Australian Government
Department of Health and Ageing
Therapeutic Goods Administration

Australian Public Assessment Report for Vildagliptin

Proprietary Product Name: Galvus, Xiliarx

Sponsor: Novartis Pharmaceuticals Australia Pty Ltd

April 2010

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The TGA is a division of the Australian Government Department of Health and Ageing, and is responsible for regulating medicines and medical devices.
- TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance), when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website.

About AusPARs

- An Australian Public Assessment Record (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission.
- AusPARs are prepared and published by the TGA.
- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations, and extensions of indications.
- An AusPAR is a static document, in that it will provide information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

Contents

I. Introduction to Product Submission

Product Details

Type of Submission	New Chemical Entity
Decision:	Approved
Date of Decision	23 February 2010
Active ingredient(s):	Vildagliptin
Product Name(s):	Galvus, Xiliarx
Sponsor's Name and Address	Novartis Pharmaceuticals Australia Pty Ltd 54 Waterloo Road North Ryde NSW 2113
Dose form(s):	Tablet
Strength(s):	50 mg
Container(s):	Blister pack
Pack size(s):	7, 14, 28, 56 or 122 tablets
Approved Therapeutic use:	Treatment of diabetes mellitus type 2 in persons 18 years of age and older, as an adjunct to diet and exercise to improve glycaemic control in patients with type 2 diabetes with one of metformin, a sulfonylurea or pioglitazone when diet, exercise and the single agent do not result in adequate glycaemic control.
Route(s) of administration:	Oral
Dosage:	50 mg once or twice daily

Product Background

The pathophysiology of Type 2 diabetes mellitus (T2DM) is characterised by deficient insulin activity arising from decreased insulin secretion secondary to beta cell failure, and/or compromised insulin action in peripheral target tissues (insulin resistance). This abnormal metabolic state is exacerbated by excess hepatic glucose production and altered metabolism of proteins and lipids, which along with hyperglycaemia, contribute to microvascular and macrovascular complications.

T2DM accounts for approximately 85% to 95% of diabetes cases in developed regions like the European Union. Age and weight are established risk factors for T2DM. The majority of patients with T2DM are overweight or obese. Diet modification and exercise is the first line of treatment for T2DM. Pharmacologic intervention with one oral antidiabetic drug (OAD) is usually the next step in treatment. After 3 to 9 years of OAD monotherapy, patients typically require an additional intervention. The recommended first line treatment is metformin, which restrains hepatic glucose production and decreases peripheral insulin resistance. Sulphonylureas, which are insulin secretagogues, may be used as an alternative to patients intolerant to metformin, or as an addition to metformin. Other second line oral treatment alternatives include alpha-glucosidase inhibitors, meglitinides and thiazolidinediones. Although being efficient in attenuating hyperglycaemia, all of these treatment alternatives

have more or less serious side effects and there is a need for development of efficient drugs without metabolic or other side effects.

Vildagliptin is one of a relatively new class of antidiabetic agents with potential for use in the treatment of diabetes mellitus type 2. Vildagliptin is a new chemical entity. It is an oral antidiabetic agent from a new class of drugs which is claimed to selectively and reversibly inhibit an enzyme, dipeptidyl peptidase-4 (DPP-4) involved in glucose homeostasis. Vildagliptin inhibits DPP– 4 and thereby delays the degradation of glucagon like peptide–1 (GLP–1) and glucose-independent insulinotropic polypeptide (GIP) that are released particularly in response to the ingestion of food. This could improve the insulin response to a meal, inhibit glucagon release and gluconeogenesis but not in the fasted state. Numerous other agents of this class are in development. Their selectivity might affect their potential for tolerability. At present, sitagliptin is the only member of the class that is registered in Australia – also registered is a fixed combination tablet containing metformin.

Exenatide (Byetta), a GLP–1 analogue, is registered in Australia and that agent is administered subcutaneously, delivering pharmacological doses of a GLP–1 analogue. Vildagliptin and sitagliptin might therefore be expected to be clinically unlike exenatide. DPP–IV inhibitors and exenatide have the potential benefit of not increasing body weight.

In the current application which was a re-submission, Novartis Pharmaceuticals Australia Pty Ltd has applied to register vildagliptin (with the two trade names Galvus and Xiliarx) to be used in combination with metformin, a sulfonylurea, a thiazolidinedione or insulin when diet, exercise and the single antidiabetic agent do not result in adequate glycaemic control in patients with type 2 diabetes mellitus. The recommended dose is 50 mg orally once or twice daily.

Regulatory Status

A similar application to the current Australian submission has been approved in the European Union on 26 September 2007. The approved indication is as follows:

for the treatment of type 2 diabetes mellitus, as dual oral therapy in combination with:

- *metformin, in patients with insufficient glycaemic control despite maximal tolerated dose of monotherapy with metformin*
- *a sulphonylurea, in patients with insufficient glycaemic control despite maximal tolerated dose of a sulphonylurea and for whom metformin is inappropriate due to contraindications or intolerance*
- *a thiazolidinedione, in patients with insufficient glycaemic control and for whom the use of a thiazolidinedione is appropriate.*

An application has also been approved in New Zealand (November 2008) and Switzerland (30 April 2008) with the same indication as follows:

An adjunct to diet and exercise to improve glycaemic control in patients with type 2 diabetes mellitus.

- *as monotherapy*
- *in dual combination with metformin, a sulphonylurea (SU), a thiazolidinedione (TZD) or insulin when diet, exercise and a single antidiabetic agent do not result in adequate glycaemic control.*

Product Information

The approved product information current at the time this AusPAR was prepared is at Attachment 1.

II. Quality Findings

Quality Summary and Conclusions

Quality data were not required for a re-submission of this type.

III. Nonclinical Findings

Introduction

Novartis Pharmaceuticals Australia Pty Ltd has re-submitted a Category 1 application for the new chemical entity, vildagliptin (Galvus and Xiliarx). The product is proposed to be used as combination therapy with metformin, a sulfonylurea, a thiazolidinedione or insulin, to improve glycaemic control in patients with type 2 diabetes mellitus, when diet, exercise and the single antidiabetic agent do not result in adequate glycaemic control. In contrast to the previous submission, Novartis is not seeking a monotherapy indication at this time. The dosing regimen has also changed from a maximum of 100 mg once daily to 50 mg twice daily. Nonclinical data in the current submission for vildagliptin contained mechanistic studies on skin lesion formation in monkeys treated with vildagliptin. This report integrates evaluations of new and previously submitted data. Previously calculated exposure ratios have been updated to reflect changes in the clinical maximal plasma concentration (C_{max}) and area under the plasma concentration time curve (AUC) associated with the revised dosing regimen.

Background

The closely related peptides glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic peptide (GIP) are termed incretins — gastrointestinal hormones that potentiate glucose-induced insulin secretion (Meier & Nauck, 2005). Both GLP-1 and GIP undergo inactivation by the enzyme dipeptidyl peptidase-4 (DPP-4) which cleaves the amino-terminal dipeptides from the hormones (Kieffer *et al.*, 1995). Inhibition of DPP-4, resulting in increased GLP-1 and GIP activity, represents a new approach to the therapy of type 2 diabetes mellitus.

DPP-4 has a wide variety of other functions, some unrelated to its peptidase activity, and the potential consequences of inhibiting these functions may be adverse (Hildebrandt *et al.*, 2000; Boonacker & Van Noorden, 2003). However, Fischer rats that lack DPP-4 exhibited only minor physiological defects suggesting that other proteins are able to perform similar functions (Tiruppathi *et al.*, 1993). In humans, DPP-4 is expressed on T, B and NK cells, epithelial and endothelial cells of liver, intestine, kidney, and as a circulating soluble form. With regard to peptidase activity, more than 30 possible substrates of DPP-4 have been reported in the literature, including some involved in inflammatory and neurological processes (Boonacker & Van Noorden, 2003). Apart from its peptidase activity, DPP-4 interacts with several proteins including adenosine deaminase, HIV gp120, fibronectin, collagen, the chemokine receptor CXCR4, and the tyrosine phosphatase CD45. DPP-4 is expressed on a specific set of T lymphocytes, where it is up-regulated after activation. The role of DPP-4 within the immune system is a combination of its peptidase activity and its interactions with different molecules. DPP-4 acts as a co-stimulatory molecule influencing T cell activity and chemotaxis.

Pharmacology

Primary Pharmacodynamics

In vitro

Vildagliptin was shown to inhibit DPP-4 derived from human, cynomolgus monkey and rat with similar potency (median inhibitory concentration [IC_{50}] 2–20 nM and K_i values 2–19 nM). The kinetics of DPP-4 inhibition by vildagliptin were characterised by a fast *on* rate and a slow *off* rate resulting in enzyme-inhibitor complex half-lives of approximately 40–130 minutes. Several metabolites of vildagliptin were examined for DPP-4 inhibition. The carboxylic acid (M20.7) and N-amide hydrolysis (M15.3) metabolites of vildagliptin, comprising around 64% of the drug related material in human plasma, had negligible effects on DPP-4 activity, suggesting they would not play a role in therapeutic efficacy. The major metabolite of vildagliptin in the plasma of monkeys, the glucuronide M20.2, was equipotent with vildagliptin against human and monkey DPP-4, and with a similar half-life of dissociation. *In vivo*, the M20.2 metabolite would be expected to contribute to the pharmacological action of DPP-4 inhibition. This contribution would be significant in the case of monkeys, where the exposure to M20.2 would be expected to be about 360% that of vildagliptin. In humans, the contribution of M20.2 to DPP-4 inhibition would be moderate (about 37% the vildagliptin exposure).

In vivo

In vivo primary pharmacodynamics studies were conducted in mice, rats, and monkeys by the oral route. Vildagliptin inhibited plasma DPP-4 activity resulting in increased GLP-1 and insulin levels and corresponding decreases in plasma glucose following glucose challenge. Vildagliptin reduced glycated haemoglobin A1c (HbA1c) levels in diabetic monkeys, which indicated the potential for sustained glucose-lowering efficacy. Dose levels in rats resulting in maximal pharmacological activity corresponded to exposures similar to those expected in humans receiving the maximum proposed dose. From the submitted data it was difficult to determine if reduced efficacy occurred with repeated dosing due to large variability in week to week DPP-4 inhibition data.

Inhibition of plasma DPP-4 activity was demonstrated in rats and monkeys with high levels of inhibition sustained for several hours post-dose in both species. In rats, single doses of vildagliptin resulted in dose-dependent DPP-4 inhibition with ED_{50} values of ~0.1–0.3 mg/kg. In monkeys, a single dose of 0.3 mg/kg inhibited DPP-4 activity by >85%. Inhibition of DPP-4 was associated with increased plasma levels of GLP-1, with the effect markedly more pronounced in rats compared to monkeys. In rats, levels of GLP-1 in treated animals were approximately 5- to 15-times the levels in control animals. The ED_{50} for inhibition in obese rats was 0.14 mg/kg/day. In monkeys, plasma GLP-1 levels were approximately 40% higher for vildagliptin-treated animals (0.3 mg/kg, single dose) compared to controls.

In glucose tolerance tests in rats, insulin levels were increased in response to vildagliptin-induced DPP-4 inhibition and subsequent increases in GLP-1 levels. In obese rats receiving a single dose of vildagliptin (3 mg/kg), insulin AUC values were approximately 3- to 4-fold those of controls following a glucose challenge. Daily doses of vildagliptin (3 mg/kg/day) had no effect on fasted plasma insulin levels but increased glucose-stimulated insulin release by approximately 90%. In several studies in normal and obese monkeys, insulin levels were unaffected by vildagliptin treatment with or without glucose challenge, while in one monkey study, fasting insulin levels were reduced by 47% after daily treatment with vildagliptin (0.3 mg/kg/day) for 10 weeks.

Vildagliptin treatment was associated with reductions in plasma/blood glucose levels during glucose tolerance tests. There was generally no effect on fasting glucose levels and hypoglycaemia was not associated with vildagliptin treatment. In obese rats, 30–45% reductions in glucose AUC were observed following single or daily doses of 3 mg/kg. In obese monkeys receiving vildagliptin (0.3 mg/kg), moderate reductions (15–20%) in plasma glucose levels were observed at 45, 60, and 90 minutes after glucose challenge, however glucose AUC did not differ significantly from controls.

Vildagliptin reduced levels of HbA1c, a marker of long-term blood glucose levels, in diabetic and non-diabetic insulin-resistant monkeys. HbA1c levels were significantly reduced in both groups after 10 weeks vildagliptin treatment (0.3 mg/kg/day) with a larger reduction in the diabetic group (-1.2 percentage points) compared to the non-diabetic group (-0.6 percentage points). No further reduction in HbA1c was observed following an additional 4 weeks treatment with a 10-fold higher dose of 3 mg/kg/day.

In a mouse model of pancreatic β-cell injury, vildagliptin (30 mg/kg/day for 20 days) showed evidence of enhancing the differentiation of pancreatic progenitor cells. Increased differentiation was consistent with an observed increase (60%) in the number of duct-associated insulin-positive islets at day 16, demonstrating enhanced islet neogenesis. In young normal (lean) rats, two doses of vildagliptin (60 mg/kg) produced a 2-fold increase in pancreatic beta cell mass and a 30% increase in pancreatic insulin content.

Combination efficacy

Vildagliptin is indicated as combination therapy with metformin, a sulfonylurea, a thiazolidinedione or insulin and clinical studies have been conducted with all of these combinations. A repeat-dose (10 days) combination study in obese rats with vildagliptin (3 mg/kg/day) and the thiazolidinedione, pioglitazone (20 mg/kg/day orally), gave a synergistic effect on glucose lowering. There were no nonclinical efficacy studies to support combination therapy with metformin, a sulfonylurea or insulin. It was noted that an application for the fixed combination vildagliptin/metformin has been submitted to the TGA (evaluation ongoing), and efficacy data may be contained in this new submission. In another study in obese rats, vildagliptin (3 mg/kg, single dose) in combination with nateglinide (a meglitinide; 60 mg/kg oral, single dose) resulted in an additive effect on glucose lowering.

In conclusion, the primary pharmacodynamic data showed evidence of efficacy *in vitro,* based on DPP-4 inhibition, and *in vivo,* based on a number of endpoints related to type 2 diabetes. While there was some indication of synergistic effects of vildagliptin and a thiazolidinedione, the assessment of efficacy of other proposed combination therapies will need to rely solely on clinical data.

Secondary Pharmacodynamics

Vildagliptin exhibited no appreciable inhibition of a number of unrelated peptidases/proteases and no significant binding in an assay of more than 80 receptors (at 10 µM). However, inhibitory activity was observed against two related DPP subtypes, DPP-8 and DPP-9, in both humans and monkeys. This inhibition was less than that observed for DPP-4, with a selectivity of 253 and 33 for DPP-4 over DPP-8 and DPP-9, respectively, in humans (K_i values, 65–810 nM). The selectivity of vildagliptin for DPP-4 over DPP-8 and -9 in monkeys was a little lower than in humans (154- and 14-fold selective, respectively). Vildagliptin had a much more rapid dissociation from DPP-8 and DPP-9 ($t_{½}$, <10 s) than DPP-4 ($t_{½}$, 55 minutes) suggesting a greater functional selectivity for DPP-4 than shown by the K_i values alone. Inhibition of other DPP subtypes, DPP-2 and FAPα, was minimal to weak (K_i, >9.9 µM).

The carboxylic acid (M20.7; LAY151) and N-amide hydrolysis (M15.3; LBQ770) metabolites of vildagliptin had negligible effects on the activities of tested DPP-4-related and unrelated peptidases. The glucuronide metabolite, M20.2 (BQS867), however, inhibited DPP-8 and DPP-9 with similar potency to vildagliptin. Based on a clinical C_{max} of 808 nM[1] for vildagliptin and assuming an extra 30% from M20.2, inhibition of DPP-8 and, in particular, DPP-9 may occur in patients. Inhibition of DPP-8/9 has been associated with skin and other toxicities in laboratory animal species (Lankas *et al.*, 2005).

Safety Pharmacology

The submitted safety pharmacology studies investigated central nervous system (CNS) and cardiovascular function. All *in vivo* studies used the oral route. There were no dedicated studies on gastrointestinal (GI) and renal function. There were no treatment-related effects of vildagliptin on respiratory function in dog telemetry studies or in repeat-dose toxicity studies and there were no overt effects on renal function in toxicity studies. However, the GI tract was found to be the main target organ of toxicity in the dog repeat-dose toxicity studies (see *Repeat-dose toxicity* for further details).

A CNS study in mice evaluated the neurobehavioural effects of a single high dose of vildagliptin. Mortality, clinical signs, behaviour, body temperature, and gross pathology were unaffected at 2000 mg/kg (estimated relative exposure based on C_{max} [ER_{Cmax}], 960; based on linear extrapolation of data. This is consistent with results obtained from distribution studies in rats where vildagliptin and/or metabolites did not cross the blood/brain barrier. However, in repeat-dose toxicity studies in dogs and monkeys, CNS clinical signs were associated with vildagliptin administration. Decreased locomotor activity (sometimes severe), ataxia, impaired righting reflex, and muscle tremors were observed in dogs at relative exposures ≥23, and decreased locomotor activity was observed in some of the monkey studies (but generally only at doses exceeding the maximum tolerated dose (MTD)). Neuropeptide Y (NPY) is a substrate of DPP-4 and has effects on vasomotor activity (Karl *et al.*, 2003a, 2003b). Reduction in DPP-4 activity may affect the circulating levels of active NPY with subsequent effects on neurobehaviour. As these effects were observed at such high exposures, they are unlikely to be of clinical concern at the proposed maximum dose.

A large number of cardiovascular studies were submitted and included both *in vitro* and *in vivo* studies with the majority of the studies conducted under GLP conditions. The non-GLP studies were of appropriate design and well-conducted. *In vitro* inhibition of hERG channels by vildagliptin or two of its major circulating human metabolites (M15.3 and M20.7) only occurred at very high concentrations (mM) that were not clinically relevant. Consistent with these results was the lack of action potential prolongation in rabbit Purkinje fibres or whole heart preparations.

Sodium channel inhibition and conduction abnormalities

Vildagliptin inhibited voltage-gated sodium currents in SCN5A channels *in vitro* with an IC_{50} of 366 µM, which is about 450-fold higher than the human C_{max} (808 nM) at the maximum daily dose of 50 mg bd (twice daily). Sodium channel inhibition by vildagliptin is consistent with the decrease in V_{max} and action potential duration seen in rabbit Purkinje fibres at >1 mM, and disturbances in ventricular conduction observed in the dog telemetry studies.

In a rising-dose study the death of one dog at the highest dose (75 mg/kg oral), at a time similar to the time to maximal plasma concentration (t_{max}) is of particular concern. The sudden manner of death was consistent with the pattern of mortality seen in the 26- and 52-

[1] Derived using a C_{max} value of 245 ng/mL, as reported in Clinical Study 2335 (50 mg PO dose), and using a molecular mass of 303.4.

week repeat-dose toxicity studies in dogs. Electrocardiographic (ECG) analysis attributed mortality to treatment-related disturbances in ventricular conduction, which led to ventricular tachycardia and ventricular fibrillation. Alterations in ECG parameters were also noted at the next dose down (40 mg/kg) and included sinus tachycardia, wide QRS complexes, widening S wave, ST segment elevation, and tall T waves. The results observed in this study suggest a potential risk of decrease in ventricular conduction velocity (that is. a QRS complex widening on the ECG). The No Observable Adverse Effect Level (NOAEL) dose for conduction abnormalities was 15 mg/kg, corresponding to a relative exposure (based on C_{max} at the maximum recommended human dose [MRHD]) of about 21. The Lowest Observable Effect Level (LOEL) in study 0270042 was 40 mg/kg orally, corresponding to a relative exposure of about 56 based on C_{max}. No ECG abnormalities were observed in an additional dog safety pharmacology study (dosing up to 35 mg/kg bd) nor in repeat-dose toxicity studies in dogs (≤50 mg/kg/day orally) or in 3 of 4 cynomolgus monkeys at doses up to 240 mg/kg orally, corresponding to relative exposure levels (based on C_{max}) of about 340. Decreased QT_c intervals were observed in one monkey at 160 mg/kg orally, but the ECG findings in this animal were believed to be secondary to haemodynamic changes. As adverse cardiac events occurred in only a single species and at relatively high exposures, the risk of adverse cardiac conduction events in humans would appear to be low at clinically relevant doses.

Heart rate and blood pressure

Tachycardia was noted in one study in dogs at 35 mg/kg (ER_{Cmax}, 49) while transient increases in heart rate and blood pressure were recorded at doses of ≥10 mg/kg/day in monkeys ($ER_{Cmax,}$ ≥7). The DPP-4 substrates, GLP-1 and NPY, are known to have vasodilatory and vasoconstrictive effects (Jax, 2009; Nilsson, 2000). Inhibition of DPP-4 may perturb the system thereby affecting heart rate and blood pressure. While the effects of vildagliptin occurred at moderate exposure ratios, it is unclear what this may mean clinically in diabetes mellitus type 2 patients that may have a concomitant cardiomyopathy.

Pharmacokinetics

Absorption, distribution, metabolism and excretion

Pharmacokinetic studies of vildagliptin were conducted in mice, rats, rabbits, dogs, and cynomolgus monkeys. There were no significant gender differences in any pharmacokinetic parameters. After intravenous (IV) administration, vildagliptin exhibited a moderate to high volume of distribution and was rapidly cleared. Absorption after oral administration was rapid in all animal species and in humans. Oral bioavailability was moderate in rats and rabbits and high in other species. Toxicokinetic studies showed that exposure to vildagliptin (AUC) increased with dose in a manner that was sometimes greater than dose-proportional at high dose levels indicating saturation of metabolism at these doses.

Table 1: Single dose pharmacokinetic parameters for vildagliptin

Species	IV route			Oral route	
	CL (L/h/kg)	V_{ss} (L/kg)	$t_{½}$ (h)	t_{max} (h)	F (%)

Mouse	3.5	2.3	0.26 (α), 1.5 (β)	0.5	94
Rat	2.4–2.9	3.7–8.6	0.57 (α), 8.8 (β)	0.25–0.5	45–59
Rabbit	1.6	2.0	0.71 (α), 6.8 (β)	0.9	67
Dog	1.3	1.6	0.89 (terminal)	1.5	100
Monkey	1.4	2.6	0.84 (α), 4.9 (β)	1.6	93
Human	0.6	1.0	1.7 (terminal)	1.1	85

Serum/plasma protein binding was low and independent of concentration in all species tested (8% in rats, 3% in dogs, 9% in humans). The carboxylic acid metabolite of vildagliptin (M20.7) showed no detectable plasma protein binding. Vildagliptin was evenly distributed between plasma and blood cells in all species and over all concentrations. In human samples, the extent of serum binding was very similar to that observed for plasma binding, indicating no anticoagulant effect.

^{14}C-Vildagliptin was extensively and rapidly distributed after IV and oral administration to rats. The highest tissue and fluid concentrations were found in kidney and urine, respectively, consistent with urinary excretion as the major elimination route. For the IV route, low amounts of radioactivity were detected in the brain and testes only at the first time point (5 minutes), indicating minimal passage across the blood:brain and blood:testis barriers. By 96 hours post-dose (IV), levels had declined to below the limit of quantification in all tissues except skin and uveal tract, suggesting that the compound and/or its metabolites bind to melanin. For the oral route, no radioactivity was detected in the brain at any time point while very low concentrations were observed in the testes at only one time point (4 hours). No radioactivity was detected in any tissue, fluid, or organ at≥48 hours following or al dosing, indicating no sequestration or accumulation.

Metabolites of vildagliptin were characterised in the plasma and excreta of mice, rats, rabbits, dogs, and monkeys after both IV and oral administration, and in humans (oral only). The circulating metabolites reported in humans are a carboxylic acid formed by hydrolysis (M20.7), an N-glucuronide (M20.2), and an N-amide hydrolysis product (M15.3). Percentages of these metabolites in the plasma of animals and humans are shown in Table 2. Relative to humans, higher percentages of M15.3 were observed in the plasma of rabbits and dogs, while higher percentages of the pharmacologically-active, M20.2, were observed in the plasma of rats and monkeys. For monkeys in particular, this metabolite comprised 72% of the drug-related material in the plasma with exposures 360% that of the parent compound. As this compound also inhibits DPP-4, exposure ratios based solely on vildagliptin AUC data (ER_{AUC}) for studies in monkeys are likely to be at least 3-fold under-estimates for toxicological effects associated with pharmacological action. To remain conservative, ER_{AUC} based on vildagliptin only were used.

Lower percentages of M20.7 were observed in animals compared with humans; however, this metabolite was not apparently active and had low inhibitory or binding effects against a wide panel of enzymes and substrates and therefore this is unlikely to be of toxicological concern. Moreover, M15.3 was found in rat plasma after IV administration. Given the relatively high exposures achieved in the pivotal animal toxicity studies it is likely that rats and dogs were adequately exposed to the major human metabolites in these studies.

Table 2: Metabolite levels in plasma after oral administration

Species	Metabolite (% of total AUC)			
	Parent	**M15.3**	**M20.2**	**M20.7**
Mouse	46	trace	3.8	17
Rat	40	0	11	42
Rabbit	22	53	0.9	7.4
Dog	23	26	1.4	33
Monkey	20	0.8	72	4.9
Human	26	8.1	9.5	56

In vitro incubations of rat, dog, monkey, and human liver slices with vildagliptin resulted in hydrolysis (dog, human) and glucuronidation (rat, monkey, human) as the major observed metabolic pathways. Hydrolysis of vildagliptin to yield the major carboxylic acid metabolite was observed in human liver, kidney and intestine microsomes. No metabolism of vildagliptin was observed following incubations with human liver microsomes and microsomal preparations from baculovirus-infected insect cells expressing the following recombinant human CYP450s: 1A1, 1A2, 2A6, 1B1, 2B6, 2C8, 2C9, 2C18, 2C19, 2D6, 2E1, 2J2, 3A4, 3A5, and 4A11, suggesting these enzymes are not involved in the formation of M20.7.

After oral administration, vildagliptin was predominantly (>~70%) excreted in the urine in mice, rabbits, dogs and humans, while in rats and monkeys the levels of urinary and faecal excretion of vildagliptin were similar. Due to the qualitative similarities in the absorption, metabolism and excretion of vildagliptin and/or its metabolites in the chosen species to those observed clinically, the use of these species in toxicology studies is appropriate.

Pharmacokinetic drug interactions

Induction and inhibition of CYP450 isoforms

In human liver microsomes, vildagliptin and M20.7, at concentrations up to 100 µM (124 times the human C_{max}), showed little or no inhibition of reactions mediated by the CYP isozymes 1A2, 2C8, 2C9, 2C19, 2D6, 2E1, and 3A4/5. In human hepatocytes, vildagliptin (1, 10, 50 µM) induced mRNA expression of CYP2C9, 3A4, and 3A5 in an approximately concentration-dependent manner, however induction of mRNA was not accompanied by induction of enzyme activity. Vildagliptin did not induce mRNA or enzyme activity of the remaining CYP450 isozymes: 1A1, 1A2, 2B6, 2C8, 2C19, or 3A. In liver slices, vildagliptin did not significantly induce mRNA levels or enzyme activity for any of the tested CYP450s. Based on these results, it is considered unlikely that vildagliptin will inhibit or enhance the *in vivo* metabolic clearance of co-medications metabolised by these isozymes.

Induction and inhibition of other enzymes and transporters

In human hepatocytes and liver slices vildagliptin (1, 10, or 50 µM) did not induce UGT1A1, while induction levels of the transporter proteins P-glycoprotein (ABCB1) and ABCB2 were low and unlikely to be of any clinical relevance. Transport of vildagliptin was decreased in the presence of the P-glycoprotein inhibitors verapamil and terfenadine indicating *in vivo* vildagliptin efflux due to P-glycoprotein (ABCB1). Indomethacin, an MRP transporter inhibitor, had no effect on vildagliptin transport. It is considered unlikely that vildagliptin will affect the clearance of co-administered drugs metabolised/transported by UGT1A1, ABCB1, ABCB2, or MRP; however, the pharmacokinetic parameters of vildagliptin may be affected by P-glycoprotein transporter inhibitors. No dedicated pharmacokinetic drug interaction studies were conducted with the proposed combination therapies. Whether the proposed combination therapies inhibit P-glycoprotein transport should be considered.

Toxicology

Acute toxicity

Single-dose toxicity studies were conducted in mice and rats by the IV and oral routes. The four submitted studies were GLP-compliant, used adequate animal numbers, and employed post-dose observation periods of adequate duration (15 days). For the IV route, the maximum non-lethal dose (MNLD) was 100 mg/kg (males) and 500 mg/kg (females) in mice, and 200 mg/kg in rats. In mice, severe clinical signs were observed at 500 mg/kg/IV and consisted of ataxia, tremors, laboured respiration, decreased locomotor activity and convulsions. These signs dissipated by 15 minutes post-dose. In rats dosed intravenously, clinical signs were only observed in one male and were minor (slight decrease in locomotor activity at 200 mg/kg). For the oral route, the MNLD in both species was 2000 mg/kg, the maximum dose tested, and there were no treatment-related clinical signs or effects on body weight. Food consumption was reduced in female mice at 2000 mg/kg orally. Gross pathology investigations conducted in each study revealed no treatment-related effects for either route of administration.

Repeat-dose toxicity

The submitted repeat-dose toxicity studies are summarised in the table below. Dose levels and exposure ratios corresponding to the NOAEL for each study are shown in **bold-face**. A sufficient number of high quality studies were conducted for an assessment of the toxicity of vildagliptin after repeated dosing. These studies are considered to be adequate with regard to the parameters investigated, group sizes, dose levels, dosing duration, and compliance with GLP. Most of the studies were conducted using the clinically relevant oral route of administration. Dosing durations were up to 13 weeks in mice, 26 weeks in rats, 52 weeks in dogs, and 13 weeks in monkeys with recovery periods of 4 weeks in a number of studies.

Maximum animal:human exposure ratios (ER_{AUC}) achieved in the studies were ~300 in mice and rats, and ~30 in dogs and monkeys. Overall, vildagliptin administration was associated with a relatively small spectrum of toxicological findings with the lungs, GI tract and skin/muscle as target organs in rodents, dogs and monkeys, respectively.

Table 3: Summary of repeat-dose toxicity studies

Species, strain	Duration, route	Study	Dose (mg/kg/day)	$AUC_{0–24h}$ (µg.h/mL)	Exposure ratio
Mouse (CD-1)	4 wk, PO	017042	50, 250, **750**, 1500	7.9, 63, **226**, 541	4, 31, **110**, 262
	13 wk, PO	017043	50, **250**, 750, 1500	14, **74**, 314, 671	7, **36**, 152, 325
Rat (Wistar Hannover)	2 wk, IV	0410052	10, **30**, 100	2.7, **11**, 37	1.3, **5.5**, 18
	2 wk, PO	997079	20, **100**, 500	2.7, **27**, 121	1.3, **13**, 58
	13 wk, PO	007074	**50**, 250, 900	**14,** 86, 334	**7**, 42, 162
	13 wk, PO	0170101	1500	649	315
	26 wk, PO	017029	25, 150, 900	12, 72, 575	6, 35, 279
Dog (Beagle)	2 wk, IV	0410053	5, 10, **20**	4.7, 10, **24**	2, 5, **12**
	2 wk, PO	997080	**5**, 25, 100→50	**4.3**, 23, 43	**2**, 11, 21
	13 wk, PO	007075	**5**, 25, 75→50	**4.0**, 26, 57	**2**, 13, 28
	26 wk, PO	017030	**5**, 15, 60→50→40	**3.3**, 12, 39	**1.6**, 6, 19
	52 wk, PO	0170130	5, 15, 40	4.6, 15, 55	2, 7, 27
Monkey (Cynomolgus)	6/13 wk, PO	0570341	5, 20, 80, 160	1.8, 6.6, 37, 72	0.9, 3, 18, 35
	13 wk, PO	0670701	0.3, 1, 3, 20	0.1, 0.4, **0.9**, 10	0.04, 0.15, **0.4**, 5

Note: Animal:human exposure ratios were calculated using the animal plasma $AUC_{0–24\,h}$ and the clinical plasma $AUC_{0–24\,h}$ value of 2.06 µg.h/mL for dosing at 50 mg bd derived from clinical study 2335. The 7-day rising dose IV study in rats is not included in this table. This study employed a complex dosing regimen and was effectively a range-finding study for the 2-week IV study. In the 13-week dog study, the NOAEL of 5 mg/kg/day applies to males. A NOAEL was not established for females in this study. Not all monkey studies were included in this table as only limited analyses were performed in those studies. PO=oral

Alveolar macrophage accumulation in rodents

The lung was the primary target organ of toxicity in rodents. Focal/multifocal accumulation of foamy (lipid-laden) macrophages was observed in mice and rats after administration by both the IV and oral routes. The severity of this finding was rated by the pathologist as minimal. Exposure ratios at the NOAEL ($NOAEL_{ER}$) for this effect were ~130–150 in mice and 7–13 in rats in studies of up to 13 weeks duration. A NOAEL was not established in the 26-week rat study where lung macrophage accumulation was observed at the low dose of 25 mg/kg/day (ER, ~6). In this study and in a 13-week rat study, lung macrophage accumulation was not completely reversible after a 4-week recovery period. No other lung histopathology or gross pathology was evident in the 26-week study. These effects may be attributable to the pharmacological action of vildagliptin, as GLP-1 receptors are found in the lungs of rodents (Richter *et al.*, 1991), though alternative hypotheses suggest it could be attributed to secondary pharmacodynamic effects on DPP-8/9 (Lankas *et al*., 2005). Given the minimal severity of this effect, the reasonable exposure margins achieved at the NOAEL, and the absence of such findings in dogs or monkeys, it would appear that this does not represent a risk to humans at the MRHD.

Gastrointestinal toxicity in dogs

The GI tract was the principal target organ for toxicity in dogs receiving vildagliptin orally at durations ranging from 2 weeks to one year. Consistent findings at low relative exposures included diarrhoea and soft faeces (ER, ≥2). At higher ERs (≥11) mucus and blood were found in the faeces. Minimal eosinophilia of the caecum, colon and rectum was noted in the 2- and 13-week studies. These same tissues displayed congestion, inflammation and occasionally necrosis (in premature decedents) at ERs ranging from 18–25 in the one year study. Given that GI toxicity was not evident in rats, mice or monkeys following oral dosing at systemic exposures up to 35–325-times that anticipated at the MRHD, it would appear that dogs have a unique GI sensitivity to vildagliptin and these effects are not relevant to patients.

Cutaneous toxicity in monkeys

Skin lesions were detected in monkeys at doses ≥5 mg/kg/day orally (ER, ≥0.9). Lesions were only present on the extremities, not on the torso, and the time to onset was variable. The lesions consisted of flaking or peeling skin, scabs and tail sores and blisters on hands and feet. Epidermal changes included ulceration and necrosis, inflammatory exudate and acanthosis with neutrophilic infiltrates. The severity of lesions was dose-related, and necessitated humane euthanasia of several animals at ≥80 mg/kg/day. In a 13-week study, lesions were reversed in monkeys at the lowest dose (5 mg/kg/day; ER, 0.9) despite continued treatment, but were not reversed at the highest dose (160 mg/kg/day; ER, 35) within a 4-week recovery period. The NOEL for these changes was 3 mg/kg/day with an ER_{AUC} based on vildagliptin of 0.4. However, in monkeys, the pharmacologically-active metabolite, M20.2, comprises ~70% of the drug-related material in the plasma (3.6-times more than the parent), and when concentrations of this compound are considered together with vildagliptin, the ER at the NOEL is about 3.

The mechanism postulated by the sponsor for these lesions was a secondary effect of tissue ischemia due to vasoconstriction of small vessels of the extremities. Small and medium sized arterioles in the dermis showed haemorrhage, oedema, degeneration/regeneration, necrosis and hypertrophy/hyperplasia, possibly the result of chronic stimulation of the vascular smooth muscle. Consistent clinical chemistry findings included increased serum creatine kinase, aspartate aminotransferase, alanine aminotransferase and lactate dehydrogenase; all indicators of muscle damage. Though mechanistic studies demonstrated an increase in the vasoconstrictive function of cutaneous arterioles, with effects on peripheral blood flow, increased urinary catecholamines and haemodynamic changes in monkeys, a link between vasoconstriction and lesion formation was not demonstrated.

Even though the mechanism of skin lesion formation in monkeys has not been established, it is likely of minimal clinical concern as there have apparently been no reports of blisters or skin ulcerations with vildagliptin in clinical use. However, oedema, soft tissue swelling of plantar aspects of both feet and pain in extremities occurred clinically at doses ≥400 mg/day ($AUC_{0-24\,h}$, >10.4 µg.h/mL), suggesting the vasoconstriction and vascular muscle toxicities observed in the monkey studies at similar exposure levels are applicable to humans but are not of particular clinical relevance as they occur only at doses significantly exceeding the MRHD of 100 mg/day (50 mg bd).

Other findings

In the majority of studies there was no evidence of liver or kidney toxicity. Kidney findings were limited to reversible increases in the incidence of proteinaceous casts in the 26-week rat study (at ERs ≥35; ER at the NOEL, 6), and inflammation (focal, chronic) in the 52-week dog study (at ERs ≥6; ER at the NOEL, 2).

Increased white and/or red cell counts were observed in rats, but only at high exposures (ER, 35–315), with no histopathological or functional correlates. There were no haematological findings in the mouse studies while in dogs, reversible increases in eosinophils and neutrophils were observed, secondary to GI tract toxicity.

Immunotoxicity

DPP-4 (=CD26) is a co-receptor with CD3 in T cell activation. Vildagliptin (50 µM) had no significant inhibitory effect on the proliferation of mouse bone marrow cells or T cells *in vitro* and showed only a weak concentration-dependent suppression of the human mixed lymphocyte reaction (MLR) with suppression incomplete at the highest concentration tested (71% inhibition at 10 µM; IC_{50} ~5 µM). In an assay of human peripheral blood mononuclear cell (PBMC) PHA (phytohaemagglutinin)-stimulated proliferation, vildagliptin showed weak suppression (~25%) in the concentration range 40 nM – 10 µM with no inhibition evident at approximately 10 nM. These findings are relatively minor and are not considered to be clinically relevant as they occurred at concentrations far exceeding the clinical C_{max} of 808 nM. Moreover, a dedicated immunotoxicity study in rats receiving vildagliptin orally at up to 900 mg/kg/day for 4 weeks resulted in no adverse effects on the immune system (ER,≤167). The lack of an immunotoxic effect is consistent with observations in a DPP-4 null mutant mouse (Vora *et al.*, 2009).

The predominant toxicological findings of alveolar macrophage accumulation, GI toxicity and skin toxicity occurred only in a single species or at sufficiently high exposures not to be of clinical concern at the proposed maximum dose. Toxicity studies using vildagliptin in combination with metformin or other proposed combination therapies have not been provided in this or previous submissions (though it is likely that vildagliptin/metformin toxicity studies are contained in the pending application for the fixed-dose vildagliptin/metformin combination). The skin and cutaneous vasculature are the primary targets of toxicity for vildagliptin considered to pose a potential clinical concern. Any proposed combination therapy that may exacerbate or have additive effects on the cutaneous toxicity of vildagliptin is of particular concern.

Genotoxicity

An appropriate set of genotoxicity studies was submitted, which included bacterial reverse mutation assays in *Salmonella typhimurium*, an *in vitro* mutation assay in mammalian (V79) cells, an *in vitro* chromosome aberration assay in human lymphocytes, an *in vivo* assay of DNA damage (COMET assay), and *in vivo* chromosome aberration assays in mice and rats (micronucleus assay). The assays were validated by the use of positive control compounds which elicited the expected responses in all tests. The bacterial tests were adequate with regard to the strains employed and the maximum concentration tested despite lack of toxicity, while in the other *in vitro* assays the tested concentrations extended into the cytotoxic range. The high dose of 2000 mg/kg/day orally used in the mouse and rat micronucleus assays resulted in mean AUC_{0-24h} values of 856–930 µg.h/mL which is >400-times the expected clinical value. Vildagliptin induced a concentration-dependent increase in micronuclei in the *in vitro* mutation assay in V79 cells, but only in the absence of metabolic activation, at cytotoxic concentrations (≥800 µg/mL), and after prolonged (20 hours) exposure. Given that vildagliptin was negative in the remaining *in vitro* and *in vivo* studies, the weight of evidence indicates that vildagliptin is unlikely to be genotoxic in humans at the proposed dose.

Carcinogenicity

GLP-compliant carcinogenicity studies of two-year duration were conducted in mice and rats by the oral (gavage) route. Adequate animal numbers were used in each treatment group for

both species (50–60 per sex). Dosage selection was based on the 3 and 13 week oral studies in mice and a 13 week oral study in rats.

Mammary tumours

An increase in mammary adenocarcinoma was observed in female mice.

Dose (mg/kg/day)	0	100	250	500	1000
Incidence - Mice	0/57	3/59 (5%)	2/58 (3%)	5/57 (9%)	13/59** (22%)

** $p < 0.005$

Statistical significance ($p<0.005$) was attained only at the high dose of 1000 mg/kg/day (ER_{AUC}, 185). The incidence was not significantly increased at 500 mg/kg/day, corresponding to an ER of about 80 based on AUC. In contrast, mammary adenocarcinoma was not observed in female rats at the high dose (900 mg/kg/day, ER_{AUC}, 150), and the incidence at lower doses was the same as in controls (2–3/50 females per group). Moreover, the incidence of mammary fibroadenoma decreased with dose in female rats.

Mammary adenocarcinoma is a common tumour in mice with a historical control range of about 2–8%. In the absence of genotoxicity, this tumour is commonly associated with hormonal disturbances, which in rodents frequently represents a species- or strain-specific effect of no relevance to humans. Hormonal disturbances were evident as reproductive tract changes (reduced uterus size/reduced number of uterine glands) in the 13-week mouse study with vildagliptin. Therefore, in the absence of genotoxicity, and in the absence of a positive signal in rats, the mammary adenocarcinomas are considered the product of mouse-specific hormonal changes occurring at high relative exposures that are not clinically relevant.

Haemangiosarcoma

The incidence of haemangiosarcoma was increased in mice (both sexes) and in female rats:

Mice	**Dose (mg/kg/day)**	**0**		**100**		**250**		**500**		**1000**	
		m	**f**	**m**	**f**	**m**	**f**	**m**	**f**	**m**	**f**
	Incidence (no./60)	5	5	8	5	14	4	14**	7	13	12
	Exposure ratio (AUC)	–	–	15	13	46	45	101	81	235	185
Rats	**Dose (mg/kg/day)**	**0**		**25**		**150**		**450**		**900**	
		m	**f**	**m**	**f**	**m**	**f**	**m**	**f**	**m**	**f**
	Incidence (no./50)	7	0	2	0	2	0	1	0	2	4*
	Exposure ratio (AUC)	–	–	3	3	22	24	83	82	161	150

* $p < 0.05$; ** $p < 0.01$

A biologically significant increase was observed at ≥250 mg/kg/day in male mice (ER_{AUC}, ≥46) and in female mice at 1000 mg/kg/day (ER_{AUC}, 185). At the high dose of 900 mg/kg/day in female rats a statistically significant increase was observed ($p<0.05$; ER_{AUC}, 150). There was no apparent increase in the incidence of haemangiosarcoma in male mice at an ER of 15, female mice at an ER of about 80, male rats at an ER of about 160 and in female rats at an ER of about 80. The dose-response curve for any treatment-related effect was very flat, particularly considering the large exposure range tested.

In the mouse study report, it was stated that the testing facility historical control range for haemangiosarcoma was 1–18% in males and 0–12% in females. Thus, the incidences of haemangiosarcoma in males at doses≥250 mg/kg/day (22 –23%) and in females at

1000 mg/kg/day (20%) in the mouse study exceed the historical control range and are therefore concluded to be treatment-related.

Overall, the incidence of haemangiosarcomas was only increased at large exposure margins (≥46), predominantly in male mice, and with a very flat dose-response. Therefore, in the absence of a genotoxicity signal or the occurrence of tumours at key sites of pharmacological action (for example the pancreas), vildagliptin is not considered to pose a carcinogenic risk to humans at clinically relevant doses.

Reproductive toxicity

An acceptable set of well-designed reproductive toxicity studies was submitted (Table 4). All studies complied with GLP. Vildagliptin exhibited minimal effects on reproductive parameters even at relatively high animal:human systemic exposure ratios. Vildagliptin and/or its metabolites were shown to cross the placenta in rats. There was no evidence of teratogenicity in rats or rabbits at exposure ratios up to 117 and 39, respectively.

Table 4: Exposure in reproductive toxicity studies

Species, strain	Type of study	Dosing period	Dose (mg/kg/day); PO	Exposure ratio	No. per group	Study
Rat, Wistar Hannover	Fertility and early embryonic development	See footnote[1]	25	6[2]	25/sex	0270017
			250	42[2]		
			900	162[2]		
Rat, Wistar Hannover	Embryofetal development	GD6–17	75	11	24 f	007003
			225	33		
			750	117		
Rabbit, NZW	Embryofetal development	GD7–20	15	3	20 f	007109
			50	9		
			150	39		
Rat, Wistar Hannover	Pre- and post-natal (with mating of F_1 generation)	GD6–PND20	25	6[2]	22–24 f	0270155
			150	35[2]		
			750	135[2]		

[1] Dosing periods in fertility study: Males were dosed for 29 days prior to mating, throughout mating and up to terminal necropsy. Females were dosed from 14 days before mating, throughout mating and up to GD 6.
[2] Plasma drug concentrations were not measured in these studies. Quoted exposure ratios are those from repeat-dose toxicity studies in Wistar rats (25 and 150 mg/kg/day: Study 017029; 250 and 900 mg/kg/day: Study 007074). The exposure ratio for the 750 mg/kg/day was obtained by linear scaling of the 900 mg/kg/day exposure ratio.
In the embryofetal development studies, exposure ratios were based on $AUC_{0-24\,h}$ values using a human $AUC_{0-24\,h}$ of 2.06 µg.h/mL.

Abbreviations: NZW New Zealand White, GD Gestation Day, PND Postnatal Day, PO oral

In rats, male and female fertility and early embryonic development were unaffected at any of the three tested dose levels (estimated maximum exposure ratio ~160). In the rat embryofetal development study, findings consisted of reduced maternal body weight (~6%) at 750 mg/kg/day on gestation day 21 (ER_{AUC}, 117; $NOAEL_{ER}$, 33) and a significantly increased fetal incidence of a skeletal variation (wavy ribs) at exposure ratios≥33 ($NOAEL_{ER}$, 11). In rabbits, mean fetal body weights were reduced by 7% and 16% at the mid and high dose levels of 50 and 150 mg/kg/day, respectively, corresponding to maternal exposure ratios of 9 and 39 and a $NOAEL_{ER}$ of 3. Maternal toxicity in the form of reduced food consumption and

reduced body weight gain was evident only at the high dose, and was accompanied by deficits in ossification of the metacarpal and forepaw phalanx in fetuses.

A pre/postnatal development study in rats resulted in maternal toxicity consisting of reduced gestation and lactation body weights (4 to 8%) and food consumption (4 to 19%) at each vildagliptin dose level (25, 150, and 750 mg/kg/day). F_1 litters exhibited reduced body weight at birth (3 to 7%) and at day 21 (5 to 10%) at 150 and 750 mg/kg/day with no effect at 25 mg/kg/day ($NOAEL_{ER}$, 6). F_1 males exhibited increased open field motor activity at 150 and 750 mg/kg/day with no effect at 25 mg/kg/day. As vildagliptin was readily excreted in milk, it is unclear if exposure *in utero* or during lactation resulted in lower postnatal bodyweights. Rats deficient in DPP-4 had lower body weights than wild-type animals (Karl *et al.*, 2003b), suggesting this may be a pharmacological effect.

Overall, the submitted set of reproductive toxicity studies suggested that vildagliptin has a relatively low potential for reproductive toxicity at the maximum dose proposed for humans.

Local tolerance

A GLP-compliant acute dermal irritation study in rabbits revealed very slight irritation in 1/3 animals, which resolved 24 hours after application.

Paediatric use

There were no studies performed in juvenile animals.

Impurities

The sponsor has proposed impurity limits and submitted three GLP-compliant nonclinical studies of vildagliptin spiked with those impurities. The test article in these studies contained approximately 91.5%, 2.8%, 2.0%, 2.0%, and 1.9% w/w of vildagliptin, and each of the 4 impurities, respectively. Thus, it contained levels of each impurity that are greater than the proposed expiry limits. In the 4-week repeat-dose toxicity study in rats, a single dose level of the test article was administered corresponding to 900 mg/kg/day of vildagliptin. There was no significant difference in the toxicity of the test article and an unspiked vildagliptin test article in this study. At the maximum proposed human dose of vildagliptin, animal:human dose ratios for the impurities range from 130 to 600, indicating a substantial safety margin.

Two *in vitro* genotoxicity studies on this test article were submitted. It was negative in a bacterial reverse mutation assay at vildagliptin concentrations≤5 mg/plate, and was negative in chromosome aberration assay at vildagliptin concentrations≤ ~3 mg/mL.

There were no objections on toxicological grounds to the presence of the impurities at the stated expiry limits.

Nonclinical Summary and Conclusions

Primary pharmacology studies showed that vildagliptin inhibits DPP-4 with nanomolar potency resulting in increased levels of GLP-1 and insulin and decreased levels of glucose following glucose challenge. Efficacy was further demonstrated by the observation of reduced levels of HbA1c in diabetic monkeys.

Toxicological findings of pulmonary macrophage infiltration, GI tract toxicity and skin lesions either occurred in a single species or occurred only at sufficiently high exposures to be not of particular concern.

Vildagliptin is considered unlikely to pose a genotoxic or carcinogenic risk to patients. Increased incidences of some tumours were seen in the long-term carcinogenicity studies in mice and/or rats, but only at very high relative exposure levels (≥46).

Effects on reproductive parameters occurred at sufficiently high exposures to be not of particular concern.

The absence of toxicity studies with the proposed combinations is considered a major deficiency of the application. Consequently, registration can not be supported. While the nonclinical data are adequate to support monotherapy, assessment of the safety of vildagliptin in combination with metformin, a thiazolidinedione, a sulfonylurea and insulin will need to rely on clinical data only.

After the completion of this evaluation, the nonclinical evaluator was able provide additional information. Evaluation of nonclinical data has now been completed. Briefly, there was no novel toxicity with one of the combinations in studies of up to 13 weeks duration in rats and dogs, and no exacerbation of toxicity except for an increase in the incidence and severity of intra-alveolar accumulation of foamy macrophages in rats at the highest dose tested. This effect is attributable to vildagliptin, is rodent-specific, and not considered to pose a clinical hazard.

There are no nonclinical objections to the registration of Galvus and Xiliarx for use in free combination with metformin.

IV. Clinical Findings

Introduction

The present submission contains material further to that in the previous application with the intention of addressing those issues raised by ADEC as follows:

- Two new pharmacokinetic studies.
- Two new efficacy studies.
- Further commentary and data from extension of the previously submitted Study 2311 examining use of vildagliptin with insulin.
- Analysis of hepatic safety in an integrated dataset relating to ~9,400 patient- years of exposure to vildagliptin.
- Further post-marketing experience.

As noted above, the sponsor is applying for only the 50 mg tablet and no longer requests approval for the 100 mg tablet as previously sought.

Pharmacokinetics

Study CLAF237A2117 compared the single and multiple dose pharmacokinetics of vildagliptin and its two principal metabolites, observed with administration of 100 mg once daily for 14 days, in subjects with normal and mildly impaired renal function. The study design is shown in the schema below:

Days -21 to -2	**Day -1**	**Day 1**	**Day 2**	**Day 3**	**Days 4-13**	**Day 14**	**Day 15**	**Day 16**	**Days 17-19**
Screening	Baseline	Domiciled			Daily outpatient visits	Domiciled			Outpatient visits and study completion
		Dosing days							

Sixteen individuals with mild renal impairment and 16 healthy subjects were enrolled. All were in good general health at screening, apart from the 16 with renal impairment, defined as

an estimated creatinine clearance (CrCl) of 50- ≤80 ml/min (Cockcroft-Gault), of whom 9 had T2DM. The normal subjects all had creatinine clearance >80 ml/min and were matched by sex, age (±5 years) and weight (±10% BMI) to the renal patients enrolled into the study.

Inclusion criteria included:

For all subjects:

- Age 18-75 years inclusive and body mass index (BMI)≤42 kg/m2 at screening.

For renal insufficiency patients only:

- Patients had to have stable renal disease without evidence of progressive renal disease, defined as no significant change of CrCl for 12 weeks
- Diabetic patients: had to be treated with standard anti-diabetic therapy defined as diet and exercise, sulfonylurea, insulin or metiglinides as monotherapy or combination for at least 8 weeks prior to Screening. They had to agree to continue their anti-diabetic therapy and to have been on a stable regimen over the 4 weeks prior to Screening (stable insulin therapy defined as ± 20% of total daily units).

Exclusion criteria included:

- Pregnancy or lactation
- Enrolment in a DPP-4 inhibitor study 30 days prior to baseline.
- A history of type 1 diabetes.
- Any method of dialysis (haemodialysis or peritoneal dialysis).

Plasma samples for 24-hr pharmacokinetic (PK) profiles were collected pre-dose and at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 15 and 24 hours post-dose on days 1 and 14 of dosing. Additional plasma samples were collected at 48 (Day 16), 72 (Day 17), 96 (Day 18) and 120 (Day 19) hours post-dose. All 32 enrolled subjects completed the study and there were no protocol deviations. Demographic characteristics of the two groups were similar apart from renal function.

Results

Vildagliptin

Pharmacokinetic parameters for vildagliptin on Days 1 (single dose) and 14 (multiple dose) were derived. Mean C_{max} was slightly greater in the subjects with renal impairment than in normal controls but for both single and multiple dosing, the lower 90% confidence intervals (CI) of the geometric mean ratios just overlaps unity. There was no difference in AUC_{0-24}. No accumulation is suggested by comparing Day1 and Day 14 means for C_{max} and AUC_{0-24}.

Metabolite LAY151

Renal clearance was rather less than that of the parent drug and renal impairment significantly increased exposure to this metabolite. An equal degree of accumulation over the dosing period was seen in both groups.

Metabolite vildagliptin-O-glucuronide (BQS867)

Exposure was less than for either parent drug or LAY151 and was not significantly greater in mild renal impairment. There was no accumulation over the dosing period.

Study CLAF237A2221 was a placebo-controlled assessment of the pharmacokinetics of 200 mg, 400 mg and 600 mg vildagliptin, comparing daily administration as a single dose or as two equal divided doses. Dosing extended over 10 days. Serial sampling for assay of plasma

levels of vildagliptin and the metabolites LAY151 and vildagliptin-O-glucuronide was made on Days 1, 3, and 10 and trough levels were assayed on Day 7.

This was an ascending dose study with a planned structure as shown, each patient participating in only one cohort.

Cohort	Total dose	Number of subjects	Dosing Regimen
Cohort 1	200 mg	12	200 mg od
		12	100 mg bd
		4	Placebo
Cohort 2	400 mg	12	400 mg od
		12	200 mg bd
		4	Placebo
Cohort 3	600 mg	12	600 mg od
		12	300 mg bd
		4	Placebo

Subjects were healthy, non-smoking males, aged 18-45 years with BMI 18-27 kg/m^2. The planned subject numbers were not achieved. There were some differences in demographic characteristics between the dosage groups, in particular the lower body weight of the 100 mg bd group. Subjects classified as of black race made up 70% of the total group of 71 subjects. Mean (or median) pharmacokinetic parameters for vildagliptin for a single dose (Day 1) are shown in Table 5.

Mean values of C_{max} and AUC for vildagliptin indicate reasonable dose proportionality. Exposure to the drug (AUC) over a 24-hour period is similar whether given as a single or two divided doses but the two C_{max}'s are proportionately less following each divided dose, than the C_{max} after the single dose.

Findings are consistent with those obtained in Study CLAF237A2117. Mean (or median) single dose PK parameters for the two metabolites were also derived. Mean (or median) PK parameters for vildagliptin on Days 3 and 10 do not differ consistently from results following the Day 1 doses.

As was found in Study CLAF237A2117 the carboxylic acid metabolite (LAY151) had a long T_{max} and showed evidence of accumulation over the dosing period. This was not so for the O-glucuronide metabolite (BQS867).

Table 5: PK Parameters of LAF237 following single (Day 1) oral doses of LAF237 to healthy subjects

Treatment	T_{max} (h) Median (min, max)	C_{max} (ng/mL) Mean ± SD (CV%)	AUC_{0-t}[a] (h*ng/mL) Mean ± SD (CV%)	AUC_{0-inf} (h*ng/mL) Mean ± SD (CV%)	CL/F (L/h) Mean ± SD (CV%)	$t_{1/2}$[b] (h) Mean ± SD (CV%)	CL_R (L/h) Mean ± SD (CV%)	Ae_{0-24} (%) Mean ± SD (CV%)
100 mg bd (N=11)	1.50 (1.03, 2.00)	674 ± 167 (25)	2122 ± 342 (16)	2176 ± 355 (16)	46.95 ± 6.86 (15)	2.13 ± 0.39	7.96 ± 3.00 (38)	17 ± 6.9 (41)
200 mg bd (N=11)	1.00 (0.50, 1.52)	1421 ± 364 (26)	4162 ± 642 (15)	4305 ± 669 (16)	47.47 ± 7.30 (15)	2.35 ± 0.49 (21)	11.59 ± 2.68 (23)	24 ± 3.9 (16)
300 mg bd (N=9)	1.50 (0.98, 2.50)	1626 ± 427 (26)	7052 ± 1589 (23)	7446 ± 1683 (23)	41.82 ± 7.84 (19)	2.59 ± 0.39 (15)	9.83 ± 2.97 (30)	22 ± 5.3 (24)
200 mg od (N=10)	1.50 (.50, 2.50)	1223 ± 432 (35)	4542 ± 872 (19)	4588 ± 865 (19)	44.96 ± 8.17 (18)	2.96 ± 1.10 (40)	11.36 ± 1.86 (16)	25 ± 4.2 (16)
400 mg od (N = 11)	1.50 (1.00, 2.00)	2156 ± 530 (25)	9368 ± 1843 (20)	9499 ± 1882 (20)	43.68 ± 8.94 (20)	3.58 ± 0.81 (23)	11.27 ± 3.45 (31)	26 ± 7.8 (30)
600 mg od (N=10)	1.50 (0.98, 2.48)	4045 ± 1080 (27)	16757 ± 3756 (22)	16927 ± 3862 23)	36.97 ± 7.57 (20)	3.75 ± 0.63 (17)	12.06 ± 1.33 (11)	33 ± 7.0 (21)

[a] The AUC_{0-t} is AUC_{0-12h} for BID dosing and AUC_{0-24h} for QD dosing

[b] The t½ for BID dosing was calculated over 12 h samples and for QD dosing over 24 h samples

Summary of Pharmacokinetics

Cmax for vildagliptin was slightly but not significantly greater in patients with mild renal impairment nor was there any difference in AUC_{0-24}, but there was increased exposure to the inactive metabolite LAY151.

There is reasonable linearity of pharmacokinetics at total daily doses 200-600 mg and daily exposure (AUC) is equivalent when the daily dose is given as a single dose or as two divided doses. With the latter, C_{max} decreased roughly proportionately.

Pharmacodynamics

There were no pharmacodynamic studies presented in this application.

Efficacy

Pivotal Studies

The submission contained two efficacy studies not previously submitted.

Study 2308 was an active-controlled comparison over a planned 5 years of the addition of vildagliptin 50 mg bd or glimepiride 6 mg daily, for treatment of patients with Type 2 diabetes mellitus inadequately controlled by prior metformin monotherapy*. The simple study design is represented schematically in Figure 1. The population studied comprised patients whose control could be regarded as suboptimal despite a dose of metformin, the effect of which would approach the maximum likely as monotherapy. Males slightly outnumbered females and about a quarter were aged ≥65 years; none however were aged >75

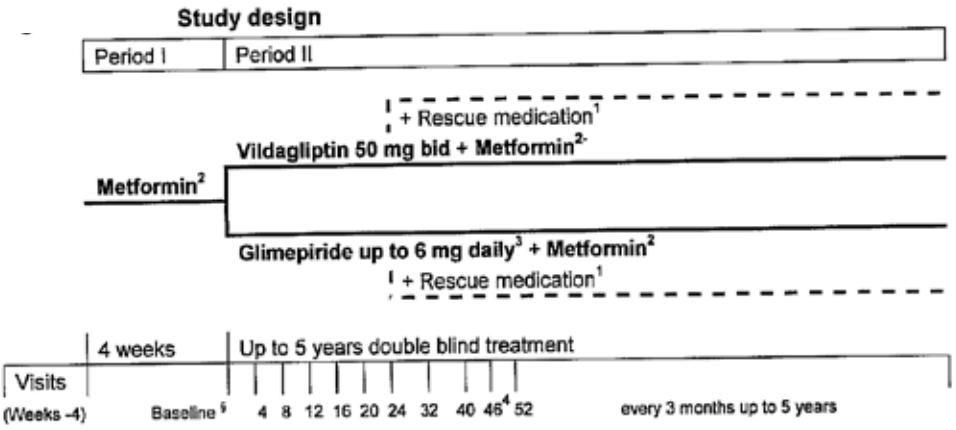
* Metformin for at least three months and at a stable maximum tolerated dose of at least 1500 mg daily for a minimum of 4 weeks prior to Visit 1 and an HbA1c >6.5% but ≤8.5% at Visit 1 The dose of metformin was to be maintained unchanged throughout the trial.

years. The dose of vildagliptin is one of those for which application has been made. The dose of the comparator, glimepiride, was titrated to a dose that exceeds the stated maximum dose of 4 mg daily; this would thus not give undue advantage in an efficacy comparison with vildagliptin. The 12-month interim report Study 2308IA was included in the submission together with a report of the modified continuation.

That report under consideration here concerns the results at 12 months from 2789 patients. The groups were well matched initially but there were more withdrawals from the glimepiride group due to adverse effects and withdrawal of consent.

The primary aim of the planned Study 2308 was to test the hypothesis that the risk of failure of glycaemic control over time (defined as HbA1c >8.0%) is lower with vildagliptin than with glimepiride. However, for this interim analysis (Study2308AI), the objective was to test the hypothesis that HbA1c reduction with vildagliptin is not inferior to that with glimepiride at Week 52 using a margin of 0.3%. This margin is more conservative than the 0.4% accepted by the FDA and was chosen to conform to a European requirement. The estimates of the primary variable were derived from an analysis of covariance (ANCOVA) model with treatment and pooled centre as the classification variables and baseline HbA1c as the covariate.

Figure 1: Study LAF237A2308 Design



[1] After Week 24, pioglitazone rescue medication was to be prescribed according to the guidelines in Section 9.4.7.
[2] metformin ≥ 1500 mg daily at stable dose.
[3] glimepiride was titrated according to the guidelines in Section 9.4.1.
[4] Telephone monitoring for suspicious symptoms of potential liver toxicity (e.g. anorexia, nausea, vomiting, fatigue, right upper abdominal discomfort, jaundice). In case of any suspicious symptoms the patient was to bee called in for an unscheduled visit to perform further evaluation within 3 days. Under these circumstances, potential causes, e.g., concomitant medications which were hepatotoxic, drug and alcohol abuse, diet, etc., were to be investigated.
[5] Day 1; randomization and first day of medication.

Results

In both treatment groups, adjusted mean HbA1c decreased from baseline to 52 weeks. The mean decrease with vildagliptin was less than that in the glimepiride group in both intention to treat (ITT) and per protocol populations (PP) but the differences indicated non-inferiority using the stated margins of 0.3% (Table 6).

The change in mean HbA1c over time is portrayed in Figure 2. HbA1c fell sharply over the initial 12 weeks and rose slowly and comparably, after 32 weeks in both groups.

A secondary efficacy variable was the proportion of responders defined by various criteria. Responder rate in the two groups were overall comparable but glimepiride was associated with significantly more responses meeting the criteria HbA1c≤ 6.5% [381/1043 (36.5%) v 440/1014 (43.4%), p=0.001] and HbA1c ≤ 6% [134/1116 (12.0) v 174/1069 (16.3) p=0.004] (Table 7).

Table 6: LAF237A2308 – ANCOVA results for change in HbA_{1c} (%) from baseline to Week 52 endpoint (interim analysis PP and ITT populations)

Treatment	n	Baseline mean (SE)	Adjusted mean change (SE)	Mean difference to Glim up to 6 mg + Met (SE)	97.5% CI
Interim analysis per protocol population					
Vilda 50 mg bd + Met	1118	7.33 (0.02)	-0.44 (0.02)	0.09 (0.03)	(0.02, 0.16)*
Glim up to 6 mg + Met	1072	7.36 (0.02)	-0.53 (0.02)		
Interim analysis Intent to Treat population					
Vilda 50 mg bd + Met	1358	7.30 (0.02)	-0.38 (0.02)	0.11 (0.03)	(0.04, 0.17)*
Glim up to 6 mg + Met	1318	7.30 (0.02)	-0.49 (0.02)		

Adjusted means and the associated standard errors (SE) and confidence intervals (CI) were from an ANCOVA model containing terms for treatment, baseline and pooled centres.
* Indicates non-inferiority to glimepiride at the one-sided 1.25% alpha level. Non-inferiority margin is 0.3

Figure 2: Graphical results for LAF237A2308

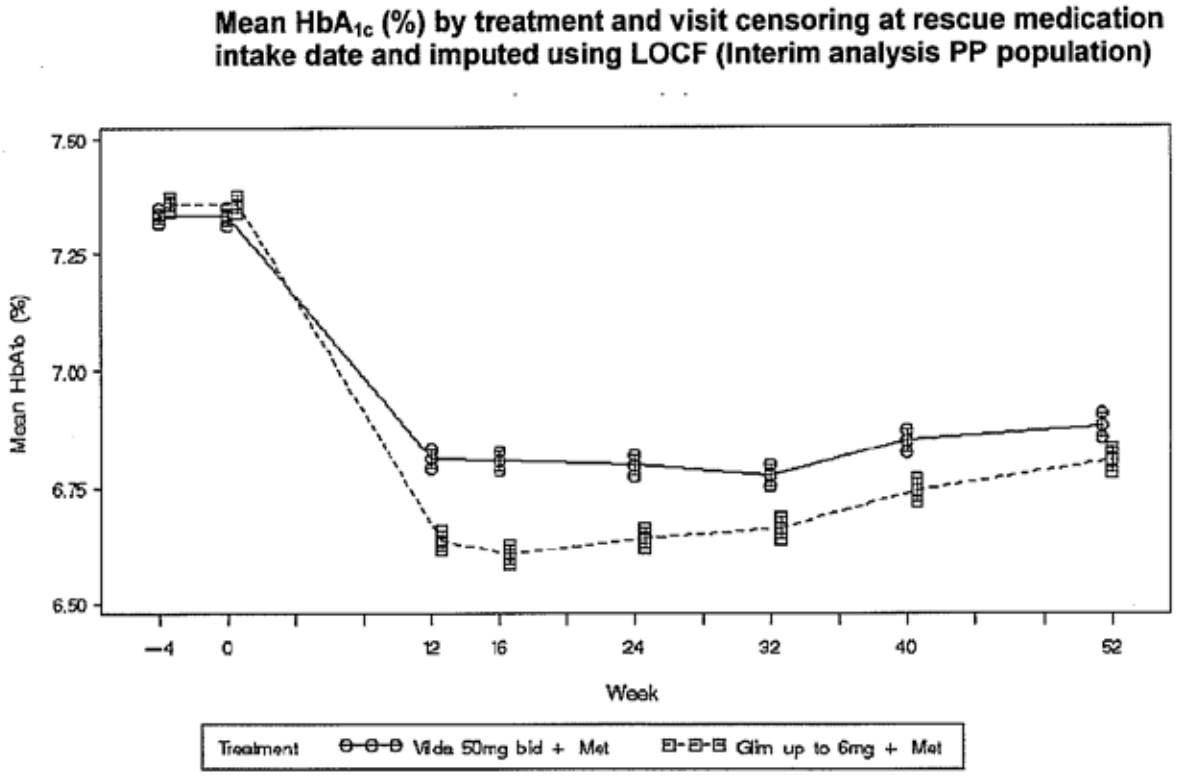


Table 7: Secondary Efficacy Results for Study LAF237A2308, number (%) of patients who responded at Week 52 endpoint (interim analysis PP and ITT populations)

	Vilda 50 mg bd + Met	**Glim up to 6 mg + Met**	**p-value**
	n(%)	**n(%)**	
Interim analysis per protocol population	N=1118	N=1072	
N	1118 (100.0)	1072 (100.0)	
Responder Criterion			
At least one criterion met	712 (63.7)	716 (66.8)	0.127
HbA_{1c} <7%	427/789 (54.1)	415/748 (55.5)	0.592
HbA_{1c} ≤6.5%	381/1043 (36.5)	440/1014 (43.4)	0.001
HbA_{1c} ≤6%	134/1116 (12.0)	174/1069 (16.3)	0.004
Reduction of HbA_{1c} ≥ 0.7%	452 (40.4)	502 (46.8)	0.003
Reduction of HbA_{1c} ≥0.5%	602 (53.8)	621 (57.9)	0.054
Interim analysis Intent to Treat population	N=1359	N=1321	
N	1358 (100.0)	1318 (100.0)	
Responder Criterion			
At least one criterion met	820 (60.4)	843 (64.0)	0.056
HbA_{1c} <7%	477/920 (51.8)	477/873 (54.6)	0.236
HbA_{1c} ≤6.5%	425/1230 (34.6)	497/1207 (41.2)	<0.001
HbA_{1c} ≤6%	160/1354 (11.8)	208/1311 (15.9)	0.002
Reduction of HbA_{1c} ≥ 0.7%	501 (36.9)	563 (42.7)	0.002
Reduction of HbA_{1c} ≥0.5%	687 (50.6)	718 (54.5)	0.044

Results for the modified extension to 104 weeks

In the extension study terminating at 104 weeks treatment, the various populations analysed are tabulated and the distribution is comparable for the two treatment groups.

Number (%) of Patients in analysis populations (randomized population)

Population	**Vilda 50 mg bd + Met**	**Glim up to 6 mg + Met**	**Total**
	N= 1562	**N= 1556**	**N=3118**
Randomised	1562 (100%)	1556 (1005)	3118 (100%)
Safety	1553 (99.4%)	1546 (99.4%)	3099 (99.4%)
Intent to Treat	1539 (98.5%)	1520 (97.7%)	3059 (98.1%)
Per protocol	1051 (67.3%)	1009 (64.8%)	2060 (66.1%)

Demographic and disease characteristics were very similar to those from the 52 week data.

The adjusted mean HbA1c changes from the original baseline at end of study were considerably less for both treatment arms than were found at the 52-week analysis (Table 6) but they were statistically significant (Table 8). The decrease was greater in the glimepiride than in the vildagliptin group in both the ITT and PP populations. In the former, glimepiride was superior to vildagliptin but in the latter vildagliptin was non-inferior using the margin of 0.4% stipulated in the amended protocol.

Table 8: LAF237A2308 – ANCOVA results for change in HbA_{1c} (%) from baseline to Week 014 endpoint (PP and ITT populations)

Treatment	n	Baseline mean (SE)	Adjusted mean change (SE)	Mean difference to Glim up to 6 mg + Met (SE)	97.5% CI (p-value)
per protocol population					
Vilda 50 mg bd + Met	1050	7.32 (0.02)	-0.06 (0.03)	0.08 (0.04)	(0.00, 0.17)* (0.033)
Glim up to 6 mg + Met	1008	7.32 (0.02)	-0.14 (0.03)		
Intent to Treat population					
Vilda 50 mg bd + Met	1518	7.31 (0.02)	-0.03 (0.02)	0.10 (0.03)	(0.03, 0.17)* (0.002)**
Glim up to 6 mg + Met	1476	7.31 (0.02)	-0.13 (0.02)		

Adjusted means and the associated standard errors (SE) confidence intervals (CI) and p-values were from an ANCOVA model containing terms for treatment, baseline and pooled centres.

* Indicates non-inferiority to glimepiride at the one-sided 1.25% alpha level. Non-inferiority margin is 0.4

** indicates statistical significance for superiority at the 2.5% alpha level

The progress of mean HbA1c over the course of the trial and the numbers of patients contributing to those means at each time point are depicted in Figure 3. There was steady rise in mean HbA1c over the course of the second year of treatment that was seen equally with both treatments. The end of trial means, which reflect the ITT population, are of course somewhat higher than the 52 week Per Protocol figures.

The secondary endpoint of response rate declined for both treatments from those reported at one year (Table 9).

A "coefficient of failure" between weeks 24 and 104, defined as the slope of the least-squares regression line of HbA1c vs. time calculated for each individual patient, was determined for the ITT populations. This measure of durability of response over that period favoured vildagliptin over glimepiride (0.43% HbA1c/year vs. 0.52% HbA1c/year, respectively).

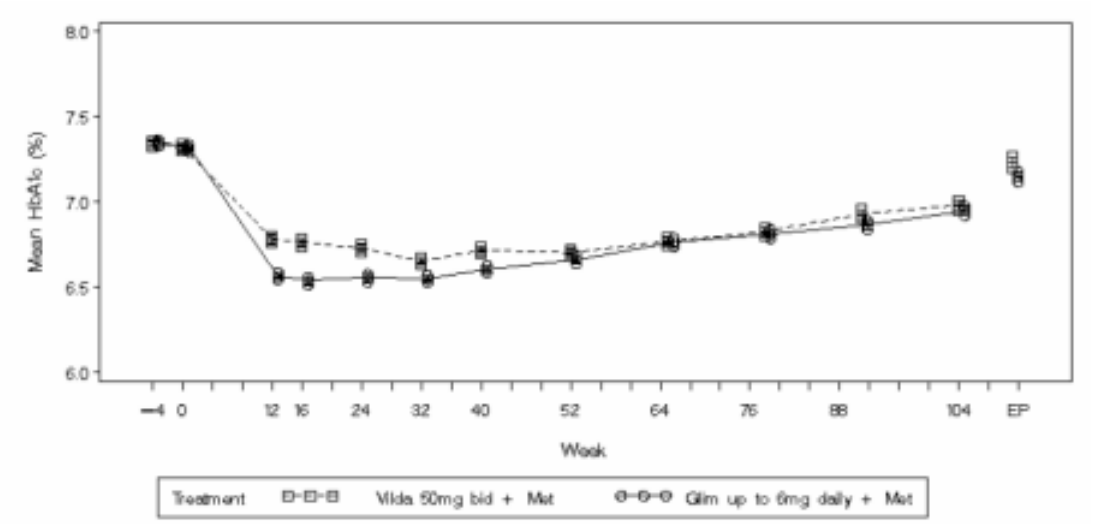
For the secondary efficacy variable fasting plasma glucose, decline from baseline was greater for glimepiride but inferiority was not demonstrated using the specified margin of 0.6 mmol/L.

Mean body weight decreased in the vildagliptin group but increased with glimepiride (-0.26 v +1.19 kg respectively; $p<0.001$).

None of the 1553 patients taking vildagliptin was discontinued due to hypoglycaemia whereas 14/1546 (0.9%) were in the glimepiride group.

Figure 3: Graphical Results to 2 Years

Mean HbA_{1c} (%) by treatment and visit censored at start of rescue medication use (Per-Protocol population)



Unadjusted means and standard error (vertical bars) are given.
EP (Week 104 Endpoint) is the final available post-randomization assessment before the start of rescue medication and up to Week 104 visit (Visit 14) inclusive.
Source: Figure 14.2-1.1a

Number of patients contributing to HbA_{1c} assessments in Fig. 11-1

Week	-4	0	12	16	24	32	40	52	65	78	91	104	EP
Vilda 50mg bid+Met	1030	1051	1022	1009	1019	975	969	945	931	914	896	845	1050
Glim up to 6mg daily+Met	983	1009	983	955	972	944	941	933	914	891	863	824	1008

Table 9: Secondary Efficacy Results for Study LAF237A2308, number (%) of patients who responded at Week 104 endpoint (PP and ITT populations)

	Vilda 50 mg bd + Met	**Glim up to 6 mg + Met**	**p-value**
	n(%)	**n(%)**	
per protocol population	N=1051	N=1009	
N	1050 (100.0)	1008 (100.0)	
Responder Criterion			
At least one criterion met	466 (44.4)	475 (47.1)	0.212
HbA_{1c} <7%	271/734 (36.9)	265/692 (38.3)	0.592
HbA_{1c} ≤6.5%	231/975 (23.7)	244/948 (25.7)	0.298
Reduction of HbA_{1c} ≥0.5%	392 (37.3)	396 (39.3)	0.364
Intent to Treat population	N=1539	N=1520	
N	1518 (100.0)	1476 (100.0)	
Responder Criterion			
At least one criterion met	645 (42.5)	664 (45.0)	0.169
HbA_{1c} <7%	361/1036 (34.8)	368/980 (37.6)	0.206
HbA_{1c} ≤6.5%	304/1377 (22.1)	327/1347 (24.3)	0.174
Reduction of HbA_{1c} ≥0.5%	534 (35.2)	547 (37.1)	0.284

Several other pharmacodynamic observations were made on a subset (approximately 10% of the per protocol population) at baseline and at 52 weeks. Prandial glucose increase was less at 52 weeks than at baseline with both treatments but the difference between them was not statistically significant (Table 10)

Insulin levels rose after the meal with both vildagliptin and glimepiride but more so with the latter and the difference from baseline between the two groups was significant. Prandial glucagon response was less at 52 weeks than at baseline in those taking vildagliptin whereas in those taking glimepiride it was slightly increased and this difference was also significant.

Table 10: ANCOVA results for change in prandial plasma glucose and related measurements to Week 52 endpoint (interim analysis, PP population)

Treatment	n	Baseline mean (SE)	Adjusted mean change (SE)	Mean difference to Glim up to 6 mg + Met (SE)	95% CI	p-value
Prandial plasma glucose AUC_{0-2hr}						
Vilda 50 mg bd + Met	109	24.37 (0.42)	-2.95 (0.37)	0.41 (0.55)	(-0.67, 1.49)	0.457
Glim up to 6 mg + Met	95	24.56 (0.55)	-3.36 (0.40)			
Adjusted prandial plasma glucose AUC_{0-2hr}						
Vilda 50 mg bd + Met	109	6.05 (0.27)	-0.99 (0.23)	-0.56 (0.34)	(-1.24, 0.12)	0.105
Glim up to 6 mg + Met	95	6.14 (0.29)	-0.43 (0.25)			
1-Hour prandial plasma glucose level (mmol/L)						
Vilda 50 mg bd + Met	108	13.33 (0.23)	-1.59 (0.22)	0.13 (0.32)	(-0.51, 0.77)	0.689
Glim up to 6 mg + Met	96	13.42 (0.28)	-1.72 (0.24)			
Prandial insulin AUC_{0-2hr}						
Vilda 50 mg bd + Met	94	395.7 (22.9)	39.61 (19.14)	-77.7 (27.91)	(-133, -22.6)	0.006*
Glim up to 6 mg + Met	84	364.6 (17.46)	117.3 (20.25)			
Prandial glucagon AUC_{0-2hr}						
Vilda 50 mg bd + Met	104	55.85 (1.61)	-7.59 (1.20)	-8.92 (1.77)	(-12.4, -5.43)	<0.001*
Glim up to 6 mg + Met	88	55.19 (2.38)	1.33 (1.30)			

* Statistical significance at 5% level

Insulin secretion rate relative to glucose rose at 52 weeks from baseline values with both drugs but to a significantly greater extent with glimepiride. Decreased fasting pro-insulin/insulin ratio consistent with improved beta-cell function was seen at 52 weeks with both drugs but for this measure, significantly more for vildagliptin. Insulin resistance as indicated by fasting insulin level and by using the homeostatic model (HOMA-IR) gave contradictory results but by both assessments glimepiride was associated with a significantly worse change in insulin resistance (Table 11).

Table 11: ANCOVA results for change in beta cell function/insulin resistance parameters to Week 52 endpoint (interim PP population, participating patients)

Treatment	n	Baseline mean (SE)	Adjusted mean change (SE)	Mean difference to Glim up to 6 mg + Met (SE)	95% CI	p-value
Beta cell function parameters						
Insulin secretion rate (ISR) relative to glucose						
Vilda 50 mg bd + Met	88	28.67 (1.17)	5.33 (0.98)	-2.99 (1.44)	(-5.83, -0.15)	0.039*
Glim up to 6 mg + Met	76	27.46 (1.10)	8.33 (1.05)			
Fasting pro-insulin/insulin ratio						
Vilda 50 mg bd + Met	817	0.51 (0.01)	-0.11 (0,01)	-0.03 (0.01)	(-0.05, -0.01)	0.001*
Glim up to 6 mg + Met	795	0.49 (0.01)	-0.08 (0.01)			
Insulin resistance parameters						
Fasting insulin						
Vilda 50 mg bd + Met	931	64.47 (1.49)	3.38 (1.52)	-11.2 (2.04)	(-15.2, -7.18)	<0.001*
Glim up to 6 mg + Met	900	68.42 (1.67)	14.57 (1.57)			
Homa-IR						
Vilda 50 mg bd + Met	919	3.93 (0.14)	-0.30 (0.11)	-0.60 (0.15)	(-0.89, -0.32)	<0.001*
Glim up to 6 mg + Met	889	4.11 (0.12)	0.31 (0.11)			

* Statistical significance at 5% level

With vildagliptin, triglyceride and total, LDL- and VLDL- cholesterol levels at 52 weeks and HDL cholesterol rose. With glimepiride, triglycerides and LDL- and VLDL-cholesterol rose as did HDL-cholesterol (Table 12).

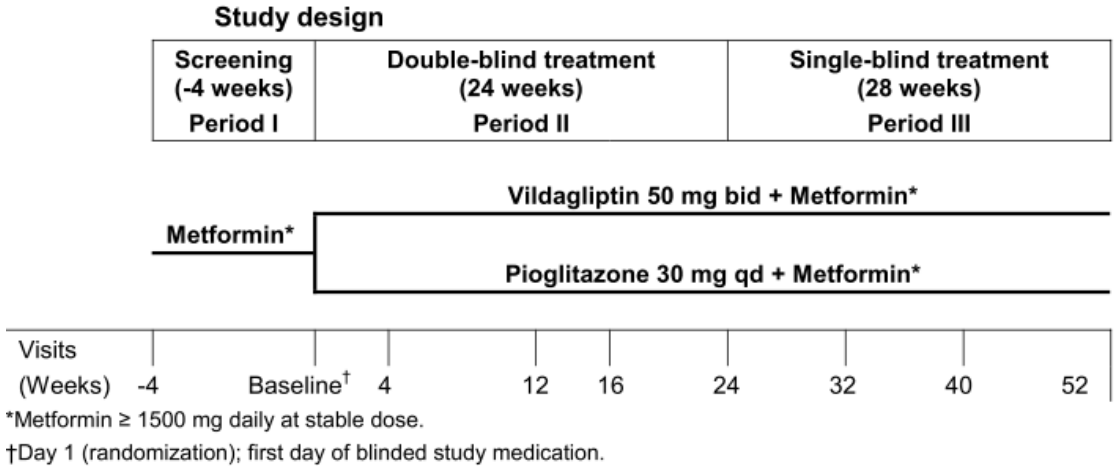
Table 12: ANCOVA results for percent change in fasting lipid parameters to Week 52 endpoint (interim analysis, PP population)

Treatment	n	Baseline mean (SE)	Adjusted mean change (SE)	Mean difference to Glim up to 6 mg + Met (SE)	95% CI	p-value
Triglycerides (mmol/L)						
Vilda 50 mg bd + Met	1115	2.17 (0.04)	-0.05 (1.26)	-5.81 (1.73)	(-9.20, -2.42)	<0.001*
Glim up to 6 mg + Met	1070	2.07 (0.04)	5.76 (1.29)			
Total cholesterol (mmol/L)						
Vilda 50 mg bd + Met	1115	5.14 (0.03)	-2.62 (0.45)	-2.31 (0.62)	(-3.53, -1.08)	<0.001*
Glim up to 6 mg + Met	1070	5.06 (0.03)	-0.31 (0.46)			
LDL cholesterol (mmol/L)						
Vilda 50 mg bd + Met	1069	2.93 (0.03)	-2.26 (4.98)	-8.88 (6.85)	(-22.3, 4.56)	0.195
Glim up to 6 mg + Met	1024	2.91 (0,03)	6.62 (5.10)			
HDL cholesterol (mmol/L)						
Vilda 50 mg bd + Met	1103	1.25 (0.01)	2.70 (0.51)	0.58 (0.70)	(-0.78, 1.95)	0.402
Glim up to 6 mg + Met	1061	1.25 (0.01)	2.11 (0.52)			
non-HDL cholesterol (mmol/L)						
Vilda 50 mg bd + Met	1103	3.88 (0.03)	-3.52 (0.62)	-3.07 (0.86)	(-4.75, -1.39)	<0.001*
Glim up to 6 mg + Met	1061	3.81 (0.03)	-0.46 (0.64)			
VLDL cholesterol (mmol/L)						
Vilda 50 mg bd + Met	1083	0.91 (0.01)	-0.83 (1.10)	-3.97 (1.51)	(-6.93, -1.00)	0.009*
Glim up to 6 mg + Met	1033	0.87 (0.01)	3.14 (1.13)			

* Statistical significance at 5% level

Study 2354 comprised an initial 24 week double-blind comparison of vildagliptin 50 mg bd and pioglitazone as add-on treatment for patients with Type 2 diabetes mellitus inadequately controlled by metformin.

This was followed by a 28 week extension during which the patients and investigators remained blinded. But the sponsor was unblinded to permit an interim analysis of results from the initial 24 weeks.



Entry was available to patients with HbA1c 7.5-11% after at least 4 weeks of metformin at a stable dose of up to 1500 mg/day.

The primary efficacy variable was change in HbA1c from baseline to end of study.. Of the 576 patients randomised, 506 completed the first 24 weeks of the study, with a comparable proportion of patients prematurely discontinuing the study across the two treatment groups.

A total of 468 patients completed Period III with reasons for withdrawal being comparable in the two groups although, over the whole 52 weeks, more patients on pioglitazone withdrew their consent than did those on vildagliptin and more on vildagliptin withdrew due to lack of therapeutic effect and protocol violation.

Demographic and disease characteristics for randomized patients were well matched except for somewhat more patients taking pioglitazone being aged≥65 years.

Results

Mean reduction in HbA1c from baseline at end of study was statistically significant in both groups. The reduction was larger for pioglitazone treatment (0.64% v 0.58% for pioglitazone and vildagliptin respectively) but no statistical analysis between the two groups is presented for this interim analysis (Table 13).

Table 13: Change in baseline in HbA_{1c} (%) at endpoint (ITT population)

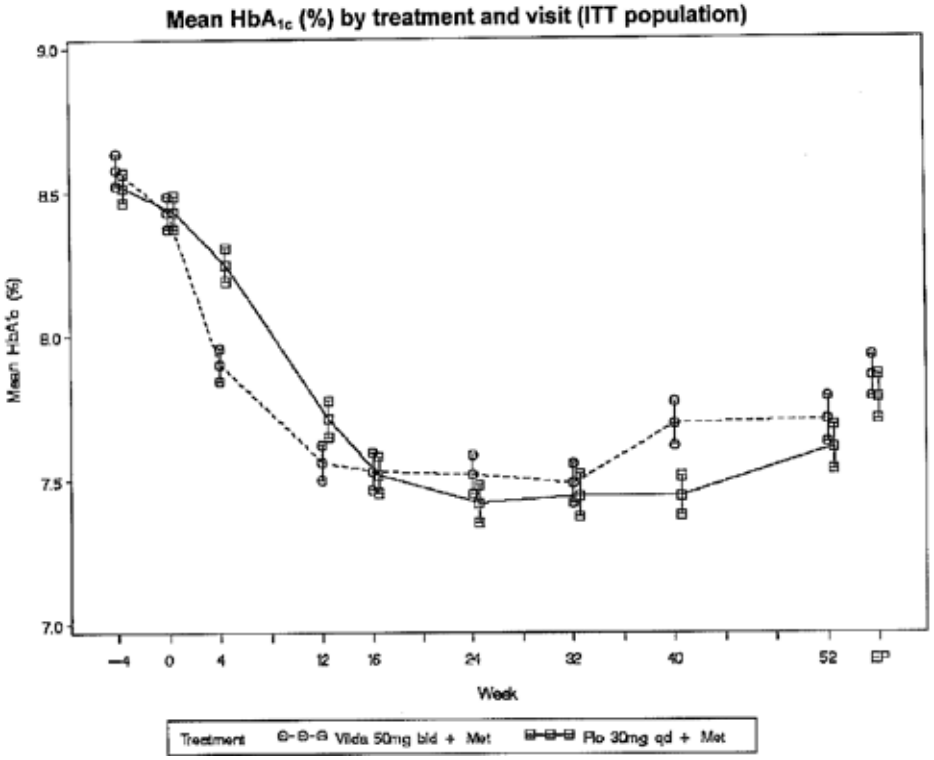
Treatment	n	Baseline mean (SE)	Unadjusted mean change from baseline (SE)	95% CI for change from baseline	p-value for change from baseline
Vilda 50 mg bd + Met	293	8.44 (0.06)	-0.58 (0.07)	(-0.71, -0.45)	<0.001*
Pio 30 mg od + Met	277	8.43 (0.06)	-0.64 (0.06)	(-0.77, -0.52)	<0.001*

* Statistical significance at 5% level

The progress of decrease in HbA1c is depicted in Figure 4. Significant decrease was seen by 4 weeks with a nadir at 32 weeks followed by a small increase in both groups by the end of study.

Both treatments significantly reduced fasting plasma glucose, pioglitazone being more effective than vildagliptin (1.64 v 0.98 mmol/L respectively). No statistical analysis of the difference between treatments is included but the 95% CIs do not overlap.

Figure 4: Graphical Display of results for Study CLAF237A2354



Pioglitazone was associated with a small but significant gain in weight (2.61± 0.25 kg) whereas the vildagliptin group gained a non-significant amount (0.21±0.19 kg).

Oedema was reported frequently but equally for the two treatments 10.8% vs. 11.1% for vildagliptin and pioglitazone respectively with 4.7% vs. 5.5% suspected to be drug related.

Extensions of Previously Submitted Trials

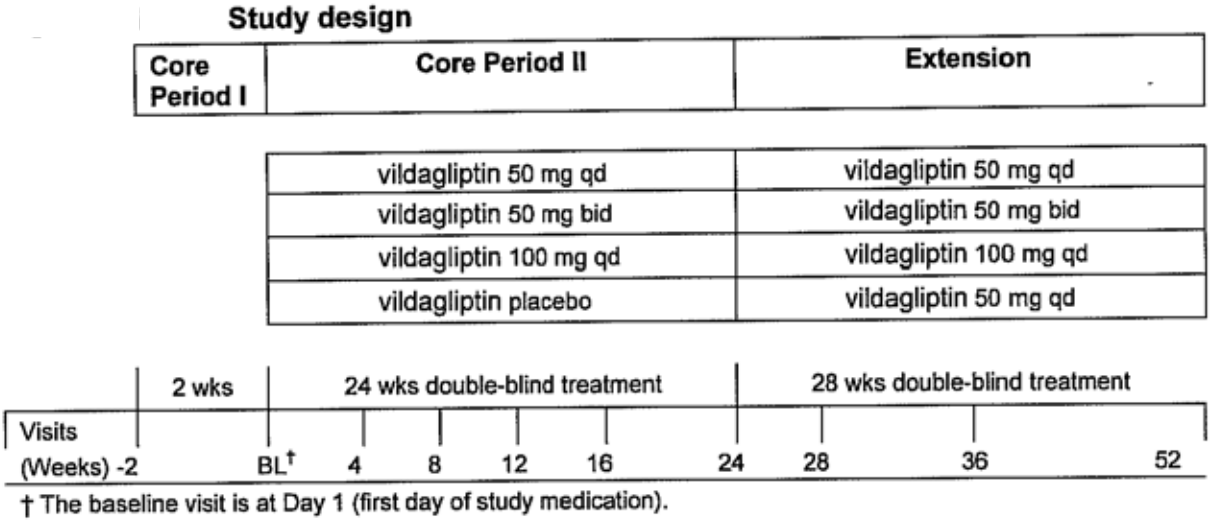
Study CLAF237A2301E1 was an extension to 52 weeks of the 24 week Study 2301 included in the earlier submission, comparing 3 doses of vildagliptin (50 mg once daily [od], 50 mg bd, 100mg daily) and placebo. In this extension, those initially receiving placebo were allocated to the 50 mg daily dose, so it was essentially uncontrolled. This is illustrated in Figure 5. After Week 28, if fasting plasma glucose was≥10 mmol./L, rescue metformin could be added to the allocated regimen according to local prescribing practice.

Inclusion criteria may be summarized as follows;

- Male and female drug naïve patients with type 2 diabetes aged in the range of 18 to 80 years
- Body mass index (BMI) in the range of 22-45 kg/m2 inclusive at Visit 1.
- HbA1c in the range of 7.5 to 10% inclusive, and FPG < 270 mg/dL (15 mmol/L) at visit 1.
- Agreement to maintain prior diet and exercise habits during the full course of the study, and ability to comply with all study requirements.

The final visit of the core study (Visit 7, Week 24) was also the first visit of the extension study. Additional extension study visits were scheduled at Weeks 28, 36 and 52..

Figure 5: Study Design for CLAF237A2301E1



The primary efficacy variable was the change in HbA1c from core baseline at the end of the extension study. HbA1c measurements obtained after patients started rescue medication were excluded from primary analysis. Endpoint was

- the last available post-Week 24 assessment obtained before or at the start of rescue medication, or
- up to the last regular scheduled visit for patients not on rescue medication.

Baseline HbA1c was the measurement obtained on the day of randomization (Day 1, Visit 2), or the closest prior measurement to Day 1 (including scheduled and unscheduled visits) if the Day 1 measurement was missing.

Of the 440 patients eligible and agreeing to continue into this extension study, 390 (89%) completed their participation. Baseline demographic and disease characteristics were acceptably matched.

Results

A decrease in mean HbA1c, the primary efficacy variable, was found for all groups but was least and not statistically significant for the placebo/vildagliptin 50 mg daily group. These results are shown in Table 14. However, comparison with the mean % change from the Week 24 value (Table 15) shows that for those taking vildagliptin throughout, HbA1c had risen by the end of the extension, to account for ~ half of the improvement observed at the end of the core study.

Table 14: Change in HbA_{1c} (%) from core baseline to extension study endpoint (extension ITT and extension PP population)

Treatment	n	Baseline mean (SE)	Unadjusted mean change from baseline (SE)	95% CI for change from baseline	p-value for change from baseline
Extension ITT population					
Vilda 50 mg od (core + ext)	90	7.98 (0.08)	-0.50 (0.15)	(-0.81, -0.20)	0.001*
Vilda 50 mg bd (core + ext)	87	8.09 (0.10)	-0.58 (0.17)	(-0.92, -0.24)	0.001*
Vilda 100 mg od (core + ext)	89	8.04 (0.10)	-0.65 (0.14)	(-0.93, -0.36)	<0.001*
Placebo/Vilda 50 mg od	83	8.03 (0.10)	-0.29 (0.18)	(-0.64, 0.06)	0.106
Extension PP population					
Vilda 50 mg od (core + ext)	59	8.07 (0.08)	-0.73 (0.18)	(-1.08, -0.37)	<0.001*
Vilda 50 mg bd (core + ext)	59	8.43 (0.11)	-0.94 (0.18)	(-1.30, -0.57)	<0.001*
Vilda 100 mg od (core + ext)	66	8.33 (0.09)	-080 (0.16)	(-1.12, -0.48)	<0.001*
Placebo/Vilda 50 mg od	58	8.37 (0.10)	-0.72 (0.18)	(-1.09, -0.36)	<0.001*

* Statistical significance at 5% level

Table 15: Change in HbA_{1c} (%) from Week 24 to extension study endpoint (extension ITT and extension PP population)

Treatment	n	Week 24 mean (SE)	Unadjusted mean change from Week 24 (SE)	95% CI for change from Week 24	p-value for change from Week 24
Extension ITT population					
Vilda 50 mg od (core + ext)	111	7.18 (0.10)	0.40 (0.08)	(0.24, 0.56)	<0.001*
Vilda 50 mg bd (core + ext)	106	7.09 (0.12)	0.40 (0.06)	(0.28, 0.53)	<0.001*
Vilda 100 mg od (core + ext)	110	7.05 (0.09)	0.38 (0.07)	(0.23, 0.52)	<0.001*
Placebo/Vilda 50 mg od	104	7.58 (0.13)	0.11 (0.09)	(-0.07, 0.30)	0.225
Extension PP population					
Vilda 50 mg od (core + ext)	78	7.03 (0.11)	0.44 (0.09)	(0.26, 0.62)	<0.001*
Vilda 50 mg bd (core + ext)	76	7.04 (0.12)	0.40 (0.08)	(0.24, 0.56)	<0.001*
Vilda 100 mg od (core + ext)	85	7.13 (0.10)	0.37 (0.08)	(0.20, 0.54)	<0.001*
Placebo/Vilda 50 mg od	76	7.53 (0.14)	0.02 (0.08)	(-0.14, 0.17)	0.825

* Statistical significance at 5% level

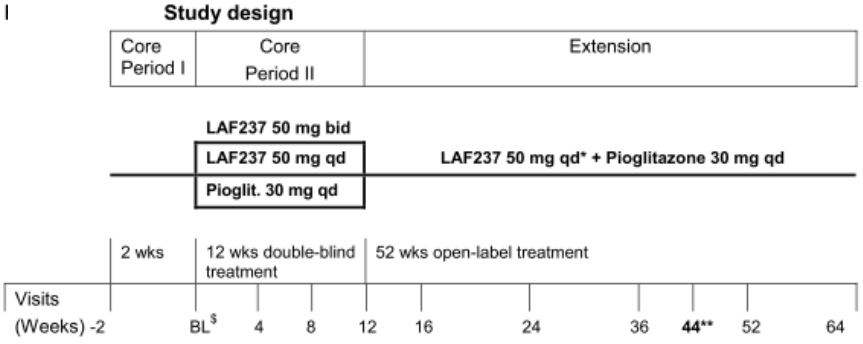
For those initially on placebo, commencing vildagliptin at Week 24 was followed by a mean increase in HbA1c by the end of study accounting for ~a third of the reduction that had been observed while on placebo. The mean fall in HbA1c during the 24 week placebo core study period, had been <half of the falls seen with vildagliptin dosing. The above conclusions based

on the mean figures have limited value for evaluating durability of the response to vildagliptin, since they are from the ITT population so that mean values for the two baselines and endpoint do not reflect the actual observed HbA1c levels at the stated times. However values from the PP population who completed≥24 weeks of the extension phase show similar results. Nonetheless, no firm conclusions can be drawn in the absence of a placebo group during the extension phase.

The proportion of patients classified as a responder by various criteria was a secondary variable. Between 37.5% and 42.5% of those taking vildagliptin throughout achieved an HbA1c <7% and 22.9-26.4%, an HbA1c <6.5%. The performance of the placebo/vildagliptin group was comparable (34.9% and 22.3 respectively).

Study 2329E1 was a 52 week extension of the 12-week study 2329, that was part of the original submission. The primary variable in the latter compared responses to vildagliptin 50 mg once daily and bd dosing but included a group treated with pioglitazone 30 mg daily. In Study 2329E1, all consenting patients who had achieved a reduction of HbA1c from baseline of 0.3 % or more, were transferred to vildagliptin 50 mg plus pioglitazone 30 mg, each once daily. From Week 24 onwards, vildagliptin was to be titrated to 50 mg bd if FPG was >10mmol/L.

I **Study design**



$ The baseline visit is at Day 1 (first day of study medication).

* From week 24 onwards, vildagliptin was to be titrated to 50 mg bid if FPG was >180mg/dL (10mmol/L).

** Additional visit required in Canada only.

The main focus was on longer term safety but a primary efficacy variable nominated was change in HbA1c at endpoint from the value at Week 12. A total of 200 patients entered the study. Of the 200 patients enrolling in the extension phase of the study, 43 (21.5%) had the vildagliptin dose increased to 50 mg bd after Week 24 (see above).

Mean reduction of HbA1c at endpoint from a Week 12 baseline, are shown in Table 16. The mean reduction for the whole group was 0.83%. The decrease was less for those taking vildagliptin 50 mg bd in Study 2329 possibly due to the more effective lowering of HbA1c by the higher dose during the core study reflected in the lower Week 12 baseline. No formal statistical evaluation was performed.

Around one third of patients were classified as responders, slightly more if the criterion used was HbA1c ≤7.0%, and slightly fewer if the cut-off was ≤6.5%.

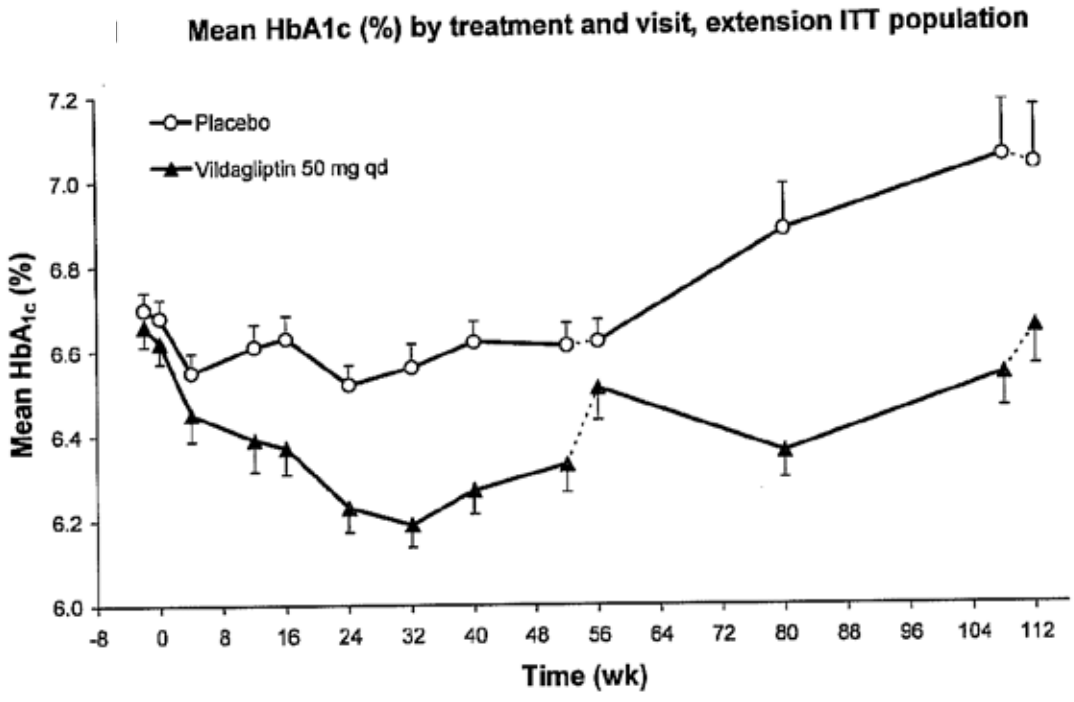
Table 16: Study CLAF237A2329E1 – Mean change in HbA_{1c} (%) from extension baseline to endpoint (extension ITT and PP population)

Treatment	n	Corresponding baseline mean (SE)	Mean change (CI)
Extension ITT population			
Vilda 50 mg od	78	8.40 (0.16)	-0.99 (-1.18, -0.81)
Vilda 50 mg bd	83	8.11 (0.16)	-0.80 (-1.82, -0.38)
Pio 30 mg od	33	8.17 (0.29)	-1.03 (-1.34, -0.72)
Total	194	8.24 (0.11)	-0.83 (-0.96, -0.70)
Extension PP population			
Vilda 50 mg od	55	8.00 (0.14)	-1.06 (-1.29, -0.83)
Vilda 50 mg bd	61	7.88 (0.16)	-0.72 (-0.98, -0.46)
Pio 30 mg od	26	7.97 (0.26)	-1.14 (-1.51, -0.78)
Total	142	7.94 (0.10)	-0.93 (-1.09, -0.77)

Study 2307E1 compared the effect of an extension of 52 weeks treatment with vildagliptin 50 mg once daily to that of placebo in drug- naïve patients with Type 2 Diabetes and mild hyperglycemia (HbA1c 6.2-7.5%). Mean exposure through core and extension studies was >100 weeks in both vildagliptin and placebo arms.

The end of study result indicated that in the placebo group, the HbA1c had risen significantly from core study baseline but that for the vildagliptin group, the rise was neither statistically nor clinically significant (Figure 6).

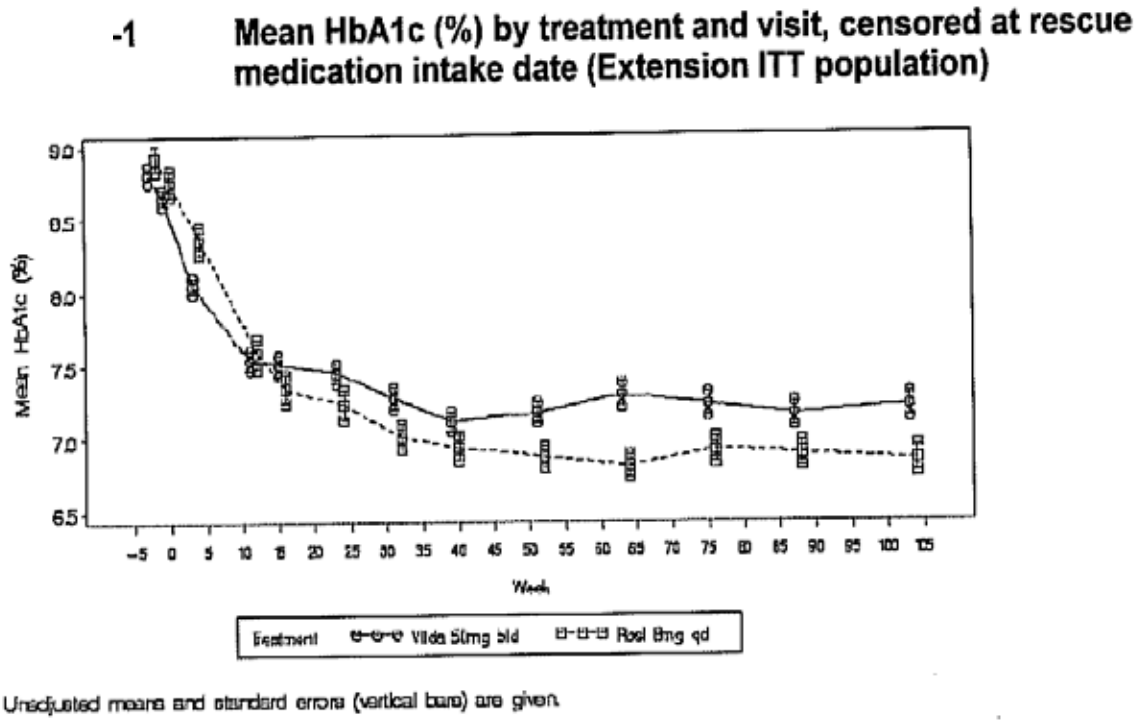
Figure 6: Graphical Results for Study CLAF237A2307E1



Study 2327E1 was an 80-week extension of a 24-week comparison of vildagliptin 50 mg bd and rosiglitazone 8 mg daily in patients with HbA1c 7.5-11.0%. Mean exposure through the core and extension phases was 93 and 94 weeks for vildagliptin and rosiglitazone respectively.

Both treatments maintained clinically and statistically significant decreases from baseline in mean HbA1c at end of study, however this was greater with rosiglitazone (Figure 7).

Figure 7: Graphical Results for Study LAF237A2327E1



Other Studies

Study 2398 compared vildagliptin 100 mg once daily and metformin 1500 mg /day in treatment for 24 weeks, of patients aged ≥65 years with Type 2 diabetes mellitus. The results are thus not directly relevant to the claimed indication as add-on treatment to metformin. The results of the trial indicated non-inferiority of vildagliptin to metformin using a margin of 0.3% but the difference (vildagliptin-metformin) of 0.11%, 95% CI (-0.08, –0.28) shows that the study narrowly missed demonstrating superiority of metformin monotherapy.

Other Issues

The objections raised by ADEC to the use of vildagliptin as an adjunct to insulin, have been addressed by the sponsor with the following arguments:

- Study 2311, previously submitted, showed at 24 weeks a small but statistically significant beneficial effect on HbA1c of vildagliptin 50 mg bd compared to placebo when added to an insulin regimen. In the previously submitted extension (Study 2311E1) the unadjusted mean change from the original baseline was maintained at end of study with a non-significant increase of 0.04% whereas the unadjusted mean decrease in the original

placebo group who received vildagliptin from week 24, was –0.35%. These statements are confirmed by reference to tables included in the two previous evaluations.

- A subset analysis of data from Study 2311 found greater responses to vildagliptin at week 24 in patients aged ≥65 years than that seen in the whole cohort during treatment with vildagliptin (-0.7% v -0.51%). In the extension this was more marked (-0.9% v –0.24%). The sponsor further claims that a previously submitted subset analysis of adverse events revealed no age-related difference in occurrence of adverse events. Data to substantiate these claims were not available to the evaluator but are stated to have been provided in prior submissions.
- In Study 2311 there was a difference in incidence of hypoglycaemia (1.95 v 2.96 events / patient year) favouring vildagliptin. Also fewer were severe episodes, that is, requiring assistance (0 v 0.1 events /patient year). In the vildagliptin group 33/125 patients reported 113 events and in the placebo group 45/131 patients reported 185 events, 6/46 of them severe. The corresponding figures for patients aged≥65 years were 6 patients reporting 43 events for vildagliptin and 12/47 patients reporting 50 events for placebo. The speculation put forward is that an improvement in alpha-cell function due to vildagliptin optimises glucagon responses thus reducing hypoglycaemia. This may be possible, but is unsupported in the present submission. Reference to information available in previous evaluations generally support that hypoglycaemia was less common when vildagliptin was added to insulin but the figures quoted do not exactly match those given above. No data for the older group appear in the earlier evaluation.

Summary of Efficacy

In an interim analysis of a planned 5-year comparison of vildagliptin 50 mg bd and glimepiride 6 mg daily, the former was found to be non-inferior to glimepiride using a margin of 0.3%. However mean reduction in HbA1c was less with vildagliptin. The mean reduction in HbA1c rose to a similar extent with both drugs from a nadir at ~32 weeks.

In a comparison over 12 months of vildagliptin 50 mg bd and pioglitazone 30 mg daily, as add-on to metformin, both drugs resulted in statistically significant reductions in HbA1c level at end of study. The decrease reached a nadir at ~32 weeks followed by a small rise in both groups. No analysis was made of difference between the groups.

Three extensions of previously reviewed studies are consistent with maintenance of a reduction of HbA1c from baseline due to vildagliptin, but that it may diminish with time. One extension study of 50 mg once daily found no reduction after 2 years maintenance of reduction of HbA1c. However the placebo group in that study experienced a clinically and statistically significant rise in mean HbA1c over that period.

The sponsor has responded to ADEC's concerns about vildagliptin as an add-on to insulin by quoting results of a pre-specified sub-group analysis showing that patients aged≥65 years have a substantially more robust and sustained response to the addition of vildagliptin than was seen with the whole population. In the full dataset, the mean increase in daily insulin dose was 2.33 U greater with placebo than with vildagliptin. However hypoglycaemic events were somewhat less frequent or severe (22.9%, 0 severe v 29.6%, 6 severe).

Safety

Integrated summary

Discussion of safety in a previous evaluation of vildagliptin was based on data from trials completed at that time. The summary submitted with this application brings the compilation

up to date as of August 2008, including data from the 36 trials. The extent of exposure to the various regimens is shown in Table 17.

Table 17: Duration of Exposure and Total Subject Exposure

	Vilda 50 mg od	Vilda 50 mg bd	Vilda 100 mg od	Total Vilda	Total Placebo	Total Comparators
All studies safety (excl open label) population*						
Patient (N)	2033	5601	1592	9226	1426	5667
Mean duration (weeks)	31.8	63.9	24.2	50.0	25.3	55.4
Exposure (SYE)	1239.9	6860.9	736.9	8837.7	691.8	6021.5
All studies safety (incl open label) population*						
Patient (N)	2190	5644	3439	11273	1426	6539
Mean duration (weeks)	32.7	63.8	17.6	43.6	25.3	49.6
Exposure (SYE)	1371.2	6898.4	1157.2	9426.8	691.8	6214.1

SYE (years) For each treatment is calculated as (duration of exposure in days, disregarding any treatment interruptions, for all subjects on that treatment group)/365.25.
* In studies followed by an extension, the "switch" patients (those who changed treatment from core phase to extension phase) contributed twice to the all studies safety population.

Demographic characteristics were similar for all regimens apart from more Hispanic and fewer Caucasians in the vildagliptin 100mg once a day population.

Those adverse events (AEs) occurring in ≥2% of any group are listed in Table 18. Total incidence of AEs was greater with the 50 mg bd dose than with either 50mg or 100 mg once daily, presumably due to greater exposure. The sponsor plausibly suggests that comparison of vildagliptin 50 mg bd and all comparators is most informative because those populations are most similar in size and exposure. The nature and incidence of AEs between them is very similar except for tremor (3.1% v 7.9%), hyperhidrosis (2.9% v 7.0%) and hypoglycaemia reported as such (1.7% v 6.2%) being less frequent in the vildagliptin group. Deaths, serious AEs (SAEs) and discontinuations were reported equally for the two.

The safety population excluding open label studies was categorized according to eGFR (MDRD formula) and incidence of reported AEs compared according to renal function. Exposure was comparable for normal (≥80 ml/min) and mild impairment (≤80 ml/min ≥50 ml/min) but numbers with moderate and severe impairment were small.

Total AE's, total SAEs and discontinuations due to AEs for vildagliptin 50 mg bd and all comparators were of similar incidence in those with normal and mildly impaired renal function. Greater degrees of renal impairment seemed to be associated with higher incidence of these events affecting both vildagliptin and all comparators but more so the former. However the numbers are too small to engender any confidence in that conclusion.

Table 18: Number (%) of Patients Reporting Common AEs (>2% in any pooled group) by Preferred Term

	Vilda 50mg qd N: 2033	**Vilda 50mg bd N: 5601**	**Vilda 100mg qd N: 1592**	**Total Vilda N: 9226**	**Total Placebo N: 1426**	**Total Comparator N: 5667**
Any AE (N (%))	1238 (60.9)	3907 (69.8)	814 (51.1)	5959 (64.6)	882 (61.9)	3940 (69.5)
Nasopharyngitis	134 (6.6)	545 (9.7)	81 (5.1)	760 (8.2)	89 (6.2)	482 (8.5)
Headache	101 (5.0)	415 (7.4)	72 (4.5)	588 (6.4)	52 (3.6)	342 (6.0)
Dizziness	99 (4.9)	372 (6.6)	70 (4.4)	541 (5.9)	67 (4.7)	439 (7.7)
Back pain	80 (3.9)	338 (6.0)	35 (2.2)	453 (4.9)	39 (2.7)	301 (5.3)
Diarrhoea	48 (2.4)	319 (5.7)	42 (2.6)	409 (4.4)	47 (3.3)	390 (6.9)
URTI*	83 (4.1)	307 (5.5)	57 (3.6)	447 (4.8)	65 (4.6)	261 (4.6)
Bronchitis	53 (2.6)	286 (5.1)	22 (1.4)	361 (3.9)	38 (2.7)	252 (4.4)
Influenza	55 (2.7)	276 (4.9)	22 (1.4)	353 (3.8)	65 (4.6)	261 (4.6)
Arthralgia	62 (3.0)	275 (4.9)	26 (1.6)	363 (3.9)	34 (2.4)	217 (3.8)
Hypertension	56 (2.8)	268 (4.8)	39 (2.4)	363 (3.9)	29 (2.0)	279 (4.9)
Nausea	54 (2.7)	230 (4.1)	35 (2.2)	319 (3.5)	38 (2.7)	248 (4.4)
Pain in extremity	63 (3.1)	203 (3.6)	28 (1.8)	294 (3.2)	41 (2.9)	215 (3.8)
Fatigue	55 (2.7)	200 (3.6)	28 (1.8)	283 (3.1)	29 (2.0)	133 (4.1)
Cough	45 (2.2)	194 (3.5)	21 (1.3)	260 (2.8)	25 (1.8)	200 (3.5)
UTI**	56 (2.8)	192 (3.4)	31 (1.9)	279 (3.0)	33 (2.3)	170 (3.0)
Asthenia	54 (2.7)	187 (3.3)	31 (1.9)	272 (2.9)	36 (2.5)	282 (5.0)
Tremor	71 (3.5)	173 (3.1)	25 (1.6)	271 (2.9)	61 (4.3)	446 (7.9)
Oedema peripheral	51 (2.5)	172 (3.1)	26 (1.6)	249 (2.7)	23 (1.6)	213 (3.8)
Constipation	26 (1.3)	166 (3.0)	35 (2.2)	227 (2.5)	20 (1.4)	94 (1.7)
Hyperhidrosis	56 (2.8)	162 (2.9)	13 (0.8)	231 (2.5)	51 (3.6)	395 (7.0)
Dyspepsia	22 (1.1)	145 (2.6)	15 (0.9)	182 (2.0)	15 (1.1)	128 (2.3)
Abdominal pain upper	29 (1.4)	136 (2.4)	20 (1.3)	185 (2.0)	16 (1.1)	125 (2.2)
Osteoarthritis	26 (1.3)	131 (2.3)	13 (0.8)	170 (1.8)	12 (0.8)	124 (2.2)
Sinusitis	44 (2.2)	129 (2.3)	25 (1.6)	198 (2.1)	39 (2.7)	130 (2.3)
Musculoskeletal pain	27 (1.3)	126 (2.2)	15 (0.9)	168 (1.8)	19 (1.3)	126 (2.2)
Vomiting	20 (1.0)	124 (2.2)	20 (1.3)	164 (1.8)	19 (1.3)	97 (1.7)
Depression	25 (1.2)	122 (2.2)	9 (0.6)	156 (1.7)	20 (1.4)	101 (1.8)
Abdominal pain	12 (0.6)	121 (2.2)	13 (0.8)	146 (1.6)	16 (1.1)	115 (2.0)
Paraesthesia	32 (1.6)	120 (2.1)	16 (1.0)	168 (1.8)	18 (1.3)	140 (2.5)
Myalgia	29 (1.4)	117 (2.1)	11 (0.7)	157 (1.7)	23 (1.6)	104 (1.8)
Hypoglycaemia	40 (2.0)	96 (1.7)	11 (0.7)	147 (1.6)	52 (3.6)	352 (6.2)

* URTI = upper respiratory tract infection, ** UTI = urinary tract infection

Hepatic Safety was of particular concern to ADEC. Incidence in this entire new dataset of persisting abnormalities of liver function tests (that is, found in two consecutive estimations) is higher in those taking vildagliptin than of all active comparators. The percentage of abnormalities is low in all categories and there is no increase with dose. Abnormalities are slightly more frequent with a vildagliptin dose of 50 mg bd than with either 50 mg or 100 mg once daily, again probably reflecting exposure. There were, however, no significant differences between any individual dose of vildagliptin and all comparators, for three degrees of abnormality of hepatic function tests (≥3X the upper limit of normal [ULN], ≥5X ULN or ≥3 X ULN + bilirubin >ULN). The 95% CI's for the odds ratios all overlap unity.

The incidence of more marked abnormalities was low and not clearly different between vildagliptin, placebo and other comparators.

The incidence of various hepatic adverse events shows no convincing difference among vildagliptin doses and comparators. However, that ascites occurred slightly more frequently in the vildagliptin groups is intriguing in light of the curious phenomenon of oedema reported at doses of 400 and 600 mg in an early study.

Safety of once and twice daily administration of a total daily dose

The contention that there is a safety advantage in giving a 100 mg daily dose as two divided doses rather than as a single dose is feasible since, as would be anticipated, Study 2221 demonstrated that the former method of administration resulted in lower $C_{max,}$ although the total exposure was the same. The incidence of adverse effects in that pharmacokinetic study was too small to support or refute the hypothesis. However, the integrated listing of adverse events shows that all AEs occurring with a frequency of≥2% are more frequent in the 50 mg bd than in the 100 mg once daily population (Table 18). This is also the case for SAE's, deaths and discontinuations (Table 19) and for abnormal hepatic function tests. These simple comparisons are biased by the degree of exposure.

Table 19: Number (%) of patients who had SAEs, AEs leading to discontinuation or died

	Vilda 50mg qd N: 2033	**Vilda 50mg bd N: 5601**	**Vilda 100mg qd N: 1592**	**Total Vilda N: 9226**	**Total Placebo N: 1426**	**Total Comparator N: 5667**
SAEs	110 (5.4)	511 (9.1)	47 (3.0)	668 (7.2)	83 (5.8)	508 (9.0)
Discontinuation of study drug due to AEs	95 (4.7)	313 (5.6)	53 (3.3)	461 (5.0)	47 (3.3)	375 (6.6)
Deaths	1 (0.0)	23 (0.4)	2 (0.1)	26 (0.3)	2 (0.1)	22 (0.4)

Long-term safety

Safety data from the new studies 2308 and 2354 were included in the integrated safety summary.

In **Study 2308**, exposure to vildagliptin 50 mg bd and the comparator glimepiride 6mg /day, were very similar (mean 46.83 v 44.77 weeks; median ~52 for both).

Most adverse events were reported with roughly equal frequency in the two groups but there was excess of asthenia, tremor, hyperhidrosis, hunger and nervousness – all likely to reflect hypoglycaemia - which was reported as such in 16.3% v 1.7% for glimepiride and vildagliptin respectively (Table 20). There were 2 deaths in the vildagliptin group and 3 with glimepiride. None were drug-related.

Table 20: AEs from Study 2308 – Number (%) of patients reporting common AEs up to and including Week 52 Visit (≥2% in any group) by preferred term (interim analysis safety population)

Preferred term (PT)	**Vilda 50mg bd + Met N: 1389 n (%)**	**Glim up to 6 mg + Met N: 1383 n (%)**
Any PT (N (%))	1035 (74.5)	1121 (81.1)
Nasopharyngitis	131 (9.4)	129 (9.3)
Headache	106 (7.6)	109 (7.9)
Dizziness	91 (6.6)	188 (13.6)
Influenza	79 (5.7)	60 (4.3)
Diarrhoea	76 (5.5)	71 (5.1)
Back pain	75 (5.4)	71 (5.1)
Bronchitis	63 (4.5)	62 (4.5)
Arthralgia	60 (4.3)	46 (3.3)
URTI	58 (4.2)	53 (3.9)
Cough	57 (4.1)	48 (3.5)
Fatigue	57 (4.1)	90 (6.5)
Nausea	56 (4.0)	71 (5.1)
Asthenia	53 (3.8)	144 (10.4)
Tremor	52 (3.7)	276 (20.0)
Pain in extremity	50 (3.6)	63 (4.6)
Hypertension	49 (3.5)	66 (4.8)
Constipation	48 (3.5)	28 (2.0)
Dyspepsia	47 (3.4)	37 (2.7)
Hyperhidrosis	46 (3.3)	240 (17.4)
Abdominal pain upper	45 (3.2)	26 (1.9)
Muscle spasms	36 (2.6)	21 (1.5)
Paraesthesia	35 (2.5)	43 (3.1)
UTI	35 (2.5)	33 (2.4)
Osteoarthritis	33 (2.4)	30 (2.2)
Hypoaesthesia	31 (2.2)	31 (2.2)
Musculoskeletal pain	31 (2.2)	29 (2.1)
Abdominal pain	30 (2.2)	19 (1.4)
Anxiety	28 (2.0)	30 (2.2)
Insomnia	28 (2.0)	20 (1.4)
Vomiting	28 (2.0)	19 (1.4)
Hypoglycaemia	23 (1.7)	225 (16.3)
Sinusitis	22 (1.6)	27 (2.0)
Oedema peripheral	21 (1.5)	43 (3.1)

Vertigo	19 (1.4)	43 (3.1)
Palpitations	14 (1.0)	32 (2.3)
Blood glucose increased	13 (0.9)	53 (3.8)
Malaise	12 (0.9)	39 (2.8)
Hunger	10 (0.7)	71 (5.1)
Nervousness	10 (0.7)	35 (2.5)
Muscular weakness	9 (0.6)	30 (2.2)

In **Study 2354** pioglitazone 30 mg /day was the comparator and exposure was similar for each group (mean 46.8 v 46.1 weeks, median 52.0 v 52.0 weeks, for vildagliptin and pioglitazone respectively). Both treatments were well tolerated but there were slightly more gastrointestinal complaints with vildagliptin (Table 21). There were no deaths in either group. There were many single reports of individual SAEs in 12/295 patients taking vildagliptin and 25/280 taking pioglitazone.

Table 21: AEs from Study 2354, number (%) of patients reporting common AEs up to and including Week 52 (≥2% in any group) by preferred term

Preferred term (PT)	**Vilda 50mg bd + Met N: 295 n (%)**	**Pio 30 mg + Met N: 280 n (%)**
Any primary system organ class	200 (67.8)	191 (68.2)
Oedema peripheral	32 (10.8)	31 (11.1)
Headache	19 (6.4)	17 (6.1)
Nasopharyngitis	16 (5.4)	20 (7.1)
Back pain	15 (5.1)	15 (5.4)
Dizziness	15 (5.1)	11 (3.9)
Diarrhoea	14 (4.7)	14 (5.0)
Arthralgia	12 (4.1)	9 (3.2)
Fatigue	12 (4.1)	5 (1.8)
Constipation	10 (3.4)	4 (1.4)
Nausea	10 (3.4)	5 (1.8)
Pain in extremity	10 (3.4)	11 (3.9)
Vomiting	10 (3.4)	4 (1.4)
Gastroenteritis	9 (3.1)	2 (0.7)
Influenza	9 (3.1)	9 (3.2)
Dyspepsia	8 (2.7)	3 (1.1)
Hypertension	8 (2.7)	9 (3.2)
Lower RTI	8 (2.7)	9 (3.2)
Pharyngolaryngeal pain	8 (2.7)	1 (0.4)
URTI	8 (2.7)	11 (3.9)
Bronchitis	7 (2.4)	12 (4.3)

Depression	7 (2.4)	5 (1.8)
Osteoarthritis	7 (2.4)	6 (2.1)
Hyperhidrosis	6 (2.0)	4 (1.4)
Pruritus	6 (2.0)	4 (1.4)
Cough	4 (1.4)	14 (5.0)
Paraesthesia	4 (1.4)	7 (2.5)
Sinusitis	4 (1.4)	6 (2.1)
UTI	4 (1.4)	19 (3.6)
Musculoskeletal pain	3 (1.0)	7 (2.5)

Study 2307E1 compared the effect of 52 weeks treatment with vildagliptin 50 mg once daily to that of placebo in drug- naïve patients with Type 2 Diabetes and mild hyperglycemia (HbA1c 6.2-7.5%). Mean exposure through core and extension studies was >100 weeks in both vildagliptin and placebo arms. There are considerable differences between vildagliptin and placebo arms in the incidence of individual adverse events but this probably relates to the relatively small numbers studied and the pattern does not suggest a systematic difference (Table 22). There were no deaths during treatment and the pattern of SAEs was not remarkable.

Table 22: AEs Reported in Study 2307E1, number (%) of patients reporting common AEs (greater than or equal to 3% in any group) by preferred term during the overall core and extension study period up to Week 108 (extension ITT population)

Preferred term (PT)	**Vilda 50mg od N: 68 n (%)**	**Placebo N: 63 n (%)**
Any PT	57 (83.8)	56 (88.9)
Back pain	11 (16.2)	3 (4.8)
Arthralgia	9 (13.2)	4 (6.3)
Osteoarthritis	9 (13.2)	2 (3.2)
Bronchitis	8 (11.8)	11 (17.5)
Nasopharyngitis	8 (11.8)	6 (9.5)
Depression	6 (8.8)	2 (3.2)
Hypertension	6 (8.8)	2 (3.2)
Eczema	5 (7.4)	3 (4.8)
Gastritis	5 (7.4)	2 (3.2)
Headache	5 (7.4)	1 (1.6)
Cervicobrachial syndrome	4 (5.9)	1 (1.6)
Influenza	4 (5.9)	7 (11.1)
Joint sprain	4 (5.9)	2 (3.2)
Musculoskeletal pain	4 (5.9)	4 (6.3)
Sciatica	4 (5.9)	3 (4.8)
Asthenia	3 (4.4)	2 (3.2)

Dizziness	3 (4.4)	3 (4.8)
Fatigue	3 (4.4)	2 (3.2)
Herpes zoster	3 (4.4)	0 (0.0)
Pharyngitis	3 (4.4)	2 (3.2)
UTI	3 (4.4)	3 (4.8)
Abdominal pain	2 (2.9)	2 (3.2)
Conjunctivitis	2 (2.9)	3 (4.8)
Confusion	2 (2.9)	2 (3.2)
Cough	2 (2.9)	6 (9.5)
Diarrhoea	2 (2.9)	3 (4.8)
Gastroenteritis	2 (2.9)	4 (6.3)
Hyperhidrosis	2 (2.9)	2 (3.2)
Myalgia	2 (2.9)	3 (4.8)
Oedema peripheral	2 (2.9)	2 (3.2)
Pneumonia	2 (2.9)	2 (3.2)
Vertigo	2 (2.9)	2 (3.2)
Wound	2 (2.9)	3 (4.8)
Anxiety	1 (1.5)	2 (3.2)
Cataract	1 (1.5)	2 (3.2)
Epistaxis	1 (1.5)	3 (4.8)
Hypercholesterolaemia	1 (1.5)	3 (4.8)
Hypersensitivity	1 (1.5)	2 (3.2)
Onychomycosis	1 (1.5)	2 (3.2)
Pyrexia	1 (1.5)	2 (3.2)
Sinusitis	1 (1.5)	3 (4.8)
Sleep disorder	1 (1.5)	3 (4.8)
Tremor	1 (1.5)	2 (3.2)
Anaemia	0 (0.0)	2 (3.2)
Bursitis	0 (0.0)	2 (3.2)
Conjunctivitis allergic	0 (0.0)	2 (3.2)
Electrocardiogram T wave amplitude decreased	0 (0.0)	2 (3.2)
Glaucoma	0 (0.0)	3 (4.8)
Hypoglycaemia	0 (0.0)	2 (3.2)
Melaena	0 (0.0)	2 (3.2)
Otitis externa	0 (0.0)	2 (3.2)
Rotator cuff syndrome	0 (0.0)	2 (3.2)
Vomiting	0 (0.0)	3 (4.8)

Study 2310 compared vildagliptin 50 mg bd and gliclazide up to 320 mg daily in patients with poorer control than in Study 2307 (HbA1c's of 7.5-11.0%).

Mean exposure was 89.12 and 87.95 weeks for vildagliptin and gliclazide respectively. Adverse events were not unusual in nature or frequency and did not differ greatly between the groups. There were six deaths in the vildagliptin group (2 patients died due to cardiac arrest, 3 due to myocardial infarction and one due to acute myocardial infarction) and 9 died in the gliclazide group (2 due to cardiac failure, 2 due to cerebral accident, and one patient each due to myocardial ischemia, pneumonia, peritoneal sarcoma, ischaemia and angioedema). SAEs did not differ materially between the two groups.

Study 2327E1 was an 80-week extension of a 24-week comparison of vildagliptin 50 mg bd and rosiglitazone 8 mg daily in patients with HbA1c 7.5-11.0%. Mean exposure through the core and extension phases was 93 and 94 weeks for vildagliptin and rosiglitazone respectively.

Adverse events were equally common in the two groups (85.5% and 85.9% for vildagliptin and rosiglitazone respectively). Most were not drug-related and occurred equally in the two groups. Dizziness, nausea and depression were somewhat more common with vildagliptin but weight increase, muscle spasms, hyperlipidaemia, peripheral oedema, fatigue, and pain in extremities were seen more often with rosiglitazone (Table 23).

Table 23: AEs Reported in Study 2327E1, number (%) of patients reporting common AEs (greater than or equal to 5% in any group) by preferred term, including all events regardless of rescue medication use (extension safety population)

Preferred term (PT)	**Vilda 50mg bd N: 393 n (%)**	**Rosi 8 mg od N: 198 n (%)**
Any PT	336 (85.5)	170 (85.9)
Nasopharyngitis	51 (13.0)	30 (15.2)
Dizziness	47 (12.0)	11 (5.6)
URTI	34 (8.7)	14 (7.1)
Arthralgia	33 (8.4)	14 (7.1)
Back pain	33 (8.4)	11 (5.6)
Hypertension	33 (8.4)	15 (7.6)
Bronchitis	30 (7.6)	21 (10.6)
Headache	30 (7.6)	13 (6.6)
Nausea	27 (6.9)	6 (3.0)
Diarrhoea	24 (6.1)	8 (4.0)
Depression	23 (5.9)	4 (2.0)
Sinusitis	21 (5.3)	14 (7.1)
Cough	20 (5.1)	17 (8.6)
Musculoskeletal pain	20 (5.1)	10 (5.1)
Oedema peripheral	18 (4.6)	22 (11.1)
Fatigue	16 (4.1)	14 (7.1)
Influenza	16 (4.1)	11 (5.6)
Pain in extremity	15 (3.8)	11 (5.6)

Hyperlipidaemia	11 (2.8)	11 (5.6)
Muscle spasms	7 (1.8)	10 (5.1)
Weight increased	6 (1.5)	19 (9.6)

Safety in the elderly

Study 2398 compared vildagliptin 100 mg daily with metformin 1500 mg per day in drug-naïve patients aged ≥65 years with T2DM (HbA1c 7-9%) over 24 weeks.

Mean and median exposures were 21.7 and 24 weeks for vildagliptin and 21.5 and 24 weeks for metformin.

AEs were reported less frequently than in the integrated dataset and their pattern was not remarkable. Diarrhoea was much more common with metformin.

In the integrated safety compilation, the pooled "add-on to metformin" dataset comprised ~24% of subjects aged ≥65 years. In these elderly patients receiving any dose of vildagliptin added to metformin, the incidence of hypoglycemia (0.4%) was slightly lower than that in patients <65 years of age (0.7%) and all events in the elderly subgroup were mild in severity.

Summary of Safety

The updated sponsor's integrated safety summary includes data from 8838 patient-years of exposure to vildagliptin and 6022 patient-years exposure to assorted active comparators and placebo. Hypoglycaemia and symptoms suggestive of it (tremor and hyperhidrosis) were more frequently seen in the active comparator/placebo group and hepatobiliary disorders in the vildagliptin group.

There was no difference in incidence of adverse events in patients taking vildagliptin who had mild renal impairment, compared with those with normal renal function. Moderate and severe renal impairment seem to be associated with greater frequency of adverse events associated with both vildagliptin and active comparators but the numbers of patients are insufficient to clarify the matter.

Abnormalities of liver function were not reported more frequently with vildagliptin than with active comparators but two patients were considered to have suffered drug induced liver injury, one taking vildagliptin 50 mg bd and the other, 100mg once daily with pioglitazone 30 mg daily. In both, the abnormality was reversible on withdrawal of the drug.

In five studies of 1-2 years duration, there was no consistent difference between patterns seen with vildagliptin and various comparators except for an excess of hypoglycaemia with glimepiride.

Those aged ≥65 years tolerate vildagliptin at least as well as the whole exposed group.

Post Marketing Experience

Two periodic safety update reports (PSURs) following initial marketing in Mexico on14 February 2007 have been submitted. These cover the periods 01/09/2007 to 28/02/2008 AND 01/03/2008 to 31/08/2008.

Carcinoma of breast was a new potential emerging concern, which was reported more frequently in clinical trials with vildagliptin (0.36/100 subject years exposure (SYE)) than with all comparators (0.18/100 SYE). Both rates fall within a range quoted by the sponsor from the literature of 0.06 – 0.4/100 years. There have been no spontaneous reports of breast cancer. A whole life study in mice is stated to have found increased incidence of mammary

carcinoma, at 156X human exposure (AUC). This matter will be under continuing review by the sponsor.

Clinical Summary and Conclusions

Two pharmacokinetic studies have been provided that are supplementary to data previously submitted. One found that mild renal impairment slightly, but not quite significantly, increased Cmax for vildagliptin with however no effect on AUC_{0-24} and no accumulation over 14 day dosing. The other demonstrated linear kinetics over the dose 200-600mg and that daily exposure (AUC_{0-t}) was the same whether the dose was given as a single or as two divided doses.

An interim analysis at 12 months of a planned 5-year comparison of vildagliptin 50mg bd and glimepiride 6mg daily found a smaller decrease in HbA1c with vildagliptin but that using the pre-set 0.3% margin, it could at this 12 month point be regarded as non-inferior to glimepiride.

The planned 5 year study was subsequently abandoned and a modified study of change in HbA1c from baseline at 2 years was adopted. In both treatment groups, mean HbA1c rose steadily but in both the reduced difference from baseline was significant. The rate of use of HbA1c expressed as a coefficient of failure (i.e., the rate of increase in HbA1c from week 24 to end of study) favoured vildagliptin.

A 12-month comparison of vildagliptin 50mg bd and pioglitazone 30mg daily, as add-on therapy to metformin up to 1500mg/day, found that both drugs lead to significant reduction of mean HbA1c but there was no statistical analysis of the difference between the two drugs which is in favour of pioglitazone.

In both of the above trials and in 3 extensions for varying periods up to 2 years of previously submitted studies, a reduction of mean HbA1c was observed to persist but to diminish somewhat. The pattern over time with active comparators was similar to that with vildagliptin.

The sponsor's response to the concerns of ADEC about efficacy and safety of vildagliptin as a supplement to insulin treatment emphasised that the originally reported beneficial effect was statistically significant but also that the benefit is seen more clearly in a subset of patients aged ≥65 years and in them that it is more sustained than in the total group. There was a lower incidence of hypoglycaemia in that study in those taking vildagliptin compared with those taking placebo and the severity was less. The insulin dose increase was not statistically significantly different in the two groups.

An integrated safety summary includes data from 8838 subject years of exposure (SYE) to vildagliptin and 6214 SYE for assorted active comparators. Adverse event experience was generally comparable except for hypoglycaemia being more common with active comparators and hepato-biliary disorders with vildagliptin.

There was no difference in total or severe adverse events or of discontinuations due to adverse events in patients with normal compared with mildly impaired renal function, for those taking either vildagliptin 50mg bd or all active comparators. There were insufficient numbers of patients with more marked renal impairment to give reliable information. The evidence of hepatotoxicity revealed in the collected data does not raise concern for the safety of vildagliptin in clinical use beyond that for any orally active hypoglycaemic agent.

Comparison of persisting abnormalities of liver function tests in those taking vildagliptin and various comparators in the entire dataset found a non-significantly greater increase of enzyme abnormalities in the vildagliptin group but a similarly non-significantly decreased incidence

of enzyme abnormality together with increased bilirubin. Two patients developed drug induced liver injury with positive dechallenge associated with vildagliptin.

Any difference in adverse effects associated with giving vildagliptin 100mg / day as either a single dose or as 2 divided doses favoured the former but this is most reasonably explained by greater duration of exposure with that regimen due to the duration of the studies. There is a much greater database for the 50 mg bd dose than for either 50 or 100 mg once daily. Twice daily dosing is perfectly feasible. It is likely that the 50 mg once daily dose will be adequate for relatively few patients.

There is no evidence that unexpected toxicity emerged in studies lasting up to 2 years.

In a comparison of vildagliptin and metformin in patients aged $\geq$65 years, the incidence of adverse events was less than that reported in the integrated dataset and adverse events occurred with a similar pattern and frequency with vildagliptin and metformin except for diarrhoea being much more common with the latter.

Review of the collected safety data has found that prevalence of carcinoma of the breast is greater in women taking vildagliptin than in those taking comparators but the sponsor claims that for both groups it is within the range for population values quoted in the literature. There have been no spontaneous reports of breast cancer.

Vildagliptin has efficacy in reducing HbA1c levels in type 2 diabetes mellitus superior to that of placebo but as so far demonstrated less than that of other oral agents, that is, metformin, sulphonylureas and thiazolidinediones. This effect diminishes with time but to a similar extent to that seen with comparators.

The safety profile is acceptable being similar to that of all comparators. Analysis of all controlled trial data revealed doubling of incidence of carcinoma of the breast. No new safety concerns have emerged from studies up to 2 years duration.

The present dosing schedule seems to be reasonable. There is no evidence for benefit from giving a 100mg daily dose as two divided 50mg doses. The option of increasing an initial 50mg dose to 50mg bd is a practical suggestion since some patients may benefit from the lower dose.

The sponsor has provided a comprehensive risk management programme which includes reference to the issues that have been raised at this stage of the drug's life.

Recommendation

The evaluator recommended that vildagliptin be accepted for marketing for improvement of glycaemic control in patients with type 2 diabetes mellitus in conjunction with diet and exercise and as combination therapy with metformin, a sulphonylurea, a thiazolidinedione or insulin when a single agent does not achieve glycaemic control.

A table summarising the action plans for each of 13 potential safety issues that have emerged from theoretical, pre-clinical or clinical studies, was provided.

V. Pharmacovigilance Findings

A formal risk management plan was not submitted or evaluated but the sponsor has provided a comprehensive risk management programme which includes reference to the issues that have been raised at this stage of the drug's life.

VI. Overall Conclusion and Risk/Benefit Assessment

The submission was summarised in the following Delegate's overview and recommendations:

Quality

No new data were submitted. The pharmaceutical chemistry evaluator previously assigned a two year shelf life; chemistry and quality control issues were resolved during the original submission.

Nonclinical

The Delegate had previously summarised the original submission's preclinical findings. Of note, there are still no studies performed in juvenile animals. There were no nonclinical data regarding the effect of vildagliptin on GIP or glucagon, a surprising omission given the suggested effect on these hormones.

New Data

The new data include some *in vitro* data on inhibition of recombinant cynomolgus monkey DPP-4, in vitro selectivity data for DPP-4 versus other enzymes, including DPP-8 and DPP-9, and additional dog and monkey studies. Overall, the evaluator has not revised the principal findings of fact but does not favour registration for combined use owing to a lack of data on the toxicity of vildagliptin when used with other antidiabetic agents.

As originally noted the combination of vildagliptin (3 mg/kg) with nateglinide or pioglitazone respectively yielded additive and synergistic effects on glucose lowering. There were no nonclinical studies to support combination therapy with metformin, a sulfonylurea or insulin. As stated in the latest version of the evaluation report, "The predominant toxicological findings of alveolar macrophage accumulation, GI toxicity and skin toxicity occurred only in a single species or at sufficiently high exposures not to be of clinical concern at the proposed maximum dose. Toxicity studies using vildagliptin in combination with metformin or other proposed combination therapies have not been provided in this or previous submissions (though it is likely that vildagliptin/metformin toxicity studies are contained in the pending application for the fixed-dose vildagliptin/metformin combination). The skin and cutaneous vasculature are the primary targets of toxicity for vildagliptin considered to pose a potential clinical concern. Any proposed combination therapy that may exacerbate or have additive effects on the cutaneous toxicity of vildagliptin is of particular concern."

Subsequently, however, evaluation of nonclinical data contained in the sponsor's subsequent application for registration of a fixed-dose combination of vildagliptin/metformin has now been completed. Briefly, there was no novel toxicity with the combination in studies of up to 13 weeks duration in rats and dogs, and no exacerbation of toxicity except for an increase in the incidence and severity of intra-alveolar accumulation of foamy macrophages in rats at the highest dose tested. This effect is attributable to vildagliptin, is rodent-specific and not considered to pose a clinical hazard. There were no nonclinical objections to the registration of the combination product.

In light of the new data, there are now no nonclinical objections to the registration of Galvus and Xiliarx for use in free combination with metformin.

A reappraisal of cutaneous toxicity in monkeys suggests that vasoconstriction may be causative although the mechanism has not been established.

Overall, the nonclinical data support monotherapy (which is no longer sought) and dual therapy with metformin.

Clinical

Pharmacokinetics

The new clinical data included two pharmacokinetic studies, one of which, CLA237A2117, is a study in subjects with mild renal impairment and the other, study CLA237A2221 is study comparing the effects of bd vs once daily dosing.

Study CLAF237A2117 was an open-label, parallel group study that examined the single and multiple dose pharmacokinetics of vildagliptin and its metabolites in sixteen each of normal and mildly renally impaired non-obese to overweight subjects (creatinine clearance = mean 64.4mL/min +/- standard deviation (sd) 7.0) who received vildagliptin 100mg once daily (od) for 14 days. Nine of the renally impaired subject had diabetes mellitus type 2. The study suggested no accumulation of unchanged drug or of the –O-glucuronide metabolite in patients with mild renal impairment over 14 days but some accumulation of the metabolite LAY151.

As noted in the original submission, "There was some increase in exposure to vildagliptin in patients with severe liver disease (Study 2336). Renal impairment increased exposure to vildagliptin after oral dosing, but this did not relate well to the severity of the reduction in renal function (Study 2337). Haemodialysis of unspecified nature was ineffective in removing vildagliptin."

Study CLAF237A2221 was a placebo-controlled assessment of the pharmacokinetics of 200 mg, 400 mg and 600 mg vildagliptin, comparing administration as a single dose or as two equal divided daily doses to three cohorts of healthy volunteers. Reasonable dose proportionality was shown, in the opinion of the evaluator. The pharmacokinetic results were consistent with the previous study.

Efficacy

Phase 3 Studies:

As in the original submission the two new studies employed intermediate endpoints such as HbA1c – no long term morbidity or mortality studies have been submitted. HbA1c was the primary efficacy endpoint. As before, numerous secondary endpoints were also included (for example. FPG, lipids, body weight, indices of beta cell function, postprandial glucose excursion to 4 hours etc.).

The Delegate noted that a key objective of these studies must be to support the administration of vildagliptin 50mg bd in lieu of 100mg od, given the applicant's hypothesis that such a divided dosing regimen is safer with respect to the risk of hepatotoxicity than is once daily dosing.

The studies were of acceptable design. They are add-on studies in patients who are failing metformin monotherapy. No triple therapy studies were submitted.

Study 2308 is an active-controlled, double-blind, randomised, ongoing parallel group non-inferiority study, originally planned to run for 5 years, comparing the addition to metformin of a fixed dose of vildagliptin 50 mg bd or glimepiride 2mg capsules (titrated up to 6 mg daily). The study involved 402 centres in 25 countries. The evaluator noted that the maximal dose of glimepiride was rather high. Data at weeks 52 and 104 have been reported. Patient numbers were large (approx. 3,118 enrolled).

The five year study was abandoned at 2 years due to the dropout rate. At 52 weeks, glimepiride was superior in terms of response at various targets. As noted by the evaluator, "The decrease was greater in the glimepiride than in the vildagliptin group in both the ITT

and PP populations. In the former, glimepiride was superior to vildagliptin but in the latter vildagliptin was non-inferior using the margin of 0.4% stipulated in the amended [for 104 weeks] protocol." However, the rate of deterioration tended to be greater during the second year in the glimepiride arm of the study. The mean fall from baseline of glycosylated haemoglobin against baseline are modest at 104 weeks: -0.06% with vildagliptin 50mg bd and -0.14% with glimepiride. The mean dose of glimepiride increased from baseline to week 104 from 2mg to 4.6mg. The "per protocol" results of group mean data show some deterioration of response over time (see Figure 2):

Secondary efficacy endpoints supported a greater initial response for glimepiride but a somewhat greater (non-significant) rate of decline in glycaemic control, together with more weight gain(+1.19 vs -0.26 kg respectively) and similar discontinuations due to hypoglycaemia (0.9% vs 0%). The results on insulin resistance and blood lipid results favour vildagliptin, consistent with weight loss.

The Delegate noted that this study is important in establishing combined therapy with metformin against an active comparator regimen involving two agents, not placebo add-on.

Study 2354 was an active-controlled parallel group non-inferiority study, comprising an initial blinded 24 week double-blind comparison of vildagliptin 50 mg bd or pioglitazone 30mg daily as add-on treatment for patients with Type 2 diabetes mellitus inadequately controlled by metformin up to 1,500mg per day, followed by a 28 week extension during which the sponsor was not blinded. Five hundred and seventy-six patients were randomised, 506 completed 24 weeks and 468 completed to 52 weeks. The applicant's conservative ITT analysis suggests a modest response at week 52 as shown in Table 13.

Concerning the fasting plasma glucose levels, again the sponsor's ITT analysis suggests a more rapid onset and loss of response for vildagliptin than for pioglitazone (see Figure 4) (note also the mean final results).

By request of the applicant, the Delegate presented the 24 week results:

At week 24, both add-on treatments lowered HbA1c from the common baseline value of 8. 4% by -0.9% (vildagliptin 50mg bd) and -1.0% (pioglitazone 30mg daily). The between group difference in the result was 0.1% (95%CI -0.05 – 0.26). This establishes non-inferiority. The mean reduction was greater in both arms of the study if the baseline HbA1c were >9.0% at baseline. Weight gain was seen in the pioglitazone group

The evaluator was of the view that pioglitazone was more effective than vildagliptin at lowering fasting plasma glucose. There was a sub study on insulin resistance with variable results, suggesting reduced insulin resistance during the study, perhaps less so with pioglitazone. Surprisingly, oedema was similar in both treatment arms, "Oedema was reported frequently but equally for the two treatments 10.8% vs. 11.1% for vildagliptin and pioglitazone respectively with 4.7% vs. 5.5% suspected to be drug related."

<u>Add-on to sulphonylureas – second agent therapy:</u>

No new data were submitted.

<u>Add-on to insulin – second agent therapy:</u>

No new data were submitted. The evaluator has summarised the applicant's response to ADEC, "The sponsor has responded to ADEC's concerns about vildagliptin as an add-on to insulin by quoting results of a pre-specified sub-group analysis showing that patients aged ≥65 years have a substantially more robust and sustained response to the addition of vildagliptin, than was seen with the whole population. In the full dataset, the mean increase in

daily insulin dose was 2.33 U greater with placebo than with vildagliptin. However hypoglycaemic events were somewhat less frequent or severe (22.9%, 0 severe v 29.6%, 6 severe)."

The Delegate noted that no material new information has been submitted to support combined use with insulin and the previously evaluated Study 2311 has not been followed by a specific study in older patients. As noted in the original overview, "Study 2311 was a multicentric, international, double blind, placebo controlled, parallel group study that examined the response to vildagliptin of patients with type 2 diabetes treated with ***insulin*** alone for ≥3 months at a dose of at least 30 units daily, stable for ≥4 weeks. Vildagliptin 50mg bd (n = 125) or placebo (n = 152) was added to insulin for 24 weeks and the response assessed as change from baseline of HbA1c at the end of study. Both groups improved from baseline . Of interest was a small increase in weight (mean 0.86kg) with vildagliptin. There were no differences with respect to the daily insulin dose or the number of injections but fewer hypoglycaemic episodes were claimed with vildagliptin (2.6% vs 0%)." The greater weight gain with vildagliptin + insulin may be consistent with the higher insulin dose. The difference in hypoglycaemic events is small and one must wonder about the sensitivity of detection, given the very low reported frequency. The Delegate suggested that the applicant is over-interpreting the clinical significance of the data.

Extensions of Previously Submitted Studies:

Study **LAF237A 2301** was a large phase III international, parallel group study that was a **monotherapy** study. The initial, previously evaluated phase compared 3 doses of vildagliptin, 50mg and 100mg once daily and 50mg bd, with placebo, for 24 weeks after a 2 week run-in. Six hundred and thirty-two patients with currently untreated type 2 diabetes were randomised equally into the 4 study groups. Baseline HbA1c levels were required to be 7.5 – 10% but there were significant initial problems with laboratory results and with including patients with too-low glycosylated haemoglobin levels: the study size was increased to compensate for the lost patients.

The previous evaluator found that the treatment effect was slight, "There was a mean fall of HbA1c in the placebo group, and although all 3 vildagliptin dosing regimens resulted in a significantly greater fall from baseline HbA1c than did placebo, the mean changes were modest (~ -0.5% change)."

Of the **extension** phase, the evaluator remarked, "In this extension, those initially receiving placebo were allocated to the 50 mg daily dose, so it was essentially uncontrolled." Metformin could be used as rescue therapy. Eighty-nine percent of 449 patients entering the extension phase completed it (to week 52).

The Delegate commented that this study is now of limited value for efficacy, given that it was a monotherapy study. Efficacy appears to be similar regardless of bd versus once daily (od) dosing although this comparison cannot properly be made. The evaluator also mentioned the extension phase of the monotherapy study 2307, with a suggestion of continued efficacy to >100 weeks versus placebo for patients on vildagliptin 50mg od. Also of limited interest, the monotherapy parallel group study **Study 2327E1** was an 80-week extension of a 24-week comparison of vildagliptin 50 mg bd and rosiglitazone 8 mg daily in patients with HbA1c 7.5-11.0%. Both arms showed continued response but the evaluator considered that rosiglitazone showed a more durable response.

Study 2329E1 was a 52 week extension of the 12-week study 2329 that was part of the original submission. The initial 12 week study was a Phase III dose ranging study that compared bd and od dosing. The study compared responses to vildagliptin monotherapy 50

mg once daily and bd dosing with an active control group that was treated with pioglitazone 30 mg daily.

The open label, uncontrolled **extension** phase, of an additional 52 weeks, involved switching of all **responders** (reduction of HbA1c from baseline of at least 0.3 %) to combined therapy of vildagliptin 50mg + pioglitazone 30mg daily. That is, it explored a fixed dose regimen in patients who had responded to monotherapy. The study was intended as a safety study but the evaluator observed that switching from vildagliptin 50mg bd to the combined regimen was associated with some loss of control whereas switching from vildagliptin 50mg od to the combined regimen was associated with improved control.

Safety

New studies:

In **Study 2308** (vildagliptin 50 mg bd versus glimepiride 6mg /day), most adverse events were reported with roughly equal frequency in the two groups but there was excess in the glimepiride arm of asthenia, tremor, hyperhidrosis, hunger and nervousness. Hypoglycaemia was reported in 16.3% v 1.7% of glimepiride and vildagliptin patients respectively. There were 2 deaths in the vildagliptin group and 3 with glimepiride. None was considered drug-related.

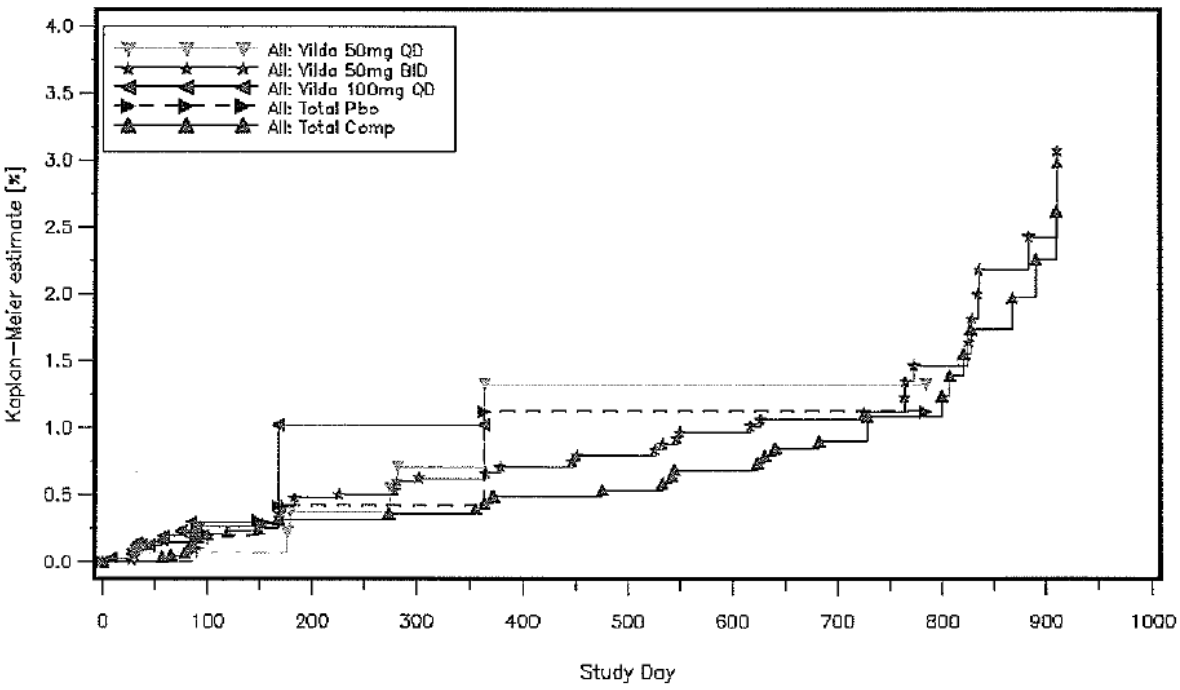
In **Study 2354**, both treatments were well tolerated but there were slightly more gastrointestinal complaints with vildagliptin. No deaths were reported. There were some single reports of individual serious adverse events (SAEs) in 12/295 patients taking vildagliptin and 25/280 taking pioglitazone. Weight gain was associated with pioglitazone use.

The Delegate commented that it was notable that the frequency of peripheral oedema with vildagliptin was quite similar to that with pioglitazone – about 11%. There was a previous suggestion, in the original submission, that peripheral oedema is associated with vildagliptin. For example, in the placebo controlled add-on studies with insulin, metformin or glimepiride, peripheral oedema was present in about combined 1.5% of 339 patients on glimepiride + vildagliptin treatment but in 0.6% of 176 patients on glimepiride + placebo; 1.6% of 441 patients on metformin + vildagliptin and 0.9% of 232 patients on metformin + placebo. With insulin alone peripheral oedema was present in 4.2% of 144 vildagliptin + insulin patients vs 3.3% of 152 insulin + placebo patients. Oedema was a dose-limiting toxicity event in healthy volunteers at doses of 400 -600mg daily.

Combined Data Set (Including the Above):

The evaluator concludes that the hepatic safety signal is small, "The evidence of hepatotoxicity revealed in the collected data does not raise concern for the safety of vildagliptin in clinical use beyond that for any orally active hypoglycaemic agent." However, figure 5-2 from the sponsor's summary suggests a signal from the formerly advocated regimen, vildagliptin 100mg od:

Figure 5-2 **Kaplan Meier estimates of the probability (%) of any persistent treatment-emergent ALT/AST greater than or equal to 3 times ULN (All studies safety [incl open label] population)**



Skin lesions and vascular events did not show any specificity for vildagliptin. The clinical evaluator commented that "the safety profile is acceptable being similar to that of all comparators. Analysis of all controlled trial data revealed doubling of incidence of carcinoma of the breast. No new safety concerns have emerged from studies up to 2 years duration."

Recommendation of the clinical evaluator

The evaluator found that, "Vildagliptin has efficacy in reducing HbA1c levels in type 2 diabetes mellitus superior to that of placebo but as so far demonstrated less than that of other oral agents, that is, metformin, sulphonylureas and thiazolidinediones. This effect diminishes with time but to a similar extent to that seen with comparators".

The evaluator recommended approval for marketing for the requested indications at the dose suggested of 50-100mg per day, the higher dose being given as 50mg bd. Some changes to the product information document were suggested.

Sponsor's Reply

A brief reply was received, confined to pointing out a few errors in the clinical evaluation report. These have been addressed in this document.

Risk-Benefit Analysis

The nonclinical studies have not, so far, predicted significant human toxicities. Only combination with metformin has so far been supported by adequate preclinical studies. Combined treatment with other agents would depend on clinical data. The clinical data on combined treatment with insulin are quite limited.

Post-marketing signals that have emerged internationally with sitagliptin include pancreatitis and renal failure. This reinforces concerns previously expressed by the ADEC in regard to vildagliptin and renal toxicity but does not necessarily preclude registration of vildagliptin.

The sponsor now requests bd dosing on safety grounds and this schedule made a relatively large contribution to the clinical data set.

As originally noted, the combined use of vildagliptin with a thiazolidinedione may be no longer appropriate: two agents are registered here. The combination of vildagliptin with a thiazolidinedione would not ameliorate the adverse effects of the latter and the benefit of vildagliptin, lack of weight gain, would be lost.

The new data reinforce the original conclusion that vildagliptin appears to be an acceptably safe add-on agent to metformin. There is still reason to be conservative about adding vildagliptin to sulphonylurea therapy. After all, there is an outstanding increase in hypoglycaemia when vildagliptin is used with glimepiride rather than other comparators.

The combination with metformin may be less likely to produce hypoglycaemia. This submission has provided no more experience with the combination of vildagliptin + sulphonylurea.

As originally stated, it is hard to know what to make of the conflicting results from the clinical trial 2311. Vildagliptin is not an insulin sensitiser (does not reduce insulin dose) but may have a role in aiding glycaemic control. This needs to be further explored in patients on a basal regimen and in those who require a basal bolus regimen. A single study with an extension to one year does not provide adequate information. For example, vildagliptin might offer the potential advantage (to the patient) of moving from a basal: bolus regimen to a basal regimen. However, the evaluator reported, "In both treatment groups there was a small increase in mean insulin dose and mean daily number of insulin injections from baseline to endpoint over 52 weeks; however, there was no significant increase in insulin

dose during the 28 week extension period." This could imply some chance confounding (closer supervision) after switching to active treatment. Use with insulin has shown no significant benefit and further studies are needed.

Triple combination therapies, involving a thiazolidinedione, could be seen in practice but this has not been tested. The data package submitted shows that the best risk and benefit is achieved with vildagliptin combined with metformin.

The product information (PI) should report only the primary study endpoints and, in particular, claims of benefits regarding serum lipids are still not acceptable. No specific lipid study has been done. It is also necessary to say that no data are yet available on vildagliptin's effects upon morbidity or mortality.

The Delegate proposed that the application should be approved. The registered indication should be for the treatment of diabetes mellitus type 2 in persons 18 years of age as an adjunct to diet and exercise to improve glycaemic control in patients with type 2 diabetes mellitus with **one of** metformin, a sulfonylurea (SU) or pioglitazone when diet, exercise and the single agent do not result in adequate glycaemic control. The product names should be Galvus 50 and Xiliarx 50. Use with insulin should be rejected due to a lack of adequate studies.

The product information document should make it clear that the role of vildagliptin in dual therapy is incompletely defined (excepting dual therapy with metformin); that the durability of effect may be less than one year in some patients; that no morbidity or mortality data are available; no claim should be made concerning beneficial effects on lipids because no specific lipid study has been conducted. If vildagliptin is approved for use with a sulphonylurea, the product information document should present data from the clinical trials to show the relatively elevated risk of hypoglycaemia.

The Australian Drug Evaluation Committee (ADEC), having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, agreed with the Delegate's proposal.

The Committee agreed with the Delegate that the new data show that vildagliptin appears to be an acceptably safe add-on agent to metformin. The Committee found that evidence for insulin was inadequate, and the data were insufficiently robust to allow the post hoc analysis. Vildagliptin use with a thiazolidinedione should be restricted to pioglitazone, which was the agent used in trials

The specific conditions of registration should include:

- The risk management plan will include adequate surveillance of hepatic adverse effects.

Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration of Galvus and Xiliarx tablets containing vildagliptin 50mg for:

Treatment of diabetes mellitus type 2 in persons 18 years of age and older, as an adjunct to diet and exercise to improve glycaemic control in patients with type 2 diabetes with one of metformin, a sulfonylurea or pioglitazone when diet, exercise and the single agent do not result in adequate glycaemic control.

Attachment 1. Product Information

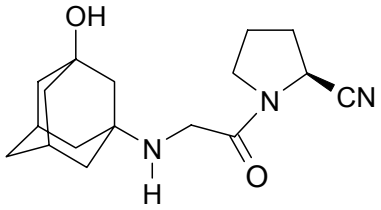
GALVUS®
Vildagliptin

Name of the medicine

The active ingredient of GALVUS is vildagliptin.

Chemical name: 1-[(3-Hydroxy-adamant-1-ylamino)acetyl]-pyrrolidine-2(S)-carbonitrile

Chemical structure:



Molecular formula: $C_{17}H_{25}N_3O_2$

Molecular weight: 303.40

CAS registry no. 274901-16-5

DESCRIPTION

Vildagliptin is a white to slightly yellowish or slightly greyish crystalline powder with a melting point/range of approximately 150°C. It is freely soluble in water.

Each GALVUS tablet contains 50 mg vildagliptin, lactose anhydrous, magnesium stearate, cellulose – microcrystalline and sodium starch glycollate.

PHARMACOLOGY

Pharmacodynamics

Vildagliptin, a member of the class that enhances islet cell insulin secretion via an augmented incretin effect, is a high affinity dipeptidyl-peptidase-4 (DPP-4) inhibitor that improves glycaemic control.

The administration of vildagliptin results in rapid and near-complete inhibition of DPP-4 activity. Vildagliptin shows weak inhibition of, and rapid dissociation from DPP-8 and DPP-9, compared to DPP-4. In patients with type 2 diabetes, administration of vildagliptin led to inhibition of DPP-4 enzyme activity for a 24-hour period. Vildagliptin inhibition of DPP-4 results in increased fasting and postprandial endogenous levels of the incretin hormones GLP-1 (glucagon-like peptide 1) and GIP (glucose-dependent insulinotropic polypeptide).

The degree of improvement in beta-cell function is dependent on the initial degree of impairment; in non-diabetic (normal glycaemic) individuals, vildagliptin does not stimulate insulin secretion or reduce glucose levels.

By increasing endogenous GLP-1 levels, vildagliptin enhances the sensitivity of alpha cells to glucose, resulting in reduced glucagon secretion. There is a reduction in inappropriate glucagon release during meals. The increase in the insulin/glucagon ratio with hyperglycaemia, due to increased incretin hormone levels, may thus be expected to decrease postprandial hepatic glucose production, leading to reduced glycaemia.

The known effect of increased GLP-1 levels to delay gastric emptying is not observed with vildagliptin treatment.

Pharmacokinetics

Linearity

Vildagliptin is rapidly absorbed with an absolute oral bioavailability of 85%. Peak plasma concentrations for vildagliptin and the area under the plasma concentration versus time curve (AUC) increased in an approximately dose-proportional manner over the therapeutic dose range.

Absorption

Following oral administration in the fasting state, vildagliptin is rapidly absorbed with peak plasma concentrations observed at 1.75 hours. Coadministration with food slightly decreases the rate of absorption of vildagliptin, as characterized by a 19% decrease in peak concentrations, and a delay in the time to peak plasma concentration to 2.5 hours. There is no change in the extent of absorption, and food does not alter the overall exposure (AUC).

Distribution

The plasma protein binding of vildagliptin is low (9.3%), and vildagliptin distributes equally between plasma and red blood cells. The mean volume of distribution of vildagliptin at steady state after intravenous administration (Vss) is 71 L, suggesting extravascular distribution.

Metabolism

Metabolism is the major elimination pathway for vildagliptin in humans, accounting for 69% of the dose. The major metabolite, LAY151, is pharmacologically inactive and is the hydrolysis product of the cyano moiety, accounting for 57% of the dose, followed by the amide hydrolysis product (4% of the dose). DPP-4 contributes partially to the hydrolysis of vildagliptin as shown in an in-vivo study using DPP-4 deficient rats. Vildagliptin is not metabolized by cytochrome P450 enzymes to any quantifiable extent. In-vitro studies demonstrated that vildagliptin does not inhibit or induce cytochrome P450 enzymes.

Excretion and Elimination

Following oral administration of [14C] - vildagliptin, approximately 85% of the dose is excreted into the urine and 15% of the dose is recovered in the faeces. Renal excretion of the unchanged vildagliptin accounts for 23% of the dose after oral administration. After an intravenous administration to healthy subjects, the total plasma and renal clearances of vildagliptin are 41 L/hour and 13 L/hour, respectively. The mean elimination half-life after intravenous administration is approximately 2 hours. The elimination half-life after oral administration is approximately 3 hours and is independent of dose.

Special Populations

Age

In otherwise healthy elderly subjects (≥70 years), the overall exposure to vildagliptin (100 mg once daily) was increased by 32% with an 18% increase in peak plasma concentration compared to younger healthy subjects (18 to 40 years). These changes are not considered to be clinically relevant. DPP-4 inhibition by Vildagliptin is not affected by age in the age groups studied.

Gender

No differences in the pharmacokinetics of vildagliptin were observed between male and female subjects with a diverse range of age and body mass index (BMI). DPP-4 inhibition by vildagliptin was unaffected by gender.

Paediatric

No pharmacokinetic data available.

Obesity

BMI does not show any impact on the pharmacokinetic parameters of vildagliptin. DPP-4 inhibition by vildagliptin was unaffected by BMI.

Hepatic Impairment

The effect of impaired hepatic function on the pharmacokinetics of vildagliptin was studied in subjects with mild, moderate, and severe hepatic impairment based on the Child-Pugh scores (ranging from 6 for mild to 12 for severe) in comparison to subjects with normal hepatic function. The exposure to vildagliptin (100 mg) after a single dose in subjects with mild and moderate hepatic impairment was decreased (20% and 8%, respectively), while the exposure to vildagliptin for subjects with severe impairment was increased by 22%. The maximum change (increase or decrease) in the exposure to vildagliptin is ~30%, which is not considered to be clinically relevant. There was no correlation between the severity of hepatic function impairment and changes in exposure to vildagliptin.

The use of vildagliptin is not recommended in patients with hepatic impairment including patients with a pre-treatment ALT or AST > 2.5X the upper limit of normal.

Chronic kidney disease

In subjects with mild, moderate, and severe chronic kidney disease, and End Stage Renal Disease (ESRD) patients on haemodialysis, systemic exposure to vildagliptin was increased (Cmax 8% to 66%; AUC 32% to 134%) compared to subjects with normal renal function. Exposure to the inactive metabolite (LAY151) increased with increasing severity of chronic kidney disease (AUC 1.6- to 6.7-fold). Changes in exposure to vildagliptin did not correlate with severity of chronic kidney disease, whereas changes in exposure to the inactive metabolite did correlate. Elimination half-life of vildagliptin was not affected by chronic kidney disease. No dosage adjustment is required in patients with mild chronic kidney disease. Due to limited experience, the use of vildagliptin is not recommended in patients with moderate or severe chronic kidney disease or in patients with ESRD on haemodialysis (See **PRECAUTIONS**, **Chronic kidney disease**).

Race

There is no evidence that race affects the pharmacokinetics of vildagliptin.

CLINICAL TRIALS

More than 15,000 patients with type 2 diabetes participated in double-blind, placebo- or active-controlled clinical trials including some studies of more than 2 years treatment duration. In these studies, vildagliptin was administered to more than 9,000 patients at daily doses of 50 mg once daily, 50 mg twice daily or 100 mg once daily. More than 5,000 male and more than 4,000 female patients received vildagliptin 50 mg once daily or 100 mg daily. More than 1,900 patients receiving vildagliptin 50 mg once daily or 100 mg daily were ≥ 65 years of age. In these trials, vildagliptin was administered as monotherapy in drug-naïve patients with type 2 diabetes or in combination in patients not adequately controlled by other antidiabetic medicinal products. Monotherapy studies suggested that vildagliptin on its own had slightly less efficacy compared to sulfonylureas or pioglitazone. The role of vildagliptin in dual therapy with sulfonylureas and pioglitazone is incompletely defined. No morbidity or mortality data are available.

Overall, vildagliptin improved glycaemic control when given as monotherapy or when used in combination with metformin, a sulfonylurea, or a thiazolidinedione as measured by clinically relevant reductions in HbA_{1c} from baseline at study endpoint (see **Table 1**). Long-term extension studies with vildagliptin as add-on therapy to metformin, glimepiride, or pioglitazone generally demonstrated continued glycaemic benefit at week 52. However, results were variable across studies. Therefore, the individual long-term response may vary.

In clinical trials, the magnitude of HbA_{1c} reductions with vildagliptin was greater in patients with higher baseline HbA_{1c}.

Table 1 Key efficacy results of vildagliptin in placebo-controlled monotherapy and in combination therapy trials (primary efficacy ITT population)

	Primary endpoint (weeks)	Mean baseline HbA_{1c} (%)	Mean change from baseline in HbA_{1c} (%)	Difference from placebo group (95%CI)	Patients achieving a ≥ 0.7% reduction in A1c (%)
Monotherapy studies					
Vildagliptin 50 mg once daily (N=104) [Study 2301]	24	8.2	-0.8	-0.5** (-0.8, -0.1)	62 (60%)
Vildagliptin 50 mg twice daily (N=90) [Study 2301]	24	8.6	-0.8	-0.5** (-0.8, -0.1)	59 (66%)
Vildagliptin 50 mg once daily (N=84) [Study 2384]	24	8.3	-0.5	-0.5** (-0.9, -0.1)	37 (44%)
Vildagliptin 50 mg twice daily (N=79) [Study 2384]	24	8.4	-0.7	-0.7** (-1.1, -0.4)	43 (54%)
Combination studies					
Vildagliptin 50 mg once daily + metformin (N=143) [Study 2303]	24	8.4	-0.5	-0.7* (-1.0, -0.5)	66 (46%)
Vildagliptin 50 mg twice daily + metformin (N=143) [Study 2303]	24	8.4	-0.9	-1.1* (-1.4, -0.8)	86 (60%)
Vildagliptin 50 mg once daily + pioglitazone (N=124) [Study 2304]	24	8.6	-0.8	-0.5* (-0.7, -0.2)	67 (54%)
Vildagliptin 50 mg twice daily + pioglitazone (N=136) [Study 2304]	24	8.7	-1.0	-0.7* (-0.9, -0.4)	93 (68%)
Vildagliptin 50 mg once daily + glimepiride (N=132) [Study 2305]	24	8.5	-0.6	-0.6* (-0.9, -0.4)	62 (47%)

* p< 0.05 for comparison versus placebo + background therapy
** p< 0.05 for comparison versus placebo

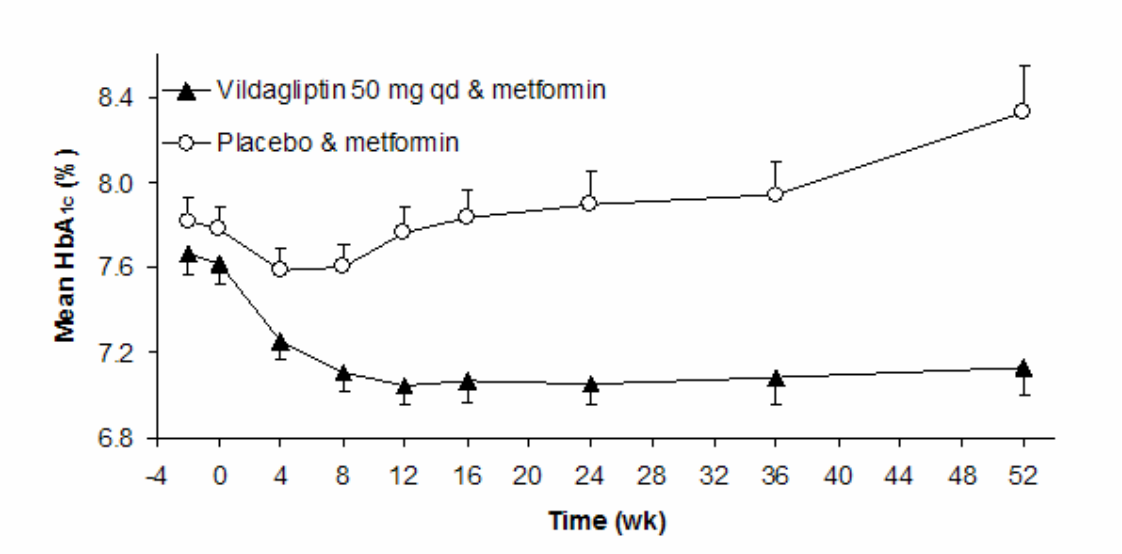
Combination with Metformin

In a double-blind, placebo-controlled 24 week trial (Study 2303; n=544) in patients with type 2 diabetes whose hyperglycaemia was inadequately controlled on a maximal dose of metformin alone (mean metformin dose at baseline = 2100 mg/day), the addition of vildagliptin (50 mg once daily or 100 mg daily, as a divided dose of 50 mg in the morning and 50 mg in the evening) to metformin for 24 weeks led to statistically significant reductions in HbA_{1c} and increased the proportion of patients achieving at least a 0.7% reduction in HbA_{1c} when compared to patients who were continued on metformin plus placebo. Group mean baseline HbA_{1c} ranged from 8.3% (placebo plus metformin) to 8.4% (in both vildagliptin plus metformin groups)(see **Table 1**). Vildagliptin combined with metformin resulted in additional statistically significant mean reductions in HbA_{1c} compared to placebo (between group differences of -0.7% to -1.1% for vildagliptin 50 mg and 100 mg, respectively). The proportion of patients who achieved a decrease of ≥0.7% in HbA_{1c} from baseline was statistically significantly higher in both vildagliptin plus metformin groups (46% and 60%, respectively) versus the metformin plus placebo group (20%). Patients on the combination of vildagliptin plus metformin did not experience a meaningful change in body weight compared to baseline. The incidence of gastrointestinal side effects ranged from 10% to 15% in the vildagliptin plus metformin groups as compared to 18% in the metformin plus placebo group. Vildagliptin added to metformin significantly reduced FPG compared to metformin plus placebo (-0.8 mmol/L for 50 mg once daily, and -1.7 mmol/L for 50 mg twice daily).

The effect of vildagliptin in combination with metformin was evaluated in another, double-blind, placebo-controlled add-on clinical trial (Study 2204E1) of 52 weeks total duration (12-week core study plus a 40-week extension) involving 132 patients with type 2 diabetes on stable doses of metformin (1500 mg-3000 mg daily). The addition of vildagliptin (50 mg once daily) to metformin resulted in an additional statistically significant reduction in mean HbA_{1c} (between group difference of -0.6%) from baseline compared to placebo plus metformin (+0.1%) at the end of the 12-week study interval (mean baseline HbA_{1c} of 7.7% and 7.9%, respectively). Of these patients, 71 continued add-on treatment with vildagliptin or placebo for an additional 40 weeks (placebo-controlled, double-blind extension). At 52 weeks, mean change from baseline in HbA_{1c} was statistically significantly greater and sustained with vildagliptin (50 mg) plus metformin versus patients continued on metformin plus placebo (between group difference of -1.1%).

These data indicate vildagliptin plus metformin provides a durable effect on glycaemic control over 52 weeks (See **Figure 1**). In contrast, glycaemic control in the metformin plus placebo group deteriorated over the course of the study.

Figure 1. Mean HbA_{1c} Over Time in a 52-Week Study (12-Week Core Study and 40-Week Extension) Comparing Vildagliptin Plus Metformin to Placebo Plus Metformin in Patients Inadequately Controlled with Metformin



In a double-blind, active-controlled 24 week trial (Study 2354; n=576), vildagliptin (100 mg/day; 50 mg in the morning and 50 mg in the evening) was compared to pioglitazone (30 mg once daily) in patients with type 2 diabetes inadequately controlled with metformin alone. Mean reductions from baseline HbA_{1c} of 8.4% were - 0.9% with vildagliptin added to metformin and -1.0% with pioglitazone added to metformin. The decrease in HbA_{1c} from baseline >9.0% was greater (-1.5%) in both treatment groups. Patients receiving pioglitazone in addition to metformin experienced an increase in weight of 1.9 kg while those receiving vildagliptin in addition to metformin experienced an increase in weight of 0.3 kg. In a 28 week extension, HbA_{1c} reductions were similar between treatment groups and the body weight difference further increased.

In a long term, double-blind, active-controlled trial of up to more than 2 years (Study 2308; n=3118), vildagliptin (100 mg/day; 50 mg in the morning and 50 mg in the evening) was compared to glimepiride (up to 6 mg/day) in patients with type 2 diabetes treated with metformin. After 1-year, mean reductions in HbA_{1c} were -0.4% with vildagliptin added to metformin and -0.5% with glimepiride added to metformin. Body weight change with vildagliptin was -0.2 kg vs + 1.6 kg with glimepiride. The incidence of hypoglycaemia was significantly lower in the vildagliptin group (1.7%) than in the glimepiride group (16.2%). At study endpoint (2 years), the HbA_{1c} was similar to baseline values in both treatment groups and the body weight changes and hypoglycaemia differences were maintained.

Combination with Glimepiride

The benefit of vildagliptin as add-on therapy was investigated in a double-blind, placebo-controlled add-on trial (Study 2305; n=515), in patients with type 2 diabetes whose hyperglycaemia was inadequately controlled after switching from half maximal recommended doses of a sulfonylurea to glimepiride (4 mg). The addition of vildagliptin (50 mg once daily or 100 mg daily, as a divided dose of 50 mg in the morning and 50 mg in the evening) for 24 weeks led to additional statistically significant reductions in HbA_{1c} from baseline versus patients continued on glimepiride plus placebo. The difference from placebo plus glimepiride was -0.64 in the 50 mg once daily group and -0.70% in the 50 mg twice daily group. Patients receiving vildagliptin in combination with glimepiride experienced either no increase in body weight (with vildagliptin 50 mg daily) or a slight increase (with vildagliptin 100 mg daily) relative to baseline values. Vildagliptin added to glimepiride reduced FPG compared to placebo plus glimepiride (-0.5 mmol/L for 50 mg once daily, and -0.6 mmol/L for 100 mg once daily, as divided dose of 50 mg in the morning and 50 mg in the evening).

Combination with Pioglitazone

In a double-blind, placebo-controlled add-on trial (Study 2304; n=463) in patients with type 2 diabetes whose hyperglycaemia was inadequately controlled with prior thiazolidinedione monotherapy, patients were randomized to either continued thiazolidinedione monotherapy (pioglitazone 45 mg once daily plus placebo) or to the combination of the thiazolidinedione (pioglitazone 45 mg) plus vildagliptin (either 50 mg once daily or 50 mg twice daily) for 24 weeks. Group mean baseline HbA_{1c} ranged from 8.6% (vildagliptin 50 mg daily plus pioglitazone) to 8.7% (vildagliptin 50 mg twice daily plus pioglitazone, or placebo plus pioglitazone).

The addition of vildagliptin led to statistically significant reductions in HbA_{1c} and increased the proportion of patients achieving at least a 0.7% reduction in HbA_{1c} when compared to patients who were continued on the thiazolidinedione alone. Vildagliptin combined with pioglitazone resulted in additional statistically significant mean reductions in HbA_{1c} compared to pioglitazone plus placebo (between group differences of -0.5% to -0.7% for vildagliptin 50 mg once daily and twice daily, respectively). The proportion of patients who achieved a decrease of ≥0.7% in HbA_{1c}, from baseline was statistically significantly higher in both vildagliptin plus pioglitazone groups (54% and 68%, respectively) versus the pioglitazone plus placebo group (38%). Patients on the combination experienced either no increase in body weight (those receiving vildagliptin 50 mg daily plus pioglitazone) or a slight increase (those receiving vildagliptin 50 mg twice daily plus pioglitazone) relative to pioglitazone plus placebo.

Vildagliptin added to pioglitazone reduced FPG compared to placebo plus pioglitazone (-0.3 mmol/L for 50 mg vildagliptin once daily, and -0.7 mmol/L for 100 mg vildagliptin once daily, as divided dose of 50 mg in the morning and 50 mg in the evening).

Fasting Plasma Glucose

When administered as monotherapy and add-on therapy, vildagliptin produced clinically relevant and consistent mean reductions from baseline in fasting plasma glucose (FPG) concentrations.

INDICATIONS

Treatment of diabetes mellitus type 2 in persons 18 years of age and older, as an adjunct to diet and exercise to improve glycaemic control in patients with type 2 diabetes with one of metformin, a sulfonylurea or pioglitazone when diet, exercise and the single agent do not result in adequate glycaemic control.

CONTRAINDICATIONS

Hypersensitivity to vildagliptin or to any of the excipients.

PRECAUTIONS

General

Vildagliptin is not a substitute for insulin in insulin-requiring patients. Vildagliptin should not be used in patients with type 1 diabetes or for the treatment of diabetic ketoacidosis.

Chronic kidney disease

There is limited experience in patients with moderate or severe chronic kidney disease and in patients with End Stage Renal Disease (ESRD) on haemodialysis. Therefore, the use of vildagliptin is not recommended in these patients.

Hepatic impairment

Vildagliptin is not recommended in patients with hepatic impairment, including patients with a pre-treatment ALT or AST > 2.5X the upper limit of normal.

Liver enzyme monitoring

Rare cases of hepatic dysfunction (including hepatitis) have been reported. In these cases, the patients were generally asymptomatic without clinical sequelae and liver function tests (LFTs) returned to normal after discontinuation of treatment. LFTs should be performed prior to the initiation of treatment with vildagliptin. Vildagliptin is not recommended in patients with a pre-treatment ALT or AST > 2.5X the upper limit of normal. LFTs should be monitored during vildagliptin treatment at three-month intervals during the first year and periodically thereafter. Patients who develop increased transaminase levels should be monitored with a second liver function evaluation to confirm the finding and be followed thereafter with frequent liver function tests until the abnormality(ies) return to normal. Should an increase in AST or ALT of 3 X upper limit of normal or greater persist, withdrawal of therapy with vildagliptin is recommended. Patients who develop jaundice or other signs suggestive of liver dysfunction should discontinue vildagliptin and contact their physician immediately. Following withdrawal of treatment with vildagliptin and LFT normalisation, vildagliptin should not be reinitiated.

Other

Vildagliptin tablets contain lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Carcinogenicity

Long-term oral studies with vildagliptin in rats and mice showed evidence of haemangiosarcomas at high exposures. Tumour incidence was increased at exposure levels 46-235 times (mice) and 150 times (rats) human exposure at the maximum clinical dose, based on AUC. No significant increase in incidence was observed at 15 to 80 (females) times human exposure in mice. No effect levels of ca 80 to 160 times human exposure were established in rats.

Mammary tumour incidence was increased in female mice at approximately 185 times the maximum anticipated human exposure to vildagliptin, but was not increased at ca 80 times. The tumours are thought to result from species-specific hormonal disturbances.

Based on the available data vildagliptin is not anticipated to present a carcinogenic risk at clinically relevant exposures.

Genotoxicity

Vildagliptin was not mutagenic in a bacterial reverse mutation assay and a human lymphocyte chromosomal aberration assay. Some clastogenic potential was exhibited in an in vitro micronucleus test in V79 Chinese hamster cells after long exposure to high, cytotoxic concentrations. However, no clastogenicity was observed in either mouse or rat micronucleus tests in vivo at up to ca 400 times the maximum human exposure, based on AUC. Furthermore, an in vivo mouse liver comet assay using the same dose was also negative. The weight of evidence indicates vildagliptin is unlikely to be genotoxic in humans at clinically relevant doses.

Effects on fertility

Vildagliptin did not impair male or female fertility or early embryonic development in rats at oral doses corresponding to 160 times human exposure at the maximum clinical dose.

Effects on skin

In a 13-week toxicology study in cynomolgus monkeys, skin lesions have been recorded at all oral doses administered (5 to 160 mg/kg/day). These were consistently located on the extremities (hands, feet, ears, scrotum and tail), and included flaking skin, peeling skin, scabs, tail sores and blisters. At 5 mg/kg/day (approximately equivalent to human AUC exposure at the 100 mg dose), lesions were reversible despite continued treatment. Necrotic lesions of the tail were observed at ≥ 80 mg/kg/day (18 times human AUC exposure at the maximum recommended clinical dose). Skin lesions were not reversible in monkeys treated at 160 mg/kg/day (35 times human AUC exposure) during a 4-week recovery period. Skin lesions have not been observed in other animal species and no excess of skin lesions with vildagliptin treatment relative to comparator treatments have been observed in the human clinical trials programme.

Use in pregnancy (Category B3)

Vildagliptin was not teratogenic in either rats or rabbits at exposures up to ca 115 times and 40 times the maximum expected human exposure, respectively. A slight treatment-related increase in the incidence of fetal rib abnormalities was observed in the fetuses of rats at oral doses of 225 mg/kg/day (approximately 30 times the human AUC exposure at the 100 mg dose). There are no adequate and well-controlled studies in pregnant women. Vildagliptin should not be used during pregnancy unless the benefit to the mother outweighs the potential risk to the foetus. Attainment of strict normoglycaemia during pregnancy may require conversion to insulin monotherapy.

Use in lactation

Vildagliptin is excreted in the milk of lactating rats. As it is not known whether vildagliptin is excreted in human milk, vildagliptin should not be administered to breastfeeding mother.

Use in children

The safety and effectiveness of vildagliptin in paediatric patients have not been established.

Use in elderly

Of the 2900 patients treated with vildagliptin, 543 (18.9%) were ≥65 years of age and 109 (3.8%) were ≥75 years of age. There were no differences observed in overall safety, tolerability, or efficacy between these patients and younger patients.

Interaction with other drugs

Vildagliptin has a low potential for drug interaction. Since vildagliptin is not a cytochrome (CYP) P450 enzyme substrate and does not inhibit or induce CYP P450 enzymes, it is not likely to interact with the concomitant medications that are substrates, inhibitors or inducers of these enzymes.

Furthermore, vildagliptin is not likely to interact with the concomitant medications that are substrates, inhibitors or inducers of CYP P450 enzymes nor does it affect metabolic clearance of co-medications metabolised by CYP1A2, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A4/5. Drug-drug interaction studies were conducted with the following commonly co-prescribed medications for patients with type 2 diabetes or medications with a narrow therapeutic window.

Glibenclamide

Coadministration of vildagliptin (100 mg twice daily) with glibenclamide (10 mg once daily) had no significant effect on the steady-state pharmacokinetics of vildagliptin. Vildagliptin did not alter the steady-state pharmacokinetics of glibenclamide.

Pioglitazone

Coadministration of vildagliptin (100 mg once daily) with pioglitazone (45 mg once daily) did not alter the steady-state pharmacokinetics of vildagliptin. Vildagliptin had no effect on the steady-state pharmacokinetics of pioglitazone measured by the parent pioglitazone and its two active metabolites, MIII and MIV.

Metformin

Coadministration of vildagliptin (100 mg once daily) with metformin (1000 mg once daily) did not alter the steady-state pharmacokinetics of metformin. Metformin (1000 mg once daily) did not affect total exposure to vildagliptin at steady state. The Cmax of vildagliptin was decreased by 18%, which is not considered to be clinically relevant.

Amlodipine

Coadministration of vildagliptin (100 mg once daily) with amlodipine (5 mg once daily) given in combination to healthy subjects, did not alter the steady-state pharmacokinetics of amlodipine (5 mg once daily). Similarly, the steady-state pharmacokinetics of vildagliptin were unaffected by coadministration of amlodipine.

Valsartan

Coadministration of vildagliptin (100 mg once daily) with valsartan (320 mg once daily) did not alter the steady-state pharmacokinetics of vildagliptin. Coadministration of vildagliptin with valsartan resulted in an increased exposure to valsartan (AUC by 24% and Cmax by 14%). However, these changes are not considered to be clinically relevant.

Ramipril

Coadministration of vildagliptin (100 mg once daily) with ramipril (5 mg once daily) to healthy subjects, did not alter the steady-state pharmacokinetics of ramipril and its active metabolite, ramiprilat. Similarly, ramipril did not affect the steady-state pharmacokinetics of vildagliptin.

Simvastatin

Coadministration of vildagliptin (100 mg once daily) with simvastatin (80 mg once daily) did not alter the steady-state pharmacokinetics of simvastatin and its active metabolite, simvastatin hydroxyacid. Similarly, simvastatin did not influence the steady-state pharmacokinetics of vildagliptin.

Digoxin

Coadministration of vildagliptin (100 mg once daily) with digoxin (0.5 mg loading dose on Day 1 and a 0.25 mg maintenance dose from Day 2 to Day 7) did not affect the pharmacokinetics of digoxin at steady state, and digoxin did not alter the pharmacokinetics of vildagliptin.

Warfarin

Coadministration of vildagliptin (100 mg once daily) with warfarin (25 mg single dose) did not alter the pharmacokinetics of warfarin and warfarin did not influence the pharmacokinetics of vildagliptin (100 mg once daily). Coadministration of vildagliptin did not affect the pharmacodynamic parameters of prothrombin times such as AUC_{PT}, PT_{max}, AUC_{INR}, INR_{max} following administration of warfarin 25 mg in comparison with coadministration of placebo.

Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. Patients who may experience dizziness should therefore avoid driving vehicles or using machines.

ADVERSE REACTIONS

Safety data were obtained from 3,784 patients exposed to vildagliptin at a daily dose of 50 mg (once daily) or 100 mg (50 mg twice daily or 100 mg once daily) in controlled trials of at least 12 week's duration. Of these patients, 2,264 patients received vildagliptin as monotherapy and 1,520 patients receiving vildagliptin in combination with another agent. 2,682 patients were treated with vildagliptin 100 mg daily (2,027 with 50 mg twice daily and 655 with 100 mg once daily) and 1,102 patients were treated with vildagliptin 50 mg once daily.

The majority of adverse reactions in these trials were mild and transient, not requiring treatment discontinuations. No association was found between adverse reactions and age, gender, ethnicity, duration of exposure or daily dose.

Rare cases of angioedema have been reported on vildagliptin at a similar rate to controls. A greater proportion of cases were reported when vildagliptin was administered in combination with an angiotensin converting enzyme inhibitor (ACE-Inhibitor). The majority of events were mild in severity and resolved with ongoing vildagliptin treatment.

Rare cases of hepatic dysfunction (including hepatitis) have been reported. In these cases, the patients were generally asymptomatic without clinical sequelae and liver function tests (LFTs) returned to normal after discontinuation of treatment. In data from controlled monotherapy and add-on therapy trials up to 24 weeks in duration, the incidence of ALT or AST elevations >= 3x ULN (classified as present on at least 2 consecutive measurements or at the final on-treatment visit) was 0.2%, 0.3% and 0.2% for vildagliptin 50 mg daily, vildagliptin 50 mg twice daily and all comparators, respectively. These elevations in transaminases were generally asymptomatic, non-progressive in nature and not associated with cholestasis or jaundice.

Adverse reactions reported in patients who received vildagliptin in double blind studies as monotherapy and add-on therapy are listed below, for each indication, by system organ class and absolute frequency. Frequencies are defined as: very common (≥ 1/10); or common (≥ 1/100, < 1/10). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Monotherapy

The overall incidence of withdrawals from monotherapy trials due to adverse reactions was no greater for patients treated with vildagliptin at a dose of 50 mg once daily (0.2%) or vildagliptin at a dose of 50mg twice daily (0.1%) than for placebo (0.6%) or comparators (0.5%).

In monotherapy studies, hypoglycaemia was uncommon, reported in 0.5% (2 of 409) of patients treated with vildagliptin 50 mg once daily and 0.3% (4 of 1373) of patients treated with vildagliptin 50mg twice daily compared to 0.2% (2 of 1,082) of patients in the groups treated with an active comparator or placebo, with no serious or severe events reported.

Vildagliptin is weight neutral when administered as monotherapy.

Table 2 Adverse reactions reported in patients who received vildagliptin 50 mg once daily (n=409) or 50 mg twice daily (n=1373) as monotherapy in double-blind studies

Nervous system disorders	
Common	Dizziness
Uncommon	Headache
Gastrointestinal disorders	
Uncommon	Constipation
General disorders and administration site conditions	
Uncommon	Oedema peripheral

Long term clinical trials of up to 2 years did not show any additional safety signals or unforeseen risks with vildagliptin monotherapy.

Combination with metformin

In clinical trials with the combination of vildagliptin plus metformin, 0.4% of patients withdrew due to adverse reactions in the vildagliptin 50 mg once daily plus metformin, and no withdrawal due to adverse reactions was reported in either the vildagliptin 50mg bid plus metformin or the placebo plus metformin treatment groups.

In clinical trials, the incidence of hypoglycaemia was uncommon in patients receiving vildagliptin 50 mg once daily in combination with metformin (0.9%), patients receiving vildagliptin 50 mg twice daily in combination with metformin (0.5%) and in patients receiving placebo plus metformin (0.4%). No severe hypoglycaemic events were reported in the vildagliptin arms.

Vildagliptin is weight neutral when administered in combination with metformin.

Table 3 Additional adverse reactions reported in patients who received vildagliptin 50 mg once daily (n=233) or 50 mg twice daily (n=183) in combination with metformin in double-blind studies

Nervous system disorders	
Common	Headache, tremor, dizziness

Long term clinical trials of up to more than 2 years did not show any additional safety signal or unforeseen risks when vildagliptin was added on to metformin.

Combination with glimepiride

In clinical trials with the combination of vildagliptin 50 mg plus glimepiride, the overall incidence of withdrawals due to adverse reactions was 0.6% in the vildagliptin 50 mg plus glimepiride vs 0% in the placebo plus glimepiride treatment group.

In clinical trials, the incidence of hypoglycaemia when vildagliptin 50 mg once daily was added to glimepiride was 1.2% versus 0.6% for placebo plus glimepiride. No severe hypoglycaemic events were reported in the vildagliptin arms.

In clinical trials, weight did not change from baseline when vildagliptin 50 mg daily was added to glimepiride (-0.1kg and -0.4 kg for vildagliptin and placebo, respectively).

Table 4 Adverse reactions reported in patients who received vildagliptin 50mg once daily in combination with a sulphonylurea in double-blind studies (n=170)

Nervous system disorders	
Common	Tremor, headache, dizziness
General disorders and administration site conditions	
Common	Asthenia

Combination with pioglitazone

In clinical trials with the combination of vildagliptin and a thiazolidinedione, 0.7% of patients withdrew for adverse reactions in the vildagliptin 50mg once daily plus pioglitazone group, and there were no withdrawals due to adverse reactions reported in either the vildagliptin 50mg twice daily plus pioglitazone or the placebo plus pioglitazone treatment groups.

In clinical trials, no hypoglycaemia events were reported in patients receiving vildagliptin 50 mg once daily plus pioglitazone 45 mg, hypoglycaemia was uncommon in patients receiving vildagliptin 50 mg twice daily plus pioglitazone 45 mg (0.6%) but common in patients receiving placebo plus pioglitazone 45 mg (1.9%). No severe hypoglycaemic events were reported in the vildagliptin arms.

In the pioglitazone add-on study, the change in body weight compared to placebo, was +0.1 kg and +1.3 kg for vildagliptin 50 mg daily and vildagliptin 50 mg twice daily respectively.

The incidence of peripheral oedema when vildagliptin was added to a maximum dose of background pioglitazone (45 mg once daily) was 8.2% as 50 mg once daily and 7.0%, as 50 mg twice daily compared to 2.5% for background pioglitazone alone. The incidence of oedema when vildagliptin was added to pioglitazone as dual initial therapy in drug naïve patients was, however, less than for pioglitazone alone (50 mg once daily 3.5%, 50 mg twice daily 6.1% vs pioglitazone 30 mg 9.3%).

Table 5 Adverse reactions reported in patients who received vildagliptin 50 mg once daily (n= 290) or 50mg twice daily (n=158) daily in combination with a thiazolidinedione in double-blind studies

Investigations	
Common	Weight increase
Vascular disorders	
Common	Oedema peripheral

Post-marketing Experience

During post-marketing experience the following additional adverse drug reaction has been reported (frequency not known): urticaria.

DOSAGE AND ADMINISTRATION

The management of antidiabetic therapy should be individualised.

When used in dual combination with metformin, a thiazolidinedione (clinical experience is with pioglitazone as dual therapy), the recommended dose of vildagliptin is 50 mg or 100 mg daily. The 50 mg dose should be administered once daily in the morning. The 100 mg dose should be administered as two divided doses of 50 mg given in the morning and evening.

When used in dual combination with a sulphonylurea (clinical experience is with glimepiride as dual therapy), the recommended dose of vildagliptin is 50 mg once daily administered in the morning. In this patient population, vildagliptin 100 mg daily was no more effective than vildagliptin 50 mg once daily and was associated with a higher rate of hypoglycaemia than the 50 mg dose.

Doses greater than 100 mg are not recommended.

Vildagliptin can be administered with or without a meal.

Patients with hepatic impairment

Vildagliptin is not recommended in patients with hepatic impairment including patients with a pre-treatment ALT or AST > 2.5X the upper limit of normal.

Patients with chronic kidney disease

Glomerular Filtration Rate (GFR) is to be estimated prior to commencement of therapy. No dosage adjustment of vildagliptin is required in patients with mild chronic kidney disease (eGFR 60-89 mL/min/1.73m^2). Vildagliptin is, however, not recommended in patients with moderate (eGFR 30-59 mL/min/1.73m^2) or severe (eGFR 15-29 mL/min/1.73m^2) chronic kidney disease or End Stage Renal Disease (ESRD) on haemodialysis (See **PRECAUTIONS**, **Chronic kidney disease** and **PHARMACOLOGY**, **Special populations**).

Elderly patients

In patients treated with vildagliptin ≥ 65 years of age and ≥ 75 years of age, no differences were observed in the overall safety, tolerability, or efficacy between this elderly population and younger patients. No dosage adjustments are therefore necessary in the elderly patients (See **Pharmacokinetics**, **Special Populations**). Experience in patients aged 75 years and older is limited and caution should be exercised when treating this population.

Paediatric patients

Vildagliptin has not been studied in patients under 18 years of age; therefore, the use of vildagliptin in paediatric patients is not recommended (see **Pharmacokinetics**, **Special Populations**).

OVERDOSAGE

In healthy subjects (seven to fourteen subjects per treatment group), GALVUS (vildagliptin) was administered in once-daily doses of 25, 50, 100, 200, 400, and 600 mg for up to 10 consecutive days. Doses up to 200 mg were well tolerated. At 600 mg, one subject experienced oedema of the feet and hands, and an excessive increase in creatine phosphokinase (CPK) levels, accompanied by elevations of aspartate aminotransferase (AST), C-reactive protein, and myoglobin. Three additional subjects in this dose group presented with oedema of both feet, accompanied by paraesthesia in two cases. At 400 mg, there were three cases of muscle pain, and individual cases of mild and transient paraesthesia, fever, oedema and transient increase in lipase levels (twice the upper limit of normal). All adverse events and laboratory abnormalities resolved after study drug discontinuation.

GALVUS is not dialysable, however the major hydrolysis metabolite (LAY151) can be removed by haemodialysis.

Contact the Poisons Information Centre on 13 11 26 for advice on management.

PRESENTATION

GALVUS (vildagliptin) is available as a 50 mg tablet.

50 mg: white to light yellowish, round, flat-faced, bevelled edge tablet. One side is debossed with "NVR" and the other side with "FB".

GALVUS is available in blisters packs containing 7, 10, 14, 28, 30, 56, 60, 112, 120, 180 or 360 tablets.

Not all pack sizes may be marketed.

Storage: Store below 30°C. Protect from moisture.

Poison Schedule: S4

SPONSOR

Novartis Pharmaceuticals Australia Pty Ltd
ABN 18 004 244 160
54 Waterloo Road
North Ryde NSW 2113

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Therapeutic Goods Administration

PO Box 100 Woden ACT 2606 Australia
Email: info@tga.gov.au Phone: 1800 020 653 Fax: 02 6232 8605
www.tga.gov.au