Combination treatment in the management of type 2 diabetes: focus on vildagliptin and metformin as a single tablet

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Abstract: Vildagliptin is a potent and selective inhibitor of dipeptidyl peptidase-IV (DPP-4), orally active, that improves glycemic control in patients with type 2 diabetes (T2DM) primarily by enhancing pancreatic (α and β) islet function. Thus vildagliptin has been shown both to improve insulin secretion and to suppress the inappropriate glucagon secretion seen in patients with T2DM. Vildagliptin reduces HbA_{1c} when given as monotherapy, without weight gain and with minimal hypoglycemia, or in combination with the most commonly prescribed classes of oral hypoglycemic drugs: metformin, a sulfonylurea, a thiazolidinedione, or insulin. Metformin, with a different mode of action not addressing β-cell dysfunction, has been used for about 50 years and still represents the universal first line therapy of all guidelines. However, given the multiple pathophysiological abnormalities in T2DM and the progressive nature of the disease, intensification of therapy with combinations is typically required over time. Recent guidelines imply that patients will require pharmacologic combinations much earlier to attain and sustain the increasingly stringent glycemic targets, with careful drug selection to avoid unwanted adverse events, especially hypoglycemia. The combination of metformin and vildagliptin offers advantages when compared to currently used combinations with additive efficacy and complimentary mechanisms of action, since it does not increase the risk of hypoglycemia and does not promote weight gain. Therefore, by specifically combining these agents in a single tablet, there is considerable potential to achieve better blood glucose control and to improve compliance to therapy.

Keywords: type 2 diabetes, dipeptidyl peptidase-4, HbA_{1c}, GLP-1, incretin hormones, Eucreas®

Management of type 2 diabetes: use of metformin and the role of combination treatment

Type 2 diabetes (T2DM) is a chronic and complex disease which involves multiple pathophysiological defects, including impaired islet function and insulin resistance, resulting in impaired glucose tolerance and inappropriately high fasting hepatic glucose production. While insulin resistance remains essentially unchanged over time, the deficit in islet function is a progressive process with quantitative and qualitative abnormalities in insulin and glucagon secretion kinetics, paralleled by a substantial reduction in the maximum capacity to secrete insulin. These defects in islet function are present early on and worsen with the natural history of the disease (Butler et al 2003; Nathan et al 2007; Virally et al 2007). Indeed, most individuals who are insulin resistant never develop T2DM because normal islets adapt to insulin resistance both by increasing glucose-potentiated insulin secretion (Kahn et al 1993) and by increasing α-cell sensitivity to the suppressive effects of glucose (Ahren 2006). Thus, the

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first patent characteristic of T2DM is inadequate islet compensation rather than absolute hypoinsulinemia or absolute hyperglucagonemia (Ahren et al 2008).

Despite clear evidence that maintenance of glycemic levels as close to normal as possible reduces the risk of diabetic complications, optimal control is seldom achieved and maintained in patients with T2DM (Brown et al 2004; Koro et al 2004). While all oral antidiabetic agents initially lower blood glucose effectively, none of them are able to address all the anomalies involved in the pathogenesis of T2DM, to stop the decline in beta-cell function, and to achieve durable glycemic control (Cook et al 2007).

Established management of T2DM starts with lifestyle changes, ie, introducing a healthier diet and increasing physical activity in order to improve glucose utilization and promote weight loss. This is accompanied by rapid or even concomitant introduction of an oral antidiabetic agent. Metformin is widely used as the first-line antidiabetic drug of choice (Consoli et al 2004; Halimi 2006). Metformin reduces hepatic glucose output, primarily by inhibiting gluconeogenesis, and, to a lesser extent, increases tissue sensitivity to insulin (Stumvoll et al 1995). Beneficial clinical properties of metformin include weight control (Golay 2007), a low risk of hypoglycemia and favorable effects on the lipid profile and the fibrinolytic pathway (Bailey and Turner 1996; Goodarzi and Bryer-Ash 2005). Metformin was reported to be equally effective in lowering glucose in non-obese and obese patients and can thus be used independent of an individual's BMI (Donnelly et al 2006). More importantly, it is the only drug which has demonstrated beneficial effects on cardiovascular events, as reported in the UKPDS substudy of overweight patients (UKPDS 34 1998). In this study, metformin was also associated with reduced all cause mortality, which was not seen in patients with equally well controlled blood glucose treated with sulfonylureas or insulin.

Metformin is therefore recommended by all guidelines as first-line therapy for T2DM. The International Diabetes Federation (IDF) suggests to use metformin in all cases inadequately controlled by non-pharmacological treatments (IDF, on line) while a recent consensus document of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) recommends to prescribe metformin at diagnosis, together with lifestyle interventions (Nathan et al 2006, 2008).

Upon progression of the disease, progressive loss of β-cell function and mass makes it difficult for patients to maintain glycemic control with monotherapy. In the UKPDS only about 50% of patients were still adequately controlled on monotherapy after 3 years (Turner et al 1999) (UKPDS-49). Even if somewhat better durability of glycemic control was achieved with TZD over 4 years in the ADOPT trial (Kahn et al 2006), high rates of secondary failure have been reported with all current oral hypoglycemic drugs (OADs), including following successful initial metformin therapy (Nichols et al 2006).

As a result, combination therapy involving agents with complementary mechanism of action is the next logical step in the management of T2DM. Established treatment options for metformin monotherapy failure include the addition of sulfonylureas (or glinides), thiazolidinediones, acarbose, or insulin. Since metformin lowers plasma glucose without affecting insulin secretion, it is often combined with an agent stimulating insulin secretion, like a sulfonylurea. Adding a sulfonylurea to metformin has thus been the conventional and the gold standard combination therapy for decades. However, while previous therapeutic goals made this combination quite attractive, the lower glycemic targets for intensification of therapy substantially increase the risk of hypoglycemia (particularly in patients with mild hyperglycemia or in the older and more fragile patients) resulting in symptoms or increased food intake to avoid or treat them. Therefore, the need for more glucose-sensitive agents as alternative combination therapies was warranted.

Recently, newer agents, which induce a glucose-dependent stimulation of insulin secretion became available and can provide an attractive alternative for use in combination with metformin. Such a novel therapy for T2DM is based on pharmacological inhibition of the enzyme dipeptidyl peptidase IV (DPP-4), which is responsible for the rapid inactivation of the incretin hormones glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic peptide (GIP) (Langley et al 2007). These intestinally derived peptides are released rapidly after eating, ie, in the presence of glucose or nutrients in the gut.

By stabilizing endogenous incretin hormones at physiological concentrations, DPP-4 inhibitors increase the sensitivity to glucose of both insulin and glucagon secretion (ie, increase insulin secretion and suppress glucagon secretion in a glucose-dependent manner), thereby lowering glucose levels. DPP-4 inhibitors are thus the first oral agents addressing the dual α- and β- islet cells dysfunction present in T2DM.

This article provides an overview of the characteristics and combined anti-diabetic effects of the DPP4 inhibitor vildagliptin and metformin.

Pharmacokinetics/ Pharmacodynamics (Pk/Pd) and mode of action (MoA) of metformin and vildagliptin, and rationale for their use in combination

PK/PD and MoA of metformin

Metformin is absorbed mainly from the small intestine, with a 60% bioavailability; the plasma half life is estimated at 1.5–4.9 hours. The drug is not significantly metabolized, and 90% is eliminated unchanged in urine in 12 hours by glomerular filtration and tubular secretion. It is distributed in most tissues, with higher concentrations in liver, kidneys, salivary glands and the intestinal walls. The drug can be removed by hemodyalisis.

Metformin has been available for treating diabetes since the 1950s, but despite decades of medical use, the mechanism of action of the drug at the molecular level is still not fully understood but is related to an action on AMP kinase (Goodarzi and Bryer-Ash 2005).

The glucose-lowering effect of metformin is mainly due to decreased basal hepatic glucose output and -to a lesser extent- enhanced peripheral glucose uptake (with muscle as its main site of action). The latter action on muscles is likely indirect and explained by the overall improved metabolic state. Additional actions that contribute to the glucose-lowering effect are the increased intestinal use of glucose and decreased fatty acid oxidation (Bailey and Turner 1996).

The most feared and widely publicized adverse effect of biguanide therapy is lactic acidosis, likely resulting from the action of biguanides to interfere with non-oxidative glucose metabolism. Lactic acidosis could occur in energy-compromised individuals leading to increased lactate production and/or reduced lactate clearance, such as in liver disease, renal dysfunction or other illness causing tissue hypoxia (such as cardiac or respiratory dysfunction). It has a high mortality, but is extremely rare with metformin, the overall incidence being estimated at one case per 30,000 patient-years. This rate of lactic acidosis events is actually almost similar to that reported in patients with T2DM not taking metformin (Brown et al 1998) indicating that lactic acidosis occurs in metformin-treated patients when energy metabolism is further altered in patients where it was already severely compromised (Tahrani et al 2007).

The most common dose-limiting adverse effects of metformin are gastrointestinal (abdominal discomfort, metallic taste and anorexia, nausea or diarrhea) but these effects are minimized with gradual upward titration and concomitant administration with meals, overall leading to drug discontinuation in less than 5%–10% of the patients (Bailey and Turner 1996; Goodarzi and Bryer-Ash 2005). However gastrointestinal discomfort is often the single factor that prevents the use of higher, more efficacious doses of metformin.

PK/PD and MoA of vildagliptin

Vildagliptin is well and rapidly absorbed after oral administration. About 70% of the orally administered vildagliptin is metabolized, hydrolysis being the main pathway, and renal excretion being the main route of elimination (85%), with some of the oral dose excreted in the urine as unchanged drug (23%). Food ingestion does not alter the pharmacokinetics of vildagliptin (Sunkara et al 2007). Vildagliptin does not inhibit or induce the major P450 enzymes and shows no drug interactions with commonly used medication (such as glyburide, metformin, pioglitazone, digoxin, warfarin, simvastatin, valsartan, amlodipine, ramipril) (Ayalasomayajula et al 2007; El Ouaghlidi et al 2007; He et al 2007a, b). Age, gender, BMI, and race do not affect the pharmacokinetics of vildagliptin (He et al 2007c, d, e).

Vildagliptin selectively inhibits DPP- 4 activity (Burkey et al 2006), resulting in increased levels (2- to 4-fold) of the two key glucoregulatory incretin hormones GLP-1 and GIP, allowing the pancreatic islet cells to better sense and more appropriately respond to raised glucose levels (Ahren et al 2005; Mari et al 2005).

The increased levels of active endogenous incretin hormones result in better post-prandial and fasting glucose control by stimulating insulin secretion, reducing glucagon levels and suppressing overnight hepatic glucose production, which all contribute to the clinical effect to lower HbA_{1c} (Ahren et al 2004b, 2005; Balas et al 2007).

Further evidence for an improvement of islet function with vildagliptin, with an increase of both α- and β-cell responsiveness to glucose, come from a number of recent studies (Azuma et al 2007; Pratley et al 2007b; Mari et al 2007). In addition, vildagliptin treatment leads to a more efficient β-cell insulin processing, providing further evidence for an amelioration of the abnormal β-cell function in patients with T2DM (Ahren et al 2007). Previous data in rodents showed that vildagliptin increases pancreatic β-cell mass by markedly stimulating β-cell replication and inhibiting apoptosis (Duttaroy et al 2005), similar to the beneficial effects reported for parenterally administered GLP-1 agonists (Tourrel et al 2002). These animal data on beta cell protection still need to translate into durable glycemic control

in humans, which can only be demonstrated in long term clinical trials.

These primary effects of vildagliptin to enhance incretin hormone levels also lead to improved insulin mediated glucose disposal which may be due in part to reduced glucose toxicity and in part to reduced stored triglycerides in muscle and liver (Azuma et al 2007). A similar improvement in insulin sensitivity and β-cell function, leading to improved postprandial glycemia, has recently been shown in subjects with impaired fasting glucose after 6 weeks of treatment with vildagliptin 100 mg/day (Utzschneider et al 2008). Furthermore, the known effects of vildagliptin on incretin levels and islet function in type 2 diabetes were reproduced in another study conducted in 179 subjects with impaired glucose tolerance over 12 weeks, with a 32% reduction in postprandial glucose excursions and no evidence of hypoglycemia or weight gain (Rosenstock et al 2007c).

Vildagliptin shows no action on gastric emptying or any evidence for delayed glucose absorption or delayed appearance of drugs co-administered in interaction studies (Vella et al 2007).

Interestingly, treatment with vildagliptin for 4 weeks improved postprandial plasma triglyceride after a fat-rich meal, and this was achieved mainly through a decrease in intestinally derived apo B-48-containing particles. These results indicate that vildagliptin treatment reduces postprandial atherogenic TRLs in the circulation and suggest that it may protect against weight gain in patients with T2DM by extracting less fat from the gut (Matikainen et al 2006).

The clinical profile of vildagliptin has been extensively assessed in the development program, providing evidence of its glucose-lowering efficacy across a wide range of clinical uses: as monotherapy or initial combination therapy in treatment-naive patients (Dejager et al 2007; Pi-Sunyer et al 2007; Rosenstock et al 2007 a, b; Schweizer et al 2007), as add-on therapy with the most commonly prescribed classes of oral hypoglycemic drugs (Bosi et al 2007; Garber et al 2007a, b), and in combination with insulin in patients with long-standing disease (Fonseca et al 2007). In monotherapy, vildagliptin produced consistent reductions from baseline in HbA$_{1c}$ of approximately 1%, sustained out to one year, was weight-neutral and well-tolerated, and had a low incidence of hypoglycemia and no episodes of severe hypoglycemia. Vildagliptin 100 mg daily was as effective as rosiglitazone 8 mg daily without the weight gain (Rosenstock et al 2007b). When compared with metformin 2000 mg daily, statistical noninferiority was not established but treatment with vildagliptin 100 mg daily for 1 year reduced HbA$_{1c}$ by

1.0% (p < 0.001) with a more favorable gastrointestinal (GI) tolerability than metformin (Schweizer et al 2007). Furthermore, the efficacy and safety profiles of vildagliptin in elderly patients (who had a high prevalence of co-morbidities and mild renal insufficiency) were comparable to those in younger patients, including a very low (0.8%) incidence of hypoglycemia and no severe hypoglycemic episode (Pratley et al 2007a). In this regard, a recent study of vildagliptin added to existing insulin therapy is interesting: hypoglycemia was significantly less frequent and less severe with vildagliptin than with placebo, despite improved glycemic control in those receiving vildagliptin (Fonseca et al 2007). In addition, recent data further confirmed the low hypoglycemic risk at the other end of the disease spectrum. In recently diagnosed patients with mild hyperglycemia (n = 306; baseline HbA$_{1c}$ ≈ 6.7%, FPG ≈ 7.1 mmol/L and nearly half of the patients over age 65) 52-week treatment with vildagliptin elicited a modest but statistically significant reduction in A1C (–0.3%), primarily due to a reduction of postprandial glucose and at least in part reflecting improved beta-cell function. Treatment with vildagliptin was weight neutral (–0.5 kg from baseline) and was well tolerated with no episode of hypoglycemia over one year in the vildagliptin group (Scherbaum et al 2007). This low hypoglycemic potential of vildagliptin likely reflects the glucose-dependent nature of both the insulinotropic and the glucagonostatic effects of GLP-1.

Rationale for the combination of vildagliptin and metformin

Because an incretin-based therapy acts by different mechanisms than metformin, combined therapy with metformin and a DPP4 inhibitor like vildagliptin was expected to be of considerable interest for the treatment of type 2 diabetes. Firstly, additive effects on plasma glucose lowering should be seen, which was first demonstrated with a combination of metformin and GLP-1 infusion in T2DM patients (Zander et al 2001). Furthermore, beyond the additive effects of the drugs, the attractive potential of this combination would be to achieve the glucose lowering effect with beneficial effects on ß-cell function, without promoting weight gain or increasing the risk of hypoglycemia and without exacerbating the GI side effects of metformin. Clinical studies have indeed confirmed these expectations as outlined below.

An additional interesting aspect regarding the combination of metformin and a DPP4 inhibitor comes from the following recent research findings. Firstly, it was indicated that metformin increases plasma active GLP-1 in obese nondiabetic subjects, suggesting that metformin may have the

additional property of inhibiting DPP IV activity (Mannucci et al 2001). This increase in active GLP-1 with metformin was further confirmed by a number of studies, while the underlying mechanism is still the subject of debate: the increase could reflect a stimulation of GLP-1 secretion from intestinal L cells, an inhibition of renal GLP-1 excretion or an increased transcription/translation of the proglucagon gene, as well as an effective inhibition of DPP IV activity (Zander et al 2001; Hinke et al 2002 a, b; Green et al 2006; Lindsay et al 2005).

The clinical potential of this mechanistic research further emerged when Dunning et al (Dunning et al 2006) compared the effects of vildagliptin on plasma levels of intact GLP-1 in drug-naïve patients with T2DM versus patients receiving concomitant metformin. Relative to patients receiving no concomitant OAD, the effects of vildagliptin to increase plasma levels of both fasting and postprandial active GLP-1 were clearly and consistently enhanced in patients receiving concomitant metformin, a finding that likely extends to DDP4 inhibitors in general (Migoya et al 2007). The fact that vildagliptin substantially enhances the incretin effect in patients receiving concomitant metformin may underlie the pronounced efficacy of vildagliptin to decrease FPG, PPG and HbA1c in metformin-treated patients, as further discussed below.

Clinical data on combination therapy of vildagliptin and metformin

The efficacy of a drug when combined with other agents can be different from that of the same drug prescribed as monotherapy: when used in combination, most drugs reduce HbA_{1c} to a lesser extent than in monotherapy (DeFronzo and Goodman 1995). Furthermore, patients failing metformin monotherapy could have different characteristics and show a different response to hypoglycemic agents. Therefore, to reliably assess the efficacy of a new drug in combination with metformin, it is important to get data in patients insufficiently controlled with metformin monotherapy at stable, maximally tolerated doses. The efficacy and safety of the vildagliptin/metformin combination was studied accordingly in 2 placebo-controlled and 1 active-controlled trials.

The combination of vildagliptin plus metformin was initially evaluated in a 12-week phase II study with a 40-week, double-blind, placebo-controlled extension (Ahren et al 2004a). In this population starting from a relatively low baseline HbA_{1c} of 7.6% and treated with metformin for a mean duration of 28 months and at a mean daily dose of 1.8 g/day,

vildagliptin 50 mg daily added to metformin reduced mean HbA_{1c} by 1.1% relative to metformin/placebo after 52 weeks of treatment ($p < 0.001$). This reflected deterioration of glycemic control in patients receiving metformin alone and a stable HbA1c of ~7.1% maintained from week 12 to week 52 in patients treated with vildagliptin plus metformin, suggesting that the addition of vildagliptin prevented the progressive deterioration in glucose control seen in patients treated with metformin/placebo (Figure 1). The percentage of patients achieving the target of $HbA_{1c} < 7\%$ at study end was 41.7% with vildagliptin plus metformin and 10.7% with placebo plus metformin (significant between-group difference) and the percentage of patients achieving a target of $\leq 6.5\%$ was 21.4% with vildagliptin versus none with placebo. Two patients receiving vildagliptin during the core phase (out of 107 patients) experienced one episode of hypoglycemia and there were no hypoglycemic episodes during the extension. The lowering of fasting plasma glucose (FPG) from baseline persisted in patients who took vildagliptin 50 mg qd plus metformin, and was significantly greater than in those taking placebo plus metformin (between group difference of 1.1 mmol/L). Body weight was unchanged with vildagliptin, showing no difference to placebo (+0.04 kg). Fasting triglycerides, as well as total and LDL cholesterol, were modestly improved with vildagliptin compared to placebo. Interestingly, additional analyses showed that the maintenance of efficacy over 52 weeks was associated with a sustained improvement in both insulin secretion and dynamic insulin sensitivity (Ahren et al 2005). Furthermore, vildagliptin significantly improved the efficiency of insulin processing by the β-cells, providing further evidence that vildagliptin treatment ameliorates abnormal β-cell function in patients with T2DM (Ahren et al 2007).

The combination of vildagliptin plus metformin was further evaluated in a 24-week phase 3 study conducted in patients with inadequate glycemic control (HbA_{1c} 7.5%–11%) despite a stable metformin dose (≥ 1500 mg/day, mean daily dose of 2100 mg with a mean duration of metformin use of 17 months) (Bosi et al 2007). Enrollees were randomized to vildagliptin 50 mg daily (given as 50 mg qd, n = 177), vildagliptin 100 mg daily (given as 50 mg bid, n = 185), or placebo (n = 182). The demographic and diabetic background characteristics of the 3 groups were well balanced at baseline, with a mean age of 54 years, a mean BMI of 32.8 kg/m^2, a mean disease duration of 6.2 years and a mean HbA_{1c} of 8.4% (Table 1). Relative to placebo the addition of vildagliptin to metformin resulted in significant and dose-related reductions in HbA_{1c} ($-1.1 \pm 0.1\%$ and $-0.7 \pm 0.1\%$ with vildagliptin 100 mg daily
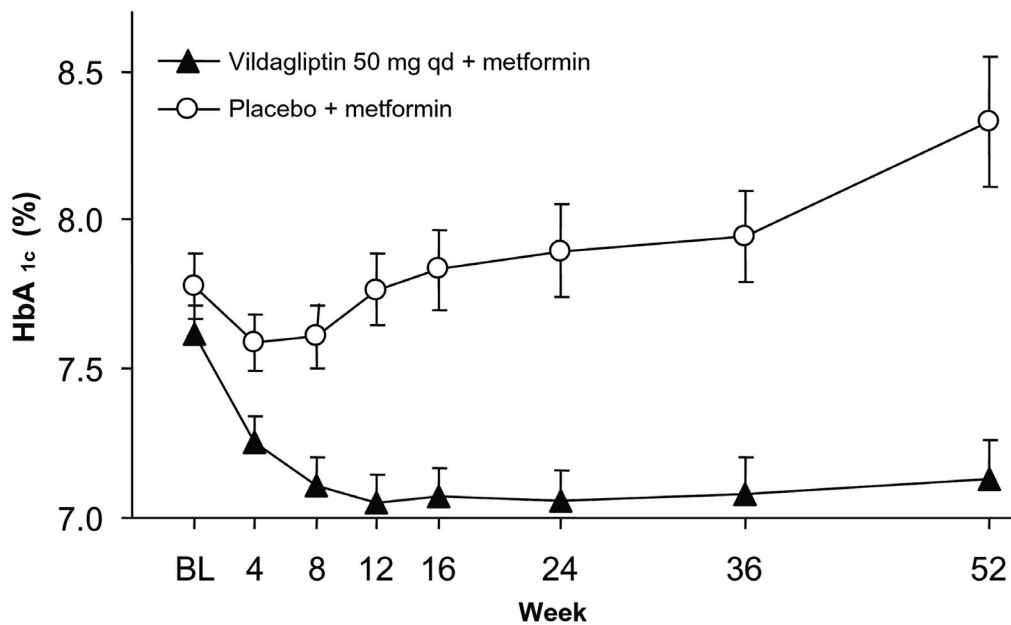
Figure 1 Mean (± SE) HbA$_{1c}$ during 52-week treatment with vildagliptin (50 mg qd, closed triangles, n = 42) and placebo (open circles, n = 29) in metformin-treated patients with T2DM. The between-group difference in HbA1c from baseline to endpoint was −1.1 ± 0.2% (p < 0.0001) (Ahren et al 2004a). Copyright © American Diabetes Association. From Diabetes Care®, Vol. 27, 2004; 2874–80. Modified with permission from The American Diabetes Association.

and 50 mg daily, respectively; p < 0.001 vs placebo for both), and in fasting plasma glucose (−1.7 ± 0.3 mmol/L [p < 0.001 vs placebo] and −0.8 ± 0.3 mmol/L [p = 0.003 vs placebo], respectively). The percentage of patients achieving the target of HbA$_{1c}$ <7% at study end was 35.5% with vildagliptin 100 mg daily plus metformin compared to 9.4% with placebo plus metformin and percentage of patients achieving a target of ≤6.5% was 18.2% with vildagliptin 100 mg daily plus metformin versus 3.1% with placebo plus metformin (both p < 0.001). In addition, treatment with vildagliptin elicited significant reductions from baseline in 2-hour postprandial glucose relative to placebo: −2.3 ± 0.6 mmol/L and −1.9 ± 0.6 mmol/L with vildagliptin 100 mg and 50 mg daily (p = 0.001 vs placebo for both). Again, these effects were associated with significant improvements in measures of β-cell function: the β-cell function index, expressed as insulin secretory rate/glucose (Pratley et al 2007b), increased significantly by 3-fold relative to placebo in both vildagliptin groups (p < 0.001). In patients aged ≥65 years, a pre-planned subgroup analysis showed a mean reduction from baseline in HbA$_{1c}$ of 1.3 ± 0.2% with vildagliptin 100 mg/d compared to a small increase of 0.2 ± 0.1% with placebo.

Vildagliptin did not induce body weight gain (change from baseline of +0.21 and −0.38 kg with vildagliptin 100 and 50 mg daily, respectively, compared to −1.02 kg with placebo). The effect of vildagliptin on fasting lipids was largely neutral, with the exception of fasting triglycerides, which increased

less in the vildagliptin treatment groups than in the placebo group (difference from placebo ranging from 14.5% to 18.4%). Effects of vildagliptin 100 mg daily and placebo on blood pressure (BP) were compared and showed modest improvements in BP in both groups with a significant benefit of vildagliptin versus placebo added to metformin (Bosi et al 2007b).

The incidence of reported adverse events (AEs) was similar among groups (65.0%, 63.3%, and 63.5% of patients receiving vildagliptin 100 mg daily, 50 mg daily, or placebo, respectively). GI side effects were reported less frequently in the vildagliptin treatment groups (14.8% and 9.6% in the 100- and 50-mg daily groups, respectively) than in the placebo group (18.2%). One patient in each of the 3 groups experienced a mild hypoglycemic event, which did not lead to discontinuation. Discontinuations due to AEs were overall marginally more frequent with vildagliptin (4.4% and 4.5% respectively with 100 and 50 mg/d) than placebo (2.2%) (not driven by any specific AE), while serious AEs (SAEs) were marginally more common with placebo (4.4%) than with vildagliptin (2.7% and 2.3% with 100 and 50 mg daily, respectively), and there were no deaths.

An additional active-controlled study (Bolli et al 2008) assessed the combination therapy of vildagliptin and metformin: a 24-week, multicenter, double-blind, randomized study, comparing vildagliptin (100 mg daily, given as equally-divided doses, n = 295) and pioglitazone (30 mg daily, given as a single qd dose, n = 281) in patients with

Table 1 Patients' baseline characteristics: addition of vildagliptin in patients with inadequate glycemic control on maximum tolerated doses of metformin alone

	Study 1[a] Extension population		Study 2[b] Randomized population			Study 3[c] Randomized population	
	Vilda 50 mg qd + Met	PBO + Met	Vilda 50 mg qd + Met	Vilda 50 mg bid + Met	PBO + Met	Vilda 50 mg bid + Met	Pio 30 mg qd + Met
N	42	29	143	143	130	295	281
Age (years) (mean ± SD)	58.4 ± 9.2	54.3 ± 12.2	54.3 ± 9.7	53.9 ± 9.5	54.5 ± 10.3	56.3 ± 9.3	57.0 ± 9.7
Male/Female (%)	62/38	76/24	57/43	62/38	53/47	62/38	64/36
BMI (kg/m^2) (mean ± SD)	29.6 ± 3.7	29.9 ± 3.6	32.1 ± 5.3	32.9 ± 5.0	33.2 ± 6.1	32.2 ± 5.6	32.1 ± 5.1
HbA$_{1c}$ (mean ± SD)	7.6 ± 0.6	7.8 ± 0.6	8.4 ± 0.9	8.4 ± 1.0	8.3 ± 0.9	8.4 ± 1.0	8.4 ± 0.9
FPG (mmol/L) (mean ± SD)	9.6 ± 1.6	10.1 ± 1.8	9.7 ± 2.2	9.9 ± 2.56	10.0 ± 2.35	10.9 ± 2.6	11.0 ± 2.7
Duration of T2DM (years) (mean ± SD)	5.8 ± 4.2	4.6 ± 3.6	6.8 ± 5.5	5.8 ± 4.7	6.2 ± 5.3	6.4 ± 4.9	6.4 ± 5.2

[a]Study 1: A 52-week study of vildagliptin 50 mg daily added to metformin (Ahren et al 2004a).
[b]Study 2: A 24-week study of vildagliptin (50 mg daily or 100 mg daily) or placebo added to metformin (Bosi et al 2007a).
[c]Study 3: A 24-week study of vildagliptin (100 mg daily) or pioglitazone (30 mg daily) added to metformin (Bolli et al 2008).
Abbreviations: Vilda, vildagliptin; Met, metformin; PBO, placebo; Pio, pioglitazone.
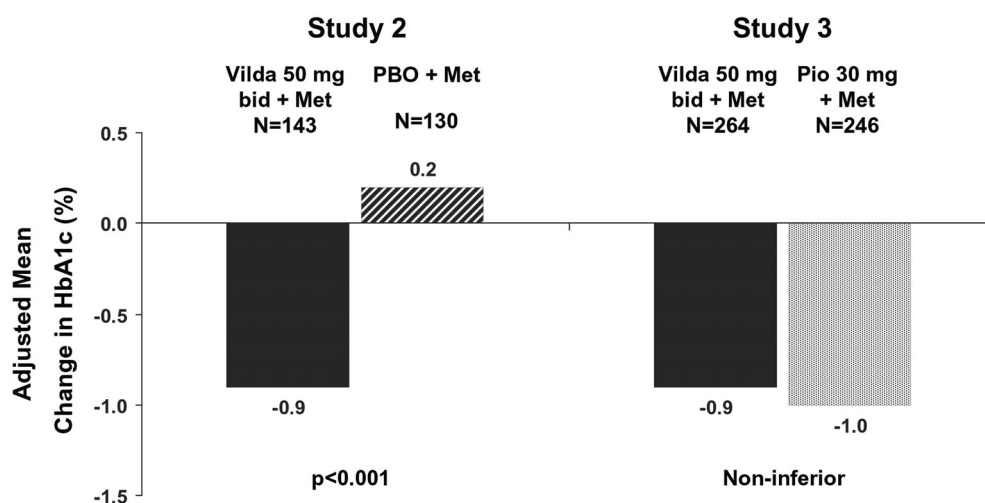
inadequate glycemic control (HbA$_{1c}$ 7.5%–11%) despite metformin monotherapy (used for an average of 43 months) at a stable dose (mean dose at baseline >2000 mg/day).

The groups were well balanced at baseline, with a mean age, BMI, HbA$_{1c}$, and FPG of ~57 years, 32.1 kg/m^2, 8.4%, and 10.9 mmol/L, respectively. Patients were predominantly Caucasian, with mean disease duration of 6.4 years. When added to a stable dose of metformin, both vildagliptin 100 mg and pioglitazone 30 mg daily were equally effective in decreasing HbA$_{1c}$ (by 0.9 ± 0.1% and 1.0 ± 0.1%, respectively) from identical baseline values (8.4 ± 0.1%) with statistical non-inferiority of vildagliptin to pioglitazone being established (Figure 2). The decrease in A1C in the pre-defined subgroup of patients with baseline A1C >9.0% was more substantial, as expected, and similar in vildagliptin-treated patients (baseline = 9.8%; mean change = −1.5 ± 0.2%) and in those receiving pioglitazone (baseline = 9.7%; mean change = −1.5 ± 0.2%). The percentage of patients who achieved the endpoint of HbA$_{1c}$ ≤6.5% was comparable in those receiving vildagliptin (19.7%) and pioglitazone (17.9%). Pioglitazone decreased FPG (−2.1 ± 0.1 mmol/L) to a greater extent than vildagliptin (1.4 ± 0.1 mmol/L), but only pioglitazone increased body weight (+1.9 ± 0.2 kg: between-group difference = −1.6 ± 0.3 kg, p < 0.001) (Figure 3). In the more obese patients (with BMI >35 kg/m^2), the mean change in body weight from baseline to endpoint was +0.1 ± 0.5 kg in patients receiving vildagliptin (baseline = 110.6 kg, n = 73), and +2.6 ± 0.5 kg in pioglitazone-treated patients (baseline = 110.3 kg, n = 70; between-treatment difference −2.5 ± 0.7 kg [p < 0.001]). On

the other hand, the efficacy tended to be more pronounced with pioglitazone in the obese patients (mean baseline BMI of 36 kg/m^2) with a mean change in HbA$_{1c}$ of −1.2% ± 0.1% versus −0.8% ± 0.1% with vildagliptin, while the reverse was true in non obese patients (mean baseline BMI 27 kg/m^2) in whom the decrease in HbA$_{1c}$ was somewhat greater in those receiving vildagliptin (1.0% ± 0.1%) than pioglitazone (0.7% ± 0.1%).

Fasting lipid levels were similar in the two treatment groups at baseline. Total-cholesterol, LDL-cholesterol and non-HDL cholesterol decreased in patients receiving vildagliptin and increased in pioglitazone-treated patients (with between-group differences of −6.9% ± 1.3% for total cholesterol, −10.2% ± 2.4% for LDL cholesterol, and −4.9% ± 1.9% for non-HDL cholesterol, all p < 0.001). Conversely, fasting triglycerides decreased more (between-treatment difference of 9.3% ± 3.2%, p = 0.004) and HDL-cholesterol increased more (between-treatment difference of −13.8% ± 1.6%, p < 0.001) in pioglitazone-treated patients. AEs were reported by 60% of patients receiving vildagliptin and by 56.4% of pioglitazone-treated patients; SAEs were reported by 2.0% and 4.6% of patients receiving vildagliptin and pioglitazone, respectively. Mild hypoglycemia was reported by 1 patient in the vildagliptin group (0.3%) and by no patient receiving pioglitazone (Bolli et al 2008).

In summary, the 3 double-blind, controlled studies evaluating combination therapy with vildagliptin and metformin showed statistically significant and clinically meaningful reductions in HbA$_{1c}$ when vildagliptin was added to metformin of ~1% (Figure 2), that were evident across all demographic and disease subgroups. In patients with T2DM

Study 2

Vilda 50 mg bid + Met
N=143

PBO + Met
N=130

Study 3

Vilda 50 mg bid + Met
N=264

Pio 30 mg + Met
N=246

Figure 2 Study 2 – Adjusted mean change from baseline to endpoint in HbA$_{1c}$ after 24 weeks of treatment with vildagliptin (50 mg bid) or placebo in metformin-treated patients with T2DM (p < 0.001) (Bosi et al 2007a).
Study 3 – Adjusted mean change from baseline to endpoint in HbA$_{1c}$ after 24 weeks of treatment with vildagliptin (50 mg bid) or pioglitazone (30 mg qd) in metformin-treated patients with T2DM; the between group difference was 0.10 ± 0.08% (95 CI: −0.05, −0.26) (Bolli et al 2008).

inadequately controlled with metformin, the addition of vildagliptin (100 mg daily) was equally effective as that of pioglitazone (30 mg daily). Efficacy was well preserved over 52 weeks in the placebo-controlled extension. Fasting and post prandial plasma glucose were significantly reduced; and the beneficial effects on glucose control was clearly accompanied by consistent improvements of parameters for β-cell function. The effects on fasting lipids were neutral and, in contrast to the pioglitazone/metformin combination (especially in the more obese patients) there was no weight gain. Overall the tolerability profile was good, with in particular no exacerbation of GI tolerability and there was no increased risk of hypoglycemia with vildagliptin and metformin combination therapy.

Vildagliptin as a fixed combination product with metformin – opportunities for improvement of adherence

While early and aggressive treatment with multiple drug combinations becomes increasingly common in the management of T2DM, adding more medications may however translate into reduced adherence to treatment. Subsequently, efforts have been made to simplify the treatment regimen with fixed-combination tablets to help improving treatment adherence in patients with T2DM who frequently take multiple medication. For this reason, vildagliptin and metformin have recently been made available in a single tablet (Eucreas®).

This new galenical formulation combines fixed doses of vildagliptin and metformin in 2 dosage strengths of 50/850

and 50/1000 mg of vildagliptin and metformin, and was developed based on 4 additional pharmacokinetic (PK) studies: 3 cross-over design PK studies in healthy subjects, to assess if the fixed combination tablet was bioequivalent to the free combination of the active components, and 1 cross-over design PK study to assess the effect of food on the absorption of the fixed combination tablet.

These PK studies demonstrated that the fixed combination tablets are bioequivalent to the co-administered vildagliptin and metformin as free combinations. The efficacy and safety of the new combination tablet can thus be based on the data already available in T2DM patients insufficiently controlled with metformin monotherapy.

What is known with compliance to OADs

Poor adherence to a treatment regimen is common (Osterberg and Blaschke 2005). At least 50% of patients do not fully benefit from their treatment due to inadequate compliance. This contributes to explain the gap between the implementation of clinical guidelines and the expected benefits. Poor compliance is a particular problem in asymptomatic and chronic diseases such as T2DM (Cramer 2004) contributing to substantial increases in morbidity and cost, with a higher risk of hospitalizations (Balkrishnan et al 2003; Lau and Nau 2004). In T2DM, poor medication adherence is associated with inadequate glycemic control (Schectman et al 2002; Pladevall et al 2004): even after adjusting for demographic and clinical characteristics, a 10% decrease in adherence to
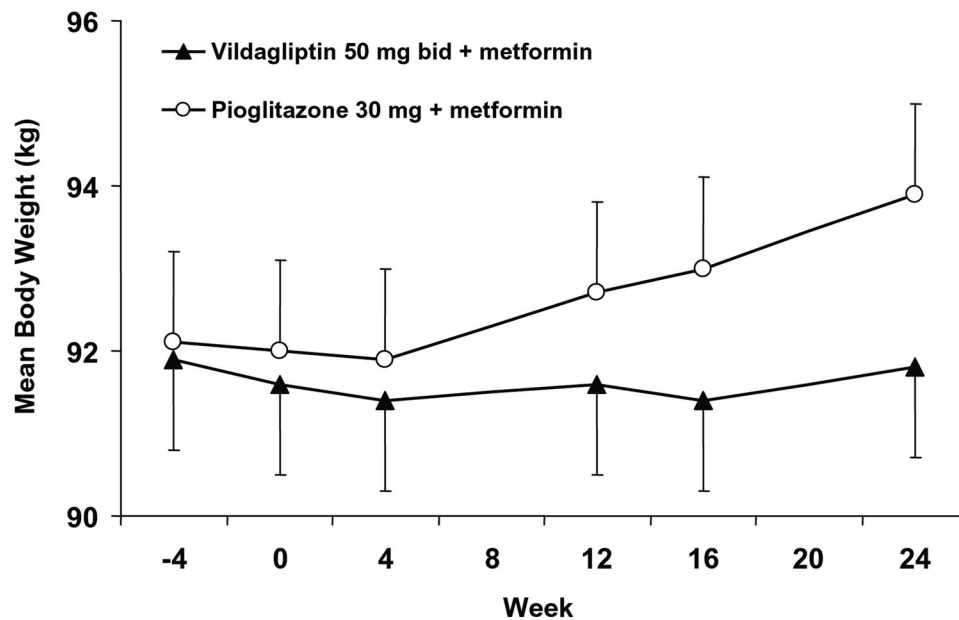
Figure 3 Study 3 – Time-course of mean body weight during 24-week treatment with vildagliptin (50 mg bid, closed triangles, n = 264) or pioglitazone (30 mg qd, open circles, n = 246) in T2DM patients continuing their previous stable metformin dose regimen (Derived from data of Bolli et al 2008).

metformin was significantly associated with an increase of 0.14% in HbA1c (Pladevall et al 2004).

Among all the factors potentially related to adherence (including demographic, psychological, social, health care provider and medical system factors), polypharmacy and the complexity of a regimen (with the number of dose-administrations) are known to be 2 important determinants of poor compliance (Paes et al 1997; Balkrishnan et al 2003). Diabetic patients are frequently polymedicated, especially older patients with multiple co morbidities (Pratley et al 2007a). They most often need medications for cardioprotection, hypertension and hyperlipidemia in addition to diabetes. While the question whether this polypharmacy adversely affects adherence among diabetic patients is still under some debate (Grant et al 2003), most studies have shown that reducing the pill burden resulted in improved compliance (Dezii et al 2002; Melikian et al 2002; Kardas 2005; Bangalore et al 2007). In particular, a large prospective study that evaluated compliance based on self reported standard questionnaire has suggested the relevance of reducing the daily dosing frequency of oral antidiabetic agents, in order to improve compliance and metabolic control (Guillausseau 2003).

Therefore, one practical way of enhancing adherence is to make the treatment regimen simpler with fixed-combination products. Given the importance of medication adherence for health outcomes of diabetes care (Pladevall et al 2004), it is surprising that only few studies have looked at the effects on adherence of fixed combination drugs versus individual drugs. One recent meta-analysis (which included 2 studies in the diabetic population) showed that fixed-dose combination reduce the risk of non-compliance by 26% compared to free-drug combination regimens (pooled relative risk [RR] 0.74; 95% confidence interval [CI], 0.69–0.80; $p < 0.0001$) (Bangalore et al 2007).

Thus, fixed-dose combination tablets may play an important role in T2DM to help improving medication compliance and the effectiveness of therapy, which should ultimately translate into better clinical outcomes.

Conclusions and place in therapy

The combination of vildagliptin and metformin, two oral antidiabetic agents with complementary mechanisms of action, provides superior efficacy and allows more patients to reach their glycemic targets compared to continuing metformin monotherapy, without increasing the risk of hypoglycemia, without exposing to weight gain and without altering common cardiovascular risk factors (hypertension and lipid profile). In addition, this combination has demonstrated favorable effects on pancreatic α- and β-cells. Whether the effect on parameters of β-cell function will translate in long term ß-cell preservation, which may modify the course of the disease, remains to be shown by long-term clinical studies. The availability of vildagliptin and metformin in a single tablet (Eucreas®) further enhances convenience and likely adherence to treatment.

As the glycemic targets recommended by guidelines are further lowered, many patients may remain inadequately

treated because of the various limitations of the current therapies, such as the increased risk of hypoglycemia with sulfonylureas or the weight gain with TZDs.

Given its characteristics, Eucreas® will be a particularly appealing treatment option for moderately hyperglycemic patients who are relatively close to target (ie, HbA1c between 6.5 to 7.5% despite metformin) but for whom glucose control is not further tightened in order to avoid hypoglycemia or to limit weight gain. This new fixed-combination of vildagliptin and metformin could thus take a promising place in therapy and become the preferred combination with metformin in these mildly hyperglycemic patients and in older and more fragile individuals.

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