Dipeptidyl peptidase IV (DPP-4) inhibitors represent a new approach for the treatment of type 2 diabetes mellitus (T2DM). DPP-4 acts rapidly to inactivate the incretin hormones glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic peptide (GIP), which are released into the bloodstream in response to food intake and stimulate the secretion of insulin in a glucose-dependent manner. GLP-1 has other potentially beneficial metabolic effects, including inhibition of glucagon release, slowing of gastric emptying and appetite suppression. In patients with T2DM, the incretin effects of GLP-1 are not reduced although GLP-1 secretion is impaired. Inhibition of DPP-4 activity enhances and prolongs the effects of GLP-1 and thus improves glycaemic control in patients with T2DM.

Vildagliptin is an orally active, potent, selective and reversible DPP-4 inhibitor, shown to be effective and well tolerated in patients with T2DM as monotherapy and in combination with other anti-diabetic agents. Vildagliptin may be administered once daily (50 mg qd) or twice daily (50 mg bid) as either monotherapy or in combination with other anti-diabetic agents. Oral administration of vildagliptin to patients with T2DM resulted in significant inhibition of DPP-4 activity at doses of 10–400 mg with a rapid onset in both non-Japanese and Japanese patients. Greater than 90% DPP-4 inhibition was achieved at all dose tested, and the duration of DPP-4 inhibition was dose-dependent. PK/PD modeling indicates that vildagliptin is a potent DPP-4 inhibitor in both non-Japanese patients (EC50 of 4.5 nM) and in Japanese patients with T2DM (EC50 of 5.0 nM), indicating that there is no evidence of ethnicity sensitivity in the pharmacodynamic endpoint of DPP-4 inhibition. DPP-4 activity was inhibited >80% throughout the entire treatment period with vildagliptin either 50 or 100 mg twice daily despite the relatively short half-life of vildagliptin. This is mostly attributed to the very high potency of DPP-4 inhibition by vildagliptin (EC50 = 5 nmol/L in both Japanese patients and non-Japanese patients). The high potency of vildagliptin is due to its unique binding characteristics at the enzyme level. Vildagliptin is itself a substrate of the DPP-4, and it is cleaved into an inactive metabolite partially by DPP-4 as well. Vildagliptin displays tight binding and slow dissociation from the enzyme, which is reflected by the relatively long dissociation half-life of ~1-hr. This contrasts with other DPP-4 inhibitors such as sitagliptin (EC50 = 25 nM), which is less potent based on the values of EC50 and only inhibit the DPP-4 enzyme competitively. The differential binding kinetics of vildagliptin than sitagliptin is one of the main factors that attributes to the higher potency of vildagliptin and the differential pharmacodynamic effects on GLP-1, glucagon and glucose fluctuation.

Vildagliptin over the dose range of 50–200 mg daily significantly increased the intact GLP-1 by approximately 2-fold and the intact GIP levels by approximately 5-fold, and significantly suppressed the postprandial glucagon levels in response to a meal and during an oral glucose tolerance test (OGTT) in patients with T2DM. As a result, both fasting and postprandial glucose levels were significantly reduced. However, 20 mg daily dose was not an effective dose for reducing glucose. The differences observed in the glucose lowering effects are reflective of the degree to which DPP-4 activity was inhibited. Vildagliptin at 50–200 mg daily produced a high degree of average inhibition (80–95%) over a twenty-four hour time period, while the 20 mg daily regimen allowed significant recovery of DPP-4 activity to a minimum of ~30% of DPP-4 inhibition, and the average DPP-4 inhibition during the entire treatment period was 68%. This finding suggests that the average DPP-4 inhibition over twenty-four hours must exceed approximately 70% to achieve clinically relevant anti-hyperglycemic effects. In a mechanistic study in patients with T2DM, a single dose of vildagliptin (100 mg) given before the evening meal inhibited DPP-4 activity >95% for over 12 hours and decreased endogenous glucose production throughout the overnight post-absorptive period. The reduction in fasting glucose was
directly proportional to that in endogenous glucose production, suggesting that evening dosing may have additional benefit on reducing fasting plasma glucose by more effectively inhibiting endogenous glucose production.

Although insulin levels in response to a meal were not altered by vildagliptin treatment in both Japanese and non-Japanese patients with T2DM, increased insulin levels were observed during OGTT, indicating that stimulation of insulin secretion after vildagliptin treatment is glucose-dependent. In addition, insulin secretion can improve without changes being observed in plasma insulin levels, and insulin levels should be considered in the context of the glucose concentration when assessing beta-cell function. The effects of vildagliptin on beta-cell function was evaluated using a model that describes insulin secretion rate (ISR) as a function of the theoretical absolute glucose levels, the rate of change of glucose (derivative factor), and a potentiation factor\(^\text{10}\). The insulin secretion rate was significantly improved by treatment with vildagliptin when the reduced glucose levels were included in the pharmacodynamic modeling, indicating the potential beneficial effects of vildagliptin on beta-cell function. Of note, a postprandial increase in glucagon was significantly suppressed by vildagliptin in response to a meal challenge or OGTT\(^\text{11,12,16}\). It is particularly interesting that the mechanism of action of vildagliptin includes a significant reduction in glucagon secretion in response to a meal, suggesting that alpha-cell function may be improved. Glucagon is a major contributor to hepatic glucose production and hyperglucagonemia, and is a central component in the pathogenesis of T2DM\(^\text{17,18}\). Abnormalities in pancreatic alpha-cell function in patients with T2DM mean that hyperglycemia does not suppress glucagon release to the extent seen in individuals with normal glucose regulation\(^\text{19,20}\). Restoring appropriate glucagon regulation is thus an important potential target for intervention. Recently, vildagliptin is also demonstrated to improve sensitivity of the alpha-cell to glucose in a glycemic clamp study in patients with T2DM\(^\text{21}\). Vildagliptin enhances alpha-cell responsiveness to both the suppressive effects of hyperglycemia and the stimulatory effects of hypoglycaemia. The glucose-dependent response in glucagon secretion with vildagliptin treatment not only leads to a more normal glycemic profile but also is likely to reduce risk of hypoglycaemia observed with other anti-diabetic agents. Indeed, low hypoglycaemic potential when vildagliptin is used in combination with other anti-diabetic agents such as insulin has been demonstrated, and this is consistent with the above mentioned mechanistic findings\(^\text{22,23}\).

In conclusion, vildagliptin demonstrated more physiological effects on reducing both fasting and postprandial glucose in response to a meal by suppressing endogenous glucose production during the overnight period, and by enhancing the islet function (improvement of both beta- and alpha-cell function) through the endogenous effects of incretin hormones.

References