (od), or 25mg twice daily (bid), or PL. * $p < 0.01$ vs PL.

- A group of previously untreated patients with type 2 diabetes (n = 380) receiving vildagliptin 50mg once or twice daily or 100mg once daily for 24 weeks in a phase III monotherapy trial had differences versus placebo in mean HbA_{1c} of −0.5%, −0.5% and −0.6% (all $p \leq 0.006$).[37]
- Pooled data from phase III placebo-controlled trials in patients receiving vildagliptin 100 mg/day for 24 weeks (n = 1301) showed that mean HbA_{1c} decreased by 1.1% from a mean baseline of 8.7% in the overall population ($p < 0.01$ vs baseline).[34] In subgroups of patients with baseline HbA_{1c} values of >8% and >9%, decreases from baseline were 1.3% and 1.7% (both $p < 0.01$ vs baseline; placebo results not reported).[34]
- Further subgroup analysis showed that there was no effect of age or BMI on the efficacy of vildagliptin 100 mg/day.[34] There was no difference in mean HbA_{1c} reduction from baseline between patients aged <65 years and those aged >65 years (both −1.1%; $p < 0.01$ vs baseline). Similarly, patients with a BMI of <30 kg/m^2 had a decrease from baseline in HbA_{1c} of 1.2% ($p < 0.01$); patients with a BMI of >30 kg/m^2 had a decrease from baseline of 1.0% ($p < 0.01$ vs baseline; mean or median and between-group statistics not reported).[34]
- Clinical guidelines for the management of blood glucose in type 2 diabetes state that target levels of HbA_{1c} should be between 6.5% and 7.5% to reduce

the risk of cardiovascular complications.[43] Approximately half of the patients with baseline HbA_{1c} levels of >7% receiving vildagliptin ≥50mg daily in placebo-controlled trials achieved HbA_{1c} levels of <7% at study endpoint.[12,13]

- Vildagliptin was noninferior to rosiglitazone in terms of glycaemic control in a 24-week phase III trial in drug-naive patients with type 2 diabetes (n = 697) [statistical analysis not reported].[10] In patients whose baseline HbA_{1c} values were ≈8.8–8.9%, 24 weeks' treatment with vildagliptin 50mg twice daily or rosiglitazone 8mg once daily resulted in an adjusted mean change in HbA_{1c} at study end of −1.1% and −1.3%.[10] In patients with a BMI <30 kg/m^2, the adjusted mean change in HbA_{1c} levels was −1.3% and −1.1% in vildagliptin and rosiglitazone recipients.[10]

- In this study, recipients of vildagliptin whose baseline HbA_{1c} levels were >9.0% had a mean decrease of 1.8%, and recipients of rosiglitazone with the same baseline HbA_{1c} level had a mean decrease of 1.9%.[10]

- Although clinically meaningful reductions from baseline in HbA_{1c} levels were seen with vildagliptin 50mg or metformin 1000mg twice daily in a 52-week phase III trial in drug-naive patients with type 2 diabetes (n = 780) [1.0% vs 1.4%], noninferiority was not established (statistical data not reported).[36]

- FPG levels were not consistently improved with vildagliptin treatment when compared with placebo treatment.[12,13] Although reductions in FPG levels from baseline with vildagliptin treatment were not significantly different from placebo in the dose-finding study,[13] in the fixed-dose comparison, vildagliptin 25mg twice daily was superior to placebo (p = 0.0043).[12]

- Mean 4-hour postprandial glucose levels were significantly improved compared with placebo in only one dose group in the dose-finding study (vildagliptin 50mg once daily; p = 0.012).[13] In contrast, a dosage of vildagliptin 25mg twice daily in the fixed-dose study produced an significant improvement in 4-hour postprandial glucose levels compared with placebo (p < 0.0001).[12]

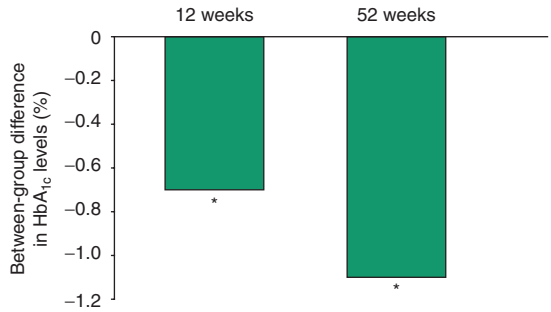


Fig. 2. Effect of vildagliptin combination therapy on glycosylated haemoglobin (HbA_{1c}) levels in patients with type 2 diabetes mellitus. Results of a randomised, double-blind, placebo-controlled, fixed-dose study of 52 weeks' duration (12-week core study plus 40-week extension).[9] Patients (n = 107 and 71 for core and extension studies) received vildagliptin 50mg once daily or placebo in addition to a stable dosage of metformin (1500–3000 mg/day).[9] * p < 0.0001 vs placebo.

Combination Therapy

- The addition of vildagliptin to underlying antidiabetic treatment significantly improved glycaemic control in patients with type 2 diabetes receiving a stable metformin treatment regimen.[9,38] Patients receiving ongoing stable treatment with metformin (1500–3000 mg/day) participating in a phase II trial of vildagliptin 50mg once daily or placebo that consisted of a 12-week core study (n = 107) plus a 40-week extension (n = 71)[9,11] had a between-group difference (vildagliptin plus metformin vs placebo plus metformin) of −0.7% at 12 weeks and −1.1% at 52 weeks (ITT population; both p < 0.0001 vs placebo plus metformin) [figure 2].[9]

- The addition of vildagliptin to metformin resulted in an increase in the proportion of patients with type 2 diabetes who achieved good glycaemic control.[9,11] After 52 weeks of treatment, 41.7% of patients taking vildagliptin plus metformin had achieved an endpoint HbA_{1c} level of <7.0% from a baseline level of 7.6–7.8%, compared with 10.7% of placebo plus metformin recipients (statistical analysis not reported).[9]

- In the core and extension studies, FPG levels also decreased significantly in patients taking vildagliptin plus metformin, compared with patients taking placebo plus metformin.[9] In the 12-week core study,[9] the between-group difference in FPG

levels was −1.2 mmol/L (p = 0.0057 vs placebo plus metformin),[9] while the between-group difference in FPG levels in the 40-week extension study was −1.1 mmol/L (vildagliptin plus metformin vs placebo plus metformin, p = 0.031).[9]

- The addition of vildagliptin to existing metformin treatment also improved glycaemic control in patients with type 2 diabetes in a phase III study (n = 416).[38] Recipients of vildagliptin 50mg once or twice daily plus metformin ≥1500 mg/day for 24 weeks had a difference in HbA_{1c} of −0.7% and −1.1% versus placebo plus metformin (both p < 0.001).[38] The reduction in HbA_{1c} seen in vildagliptin recipients occurred early and was sustained over the 24-week treatment period (figure 3).[38,42]

- The difference in FPG levels between patients receiving metformin and vildagliptin 50mg once or twice daily and placebo plus metformin recipients was −0.8 and −1.7 mmol/L (p ≤0.003 vs placebo plus metformin).[38]

- Vildagliptin in combination with pioglitazone was associated with greater glycaemic control than pioglitazone monotherapy in two phase III trials.[39] Drug-naive patients receiving once-daily vildagliptin 50mg plus pioglitazone 15mg or vildagliptin 100mg plus pioglitazone 30mg for 24 weeks had significantly reduced HbA_{1c} levels from baseline compared with recipients of pioglitazone 30mg once daily (−1.7% and −1.9% vs −1.4%; both p < 0.05) [n = 599].[39] Those with a mean baseline HbA_{1c} level of ≈10.0% (n = 54) who received vildagliptin 100mg in combination with pioglitazone 30mg had a mean decrease from baseline in HbA_{1c} levels of 2.8%.[39]

- In another 24-week trial in 398 patients previously treated with a thiazolidinedione, vildagliptin 50mg once or twice daily plus pioglitazone 45mg once daily reduced HbA_{1c} levels from baseline to a greater extent than pioglitazone 45mg once daily (−0.8% and −1.0% vs −0.3%; both p ≤ 0.001).[39]

- Patients with type 2 diabetes that was inadequately controlled with insulin therapy (n = 256) also showed an improvement in glycaemic control when vildagliptin was added to their existing insulin regimen.[40] After 24 weeks of treatment, patients receiving vildagliptin 50mg twice daily plus insulin had a reduction in HbA_{1c} levels of 0.5%, compared

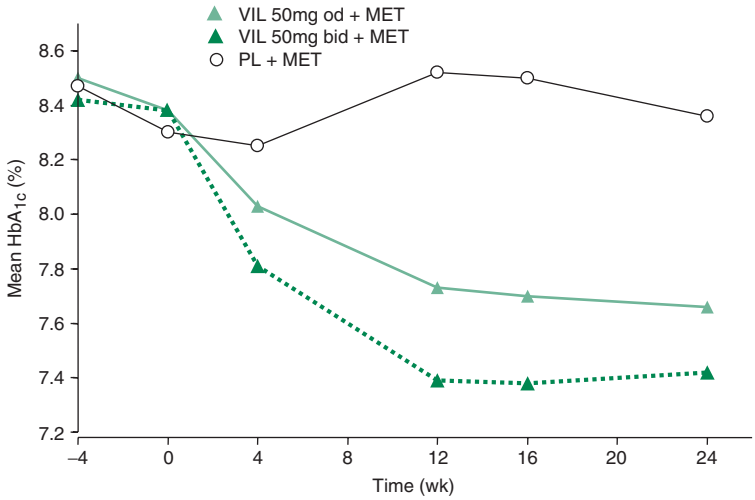


Fig. 3. Effect of vildagliptin (VIL) combination therapy on glycosylated haemoglobin (HbA_{1c}) levels over time in patients with type 2 diabetes mellitus. Results of a randomised, double-blind, placebo (PL)-controlled, fixed-dose multicentre study of 24 weeks' duration.[38,42] Patients received VIL 50mg once daily (od) [n = 143], VIL 50mg twice daily (bid) [n = 143] or PL (n= 130) in addition to a stable dosage of metformin (MET) [≥1500 mg/day].[38] The change in HbA_{1c} in recipients of VIL (50mg od or bid) plus MET was significantly (p < 0.001) greater than that seen in recipients of PL plus MET at 24 weeks (reproduced from Garber et al.,[38] with permission from The American Diabetes Association. Copyright © 2006 American Diabetes Association).

with a reduction in the placebo plus insulin group of 0.2% (p = 0.022 vs placebo plus insulin).[40]

4. Tolerability

- Vildagliptin was generally well tolerated in the phase II and III trials discussed in section 3, with most adverse events considered mild to moderate.[9,12,13,35,37-40] Adverse events were reported by 55–70% of vildagliptin recipients, 59–74% of placebo recipients, 34–75% of active comparator recipients (metformin, pioglitazone, rosiglitazone and insulin, with or without matching placebo) and 26–69% of vildagliptin plus active comparator (metformin, pioglitazone and insulin) recipients, in phase II and phase III trials of 12–52 weeks' duration.
- None of the serious adverse events reported in the fully published phase II dose-finding monotherapy trial[13] or a combination therapy trial[9] were deemed related to the study drug, apart from one adverse event in the 40-week extension of the combination therapy study (an episode of peripheral oedema with vildagliptin plus metformin).[9]
- Withdrawal rates due to adverse events were low in phase II monotherapy and combination therapy studies (3.2–7.8%[13] and 1.4%[9]), and no deaths were reported in either study.[9,13]
- A pooled analysis of the incidence of adverse events reported in phase III clinical trials by recipients of daily doses of vildagliptin 100mg, metformin ≤2000mg, rosiglitazone 8mg (all given as monotherapy) or placebo is shown in figure 4.[34] The most common (occurring in ≥5% of patients) adverse events reported in the vildagliptin group were nasopharyngitis, headache and dizziness.
- Episodes of hypoglycaemia were rare in phase II and III studies, whether vildagliptin was being used as monotherapy[12,13,35,37] or as a component of combination therapy.[9,38-40] For example, in the phase II

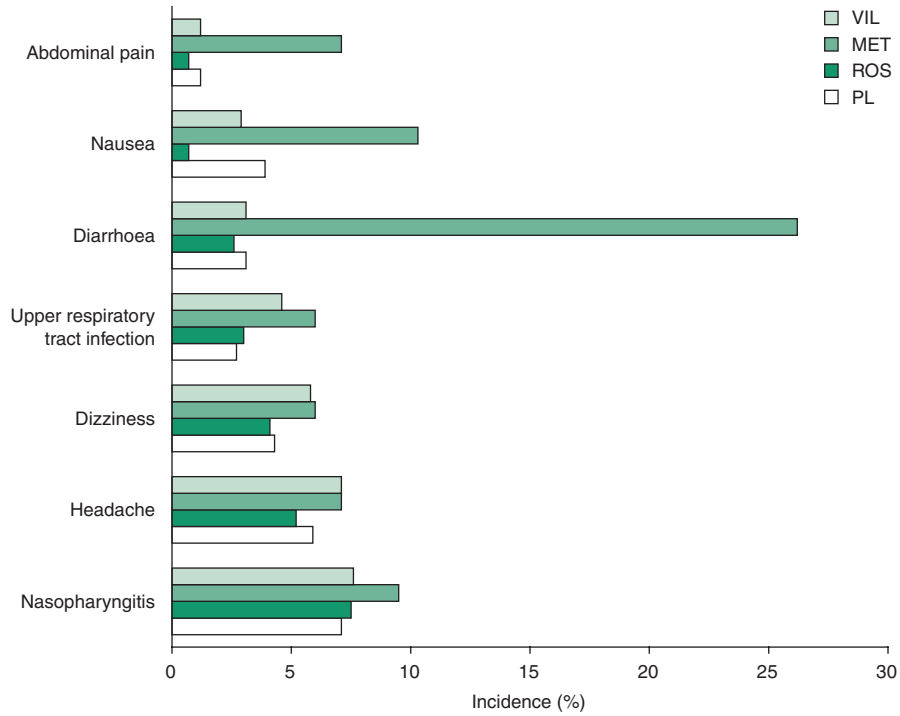


Fig. 4. Tolerability of vildagliptin (VIL) monotherapy. Adverse events occurring in ≥5% of patients receiving VIL 100 mg/day (n = 1530), metformin (MET) ≤2000 mg/day (n = 252), rosiglitazone (ROS) 8 mg/day (n = 267) or placebo (PL) [n = 255]. Pooled data from PL- or active-controlled phase III trials in patients with type 2 diabetes mellitus.[34] Statistical analysis not reported.

dose-finding study, hypoglycaemia was reported in 3.8–8.1% of vildagliptin and 5.4% of placebo recipients; none of the episodes were considered severe.[13]

- In a phase III monotherapy study,[37] 1.2%, 0%, 0.6% and 0% of patients receiving vildagliptin 50mg once daily, 50mg twice daily or 100mg once daily or placebo reported a hypoglycaemic episode; all episodes of hypoglycaemia were considered mild.[37]
- In the phase III, active comparator, monotherapy trials, one patient in each group in the vildagliptin versus rosiglitazone study reported a mild hypoglycaemic episode.[10] Mild hypoglycaemia occurred in 0.6% of patients taking vildagliptin compared with 0.4% of patients taking metformin.[36]
- Episodes of hypoglycaemia in patients receiving vildagliptin plus metformin were rare. Two patients in the 12-week phase II study of vildagliptin plus metformin reported a confirmed case of hypoglycaemia, and another reported three episodes of an asymptomatic self-monitored low blood glucose level.[9] One other patient exhibited symptoms suggestive of low blood glucose.[9] No confirmed cases of hypoglycaemia were reported during the 40-week extension study in patients receiving vildagliptin plus metformin.[9]
- In the phase III study of vildagliptin plus metformin versus placebo plus metformin, one patient in each treatment arm reported a hypoglycaemic event (severity not reported).[38]
- No severe hypoglycaemic episodes were reported with vildagliptin plus insulin, whereas six episodes of severe hypoglycaemia were reported with insulin plus placebo in another trial.[40]
- GI adverse events in patients taking vildagliptin alone or in combination with additional antidiabetic treatment were uncommon, and were generally mild to moderate in severity. In the phase II dose-finding study, GI events (constipation and/or diarrhoea) were reported by 3.2–5.9% of vildagliptin recipients and 5.4% of placebo recipients.[13] In a phase III study, GI adverse events were significantly less common with vildagliptin as monotherapy versus metformin (any GI adverse event: 21.8% vs 43.7%; $p < 0.001$).[36] For a pooled analysis of specific GI events reported by recipients of vildagliptin 100mg in phase III clinical trials,[34] see figure 4.
- Vildagliptin treatment did not cause significant bodyweight changes from baseline when used as monotherapy[10,12,13,35-37] or in combination with metformin[9] in phase II and III trials. In phase III studies comparing vildagliptin with rosiglitazone or metformin, weight was unchanged in vildagliptin recipients, whereas rosiglitazone recipients gained weight (mean weight gain of 1.6kg; $p < 0.001$ vs vildagliptin)[10] and metformin recipients had a modest weight loss (1.9kg; statistical analysis not reported).[36]
- There were no clinically relevant changes in laboratory parameters with vildagliptin used as monotherapy, nor were there any differences in vital signs or ECG results.[13] Notable laboratory abnormalities occurred rarely and at the same frequency in patients receiving vildagliptin plus metformin as patients receiving placebo plus metformin.[9]

5. Dosage and Administration

Formal recommendations for the administration of vildagliptin to patients with type 2 diabetes are not available. In phase III clinical trials, dosages of vildagliptin were 100 mg/day in monotherapy studies, and 50–100 mg/day in combination studies. In a placebo-controlled monotherapy study, vildagliptin 100mg once daily showed similar efficacy to vildagliptin 50mg twice daily, and no dose response between 50 and 100 mg/day was noted. A dosage of 50 mg/day was not investigated in active comparator studies of vildagliptin and metformin or rosiglitazone, or in the combination study of vildagliptin and insulin therapy. The lowest dosage that showed clinical efficacy in monotherapy or combination therapy trials conducted in patients in Europe and the Americas was 50 mg/day, administered as a single dose of 50mg. The optimum dose of vildagliptin for most patients is expected to be 100 mg/day.[42] Vildagliptin was taken orally, either with the morning and evening meals or before breakfast.

6. Vildagliptin: Current Status

Vildagliptin is currently undergoing pre-approval assessment in the US and Europe as an oral therapy for patients with type 2 diabetes.[44,45] In several well designed clinical trials, vildagliptin has shown efficacy in improving glycaemic control in patients with type 2 diabetes, both as monotherapy and in combination with additional antidiabetic therapies. Vildagliptin was generally well tolerated when used as monotherapy and in combination therapy. Phase III trials are ongoing in order to better characterise the safety and efficacy of vildagliptin in patients with type 2 diabetes.

Disclosure

During the peer review process, the manufacturer of the agent under review was offered an opportunity to comment on this article; changes based on any comments received were made on the basis of scientific and editorial merit.

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