The key defect in Type 2 diabetes is islet dysfunction which includes impaired insulin secretion, augmented glucagon secretion and reduced β-cell mass. The incretin hormone GLP-1 targets this islet dysfunction. GLP-1 is inactivated by DPP-4 and, consequently, DPP-4 inhibition has evolved as an efficient treatment of the hyperglycemia in type 2 diabetes since it increases the concentrations of intact GLP-1. Several DPP-4 inhibitors have been developed and all of them have shown to be efficient in improving glycemia with a low risk for adverse events. This article reviews basic and clinical studies on one of the DPP-4 inhibitors, vildagliptin. It is a specific inhibitor of DPP-4 and improves glycemia both when used in monotherapy and when used as add-on to ongoing therapy with metformin, sulphonylurea, thiazolidinedione or insulin. Clinical studies have shown that vildagliptin reduces HbA1c in association with a low risk of adverse events, including hypoglycemia, and no weight gain. Vildagliptin is also efficient in elderly patients and in patients with renal impairment. Its main place in therapy is as add-on to ongoing therapy with metformin alone is insufficient for reaching the glycemic target. Vildagliptin may also be used as monotherapy in patients in whom metformin cannot be used and as add-on to sulphonylurea or thiazolidinedione. In the future, it will also be used as add-on to insulin therapy. There is at present an extensive experience with the use of vildagliptin for at least 5 years in many countries. However, long-term surveillance of its effects and safety is still of importance.
Type 2 diabetes is a global disease, which is increasingly diagnosed, with glucose and lipid abnormalities resulting in micro- and macro-vascular complications. Reducing the burden of the disease and its complications by prevention and treatment is one of the most important health challenges of our time. For this, there is a need of well-organized health-care systems and tools for improving metabolic abnormalities.

Key importance in the management of type 2 diabetes is targeting the hyperglycemia, since elevated glucose is a risk factor both for acute symptoms of the disease and for the increased risk for retinopathy, nephropathy, and neuropathy [1]. Improving glycemia is also of importance for reducing the high cardiovascular risk in Type 2 diabetes [2]. Of importance in this management is to target the key factor underlying hyperglycemia, which is islet dysfunction, involving impaired insulin secretion [3], defective suppression of glucagon secretion [4] and reduced β-cell mass [5]. Glucose-lowering treatment guidelines from various bodies suggest metformin as the first-line pharmacologic agent when dietary and lifestyle changes are not sufficient, followed by addition of sulphonylurea, thiazolidinediones, α-glucosidase inhibitors and/or insulin when metformin alone is insufficient as pharmacological agents [6]. However, only up to 50% of the patients reach the target for glycemic control when using these therapies. Therefore, there is great hope for novel therapies. During recent years, DPP-4 inhibitors and GLP-1 receptor agonists have emerged as new classes of therapeutic agents [7].

**DPP-4 inhibition**

The rationale behind the use of the DPP-4 inhibitors in therapy of type 2 diabetes is that they inhibit the catalytic site of the widely distributed enzyme DPP-4 which inactivates the gut incretin hormones GLP-1 and glucose-dependent insulinotropic polypeptide (GIP) [8]. Therefore, DPP-4 inhibition prevents the inactivation of these hormones which results in increased the prandial endogenous levels of intact GLP-1 and GIP by approximately two-three-fold. The consequence of this is that insulin secretion is stimulated and glucagon secretion is inhibited, and these effects occur in a glucose-dependent manner. DPP-4 inhibition therefore targets the key pathophysiological factors of type 2 diabetes.

Already in the 1990s, it was suggested that inhibition of DPP-4 is a target to treat Type 2 diabetes [9]. Initial animal studies supported this assumption and paved the way for the first clinical proof-of-concept for DPP-4 inhibitors in subjects with type 2 diabetes, which was published in 2002 [10]. Several DPP-4 inhibitors have subsequently been developed and at present five different DPP-4 inhibitors are approved for clinical use in various countries (vildagliptin, sitagliptin, saxagliptin, linagliptin and alogliptin). These DPP-4 inhibitors are all small molecules that are oral agents being potent inhibitors of the enzyme. They differ in chemical structure, in mode of inhibiting the catalytic site of the enzyme, in specificity towards inhibition of other enzymes and in pharmacokinetics, as recently was reviewed [11]. In terms of clinical efficacy and safety, they have not been examined in long-term head-to-head studies. However, they are all efficacious when used both in monotherapy and in combination therapy with other treatments and by comparing the many studies involving each of them, it seems as they similarly reduce HbA1c with a similarly good tolerability and a low risk for adverse events [12]. This article is focused on vildagliptin.

**Vildagliptin: chemical & pharmacokinetic characteristics**

Vildagliptin is a small molecule with a cyano-pyrroolidine structure with a nitrile group which specifically binds to and inhibit the catalytic site of DPP-4 [13]. The binding is long-lasting, which enables vildagliptin to inhibit DPP-4 over a longer period of time than would be expected from its circulating half-life. Thus, it has been shown that the circulating half-life of vildagliptin is only approximately 2h [14] whereas the inhibition of DPP-4 activity after a single dose (of 50 mg) lasts for approximately 12 h [15].

Following oral administration, vildagliptin is rapidly absorbed with a bioavailability of approximately 85% [16]. Vildagliptin is extensively metabolized, which is primarily a hydrolysis process in many tissues, including in the liver. Only approximately 22% of administered vildagliptin is eliminated as the parent compound. As demonstrated by He and collaborators [14], there are four metabolic pathways resulting in one major and four minor metabolites, which all are devoid of DPP-4 inhibitory activity. The major metabolite (M20.7) accounts for 55% of metabolism of vildagliptin and is produced through hydrolysis of the cyanogroup. This metabolism is independent from the CYP450
complex, indicating no important interactions with drugs eliminated by this route. Of interest is that the DPP-4 enzyme itself is responsible for $\Delta 20\%$ of vildagliptin metabolism by hydrolyzing the cyano group. Vildagliptin and its metabolites are all primarily eliminated through the kidney, with only approximately $5\%$ eliminated in the faces. The renal clearance of vildagliptin and its metabolites is higher than the glomerular filtration rate, suggesting both passive filtration and active renal transportation as mechanisms for the elimination.

Since vildagliptin is cleared through kidney, its plasma levels are elevated in kidney insufficiency [14]. Therefore, when vildagliptin is used in patients with moderate (GFR $30–50$ ml/min) or severe (GFR $<30$ ml/min) renal impairment, the administered dose is reduced to $50$ mg QD whereas in subjects with normal kidney function or mild renal impairment (GFR $>50$ ml/min), the dose is $50$ mg BID. Furthermore, although vildagliptin is metabolized in the liver, no increase in vildagliptin concentrations is seen in subjects with mild or moderate hepatic insufficiency compared with subjects with normal liver function, whereas in subjects with severe hepatic insufficiency, there is an increase vildagliptin exposure after administration [17]. Table 1 summarizes the pharmacokinetic characteristics of vildagliptin.

**Vildagliptin: pharmacodynamics characteristics**

Vildagliptin augments the increase in levels of intact GLP-1 and GIP after oral glucose [18] and mixed meal [19,20]. Postprandial levels of intact GLP-1 are raised to $\Delta 15–20$ pmol/l after vildagliptin versus $\Delta 5–10$ pmol/l after placebo [19,20] and postprandial intact GIP levels are raised to $\Delta 100$ pmol/l after vildagliptin versus $\Delta 50$ pmol/l after placebo [18]. Also fasting GLP-1 and GIP levels are increased during treatment with vildagliptin, from $\Delta 3–5$ pmol/l to $\Delta 5–10$ pmol/l (GLP-1) and from $\Delta 20$ pmol/l to $\Delta 40$ pmol/l (GIP) [20]. These results show that there is increased exposure to the incretin hormones throughout the entire 24 h period. As a consequence, vildagliptin stimulates insulin secretion in a glucose-dependent manner [21]. The stimulation of insulin secretion by vildagliptin is long-standing and evident also after at least one year of treatment [22]. Vildagliptin also reduces proinsulin, which is another sign of improved $\beta$-cell function [23].

Vildagliptin also suppresses glucagon secretion, as shown after oral glucose and meal ingestion [18,19]. This suppresses hepatic glucose production [24]. The reduction in glucagon levels by vildagliptin correlates to the improved glycemia, as shown after a four week study period in drug-naïve patients [19].

It has recently been demonstrated that in contrast to the inhibition by vildagliptin of glucagon secretion during hyperglycemia, glucagon levels are not suppressed by vildagliptin at low glucose levels [25]. Hence, the effect of vildagliptin on glucagon secretion is glucose-dependent. The mechanism of the sustained glucagon secretion during hypoglycemia by vildagliptin is not known but may be explained by GIP, which has been shown to stimulate glucagon secretion during hypoglycemia [26]. It may also be explained by a reduction in insulin secretion during the hypoglycemia and/or by increased autonomic activity [25]. In any case, the sustaintment of glucagon secretion during hypoglycemia by vildagliptin is an important mechanism to prevent hypoglycemia during treatment with vildagliptin, particularly when used in combination with insulin.

Vildagliptin increases $\beta$-cell mass in streptozotocin-injected neonatal rats [27] and also improves the islet topography in diabetic mice [28]. Whether such an effect occurs in humans is not known. One study showed that one year treatment with vildagliptin increased the $\beta$ cell secretory effect, but after a 12 week washout, this effect had disappeared, suggesting that no disease modifying effect on $\beta$ cell mass or function...
is evident after one year of therapy [29]. On the other hand, a two-year study in patients with type 2 diabetes having mild hyperglycaemia may indicate that such an effect may occur [30]. Thus, during the first year of treatment, the increased insulin secretion by vildagliptin declined following a four week wash out period, whereas after the second year of treatment, insulin secretion was higher after treatment with vildagliptin than in the placebo group, also after four week wash out [30]. This needs, however, to be verified in long-term studies.

Vildagliptin has also been shown to reduce fasting lipolysis, which may be a direct adipocyte action of the incretin hormones [21]. At the same time, vildagliptin also increases postprandial lipolysis in adipose tissue (probably through increased noradrenaline levels) in association with increased postprandial muscle fat oxidation [31]. These two actions together suggest that fat accumulated in adipocytes during fasting may be mobilized and burned in muscle in the fed state during vildagliptin treatment. Furthermore, it has also been demonstrated that postprandial triglyceride-rich lipoprotein levels are reduced by vildagliptin after a fat-rich meal in patients with type 2 diabetes, mainly through reduction in Apo B-48 [32]. The mechanism explaining the reduced postprandial lipemia after vildagliptin has not been established. It is possible that the effect is mediated by GLP-1, since, interestingly, it has been reported that GLP-1 inhibits triglyceride absorption in rats [33]. Furthermore, DPP-4 inhibition (sitagliptin) and GLP-1 receptor activation (exendin-4) have been shown to reduce intestinal secretion of triglycerides and Apo B-48 in mice, and, conversely, this intestinal secretion is enhanced in mice with genetic deletion of the GLP-1 receptor [34].

Vildagliptin has also been demonstrated to increase glucose disposal during hyperinsulinemic, euglycemic clamp by an effect independent from changes in insulin levels [35]. This may be explained by reduced glucose- and/or lipotoxicitiy and by reduction in fatty acid oxidation. In contrast, vildagliptin does not seem to affect gastric empyerying, gastric volume and satiety [36].

Table 2 summarizes the islet and extra-islet effects of vildagliptin.

**Differences & similarities to other DPP-4 inhibitors**

Tables 1 & 2 show the well-documented characteristics of vildagliptin. Since there are several other DPP-4 inhibitors available for the treatment of type 2 diabetes, it is of interest to compare them. Although there is a shortage in studies directly comparing the various DPP-4 inhibitors, some similarities and differences can be concluded from the literature. In regard to the pharmacokinetic characteristics, comparisons between the DPP-4 inhibitors have been performed in detail [11,37]. In short, all available DPP-4 inhibitors are rapidly absorbed after oral intake and they are extensively distributed in the body without crossing the cell membranes. A difference between the DPP-4 inhibitors is degree of protein binding: the low protein binding of vildagliptin is similar to that of most other DPP-4 inhibitors with an exception of linagliptin, which binds extensively to proteins. Moreover, all DPP-4 inhibitors effectively prevents the inactivation of the incretin hormones by DPP-4 due to binding to the catalytic site of DPP-4 by either covalent (vildagliptin and saxagliptin) or noncovalent (sitagliptin, alogliptin, linagliptin) binding. The duration of DPP-4 inhibition is dose-dependent for the DPP-4 inhibitors, and in the clinically used doses, vildagliptin inhibits DPP-4 for 12–16 h, whereas the inhibition of the other four DPP-4 inhibitors is 24 h [11]. Therefore, vildagliptin is dosed twice daily, whereas the others are dosed once daily. Furthermore, under in vitro conditions, high doses of vildagliptin and saxagliptin also inhibit the DPP-4 like enzymes DPP-8 and DPP-9 (the function of which are unknown), whereas this does not occur for the other DPP-4 inhibitors. This is, however, probably of no importance under in vivo conditions, since these enzymes, in contrast to DPP-4, are strictly intracellular enzymes, and the DPP-4 inhibitors do not cross the plasma membranes. Furthermore, the degree of metabolism also differs between the DPP-4 inhibitors, and, like vildagliptin, also saxagliptin is metabolized, whereas sitagliptin, linagliptin and alogliptin are not metabolized [11]. Circulating half life differs also between the DPP-4 inhibitors, from the low half-life of vildagliptin and saxagliptin, through medium half life (approximately 10–24 h) for sitagliptin and alogliptin to long half life (up to 40 h) for linagliptin. In terms of elimination, linagliptin is mainly eliminated through the biliary route, whereas the others, like vildagliptin, are cleared renally.

Since the DPP-4 inhibitors all are effective inhibitors of the catalytic site of DPP-4, they all prevent the inactivation of GLP-1, which
increases the circulating level of the intact form of the incretin, stimulates insulin secretion and inhibits glucagon secretion with improvement in glycemia. This is also what has been seen in studies, as reviewed in this article for vildagliptin, although the various DPP-4 inhibitors have been studied in different studies and also with different emphasis to characterize their mechanistic actions. Finally, all DPP-4 inhibitors improve glycemia under different conditions in patients with type 2 diabetes, and they are safe with very low risk for adverse events, including hypoglycemia. Presently, there does not seem to be differences in glycemic effect, safety or tolerability when meta-analysis are performed [38]. However, head-to-head studies are required to compare the DPP-4 inhibitors in more detail.

**Vildagliptin: clinical experience in monotherapy**

The first clinical study with vildagliptin in patients with type 2 diabetes was a four-week trial when vildagliptin was administered as monotherapy to previously drug-naïve patients [18]. The patients had a baseline HbA1c of 7.2% and this was reduced by 0.53% by vildagliptin within the four-week study period. At the end of the trial, a standard meal was served and it was found that vildagliptin reduced glucose excursion and at the same time reduced glucagon levels but sustained insulin levels. This study therefore showed improved islet function in association with improved glycemia by vildagliptin. This study was followed by several studies with vildagliptin as monotherapy in patients with type 2 diabetes lasting 12–24 weeks with larger number of patients [Table 3] [39–48]. One study also examined vildagliptin in monotherapy [50 mg once daily] for 12 weeks in subjects with impaired glucose tolerance (HbA1c 5.9%) [43]. Vildagliptin reduced prandial glucose by 32% in these subjects. These studies together also show that the risk for adverse events is very low with vildagliptin. Thus, the number of adverse events reported during treatment with vildagliptin is not higher than during treatment with placebo. Of particular importance from a clinical perspective is that the degree of hypoglycemia is very low (<1%) and that no weight gain was observed with vildagliptin.

Vildagliptin has also been examined as monotherapy in head-to-head comparisons with other therapy. One study compared treatment with vildagliptin versus metformin in subjects with a mean baseline HbA1c 8.7% [44]. During the 1-year study period, HbA1c was reduced by 1.0% by vildagliptin and by 1.4% by metformin; which was not noninferior by vildagliptin compared with metformin. Body weight was not changed by vildagliptin (+0.3 kg) and reduced by metformin (-1.9 kg). The total number of adverse events was similar in the two groups, but patients treated with vildagliptin experienced lower rates of gastrointestinal adverse events than in the group treated with metformin (a 3–4-fold higher incidence of diarrhea, nausea and abdominal pain in that group); hypoglycemia was rare in both groups.

Another study compared the long-term (2-year) effect of vildagliptin with rosiglitazone when given as monotherapy to patients with
inadequate glycemic control when treated with diet and exercise alone (mean HbA1c 8.6%) [45]. It was found HbA1c was reduced by 0.8% by vildagliptin and by 1.4% by rosiglitazone, that body weight did not change during vildagliptin but was increased by 4.7 kg in the rosiglitazone-treated group, and that the number of patients with peripheral oedema was lower with vildagliptin.

Two studies have compared vildagliptin with α-glucosidase inhibitors as monotherapy, one study with voglibose in Japanese patients [46] and one study with acarbose in Chinese subjects [47]. The 12-week study in comparison with voglibose showed that vildagliptin reduced HbA1c by 0.95% and voglibose by 0.38% (baseline HbA1c 7.6%), and the 24-week study with acarbose showed that vildagliptin reduced HbA1c by 1.4% and acarbose by 1.3% (baseline HbA1c 8.6%). Both studies showed that patients on vildagliptin was associated with lower degree of gastrointestinal adverse events than were the α-glucosidase inhibitors.

Vildagliptin: clinical experience in combination with metformin

There is an extensive experience with vildagliptin as an add-on therapy to metformin in patients with type 2 diabetes who are insufficiently controlled with metformin alone, and also when used in initial combination with metformin. The conclusion from these studies is that vildagliptin is efficient in improving glycemia in association with a low risk for adverse events, including hypoglycemia, and with weight neutrality (Table 3) [48–53]. The first study examining vildagliptin as add-on to metformin was a 12 week study which was followed by a 40-week extension period in patients with baseline HbA1c of 7.8% (49). The results showed a

Table 3. Summary of clinical trials when vildagliptin has been examined in subjects with Type 2 diabetes either as monotherapy, as add-on to on-going therapy with metformin, glimepiride, pioglitazone or insulin, or as initial combination therapy with metformin.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Duration (weeks)</th>
<th>Baseline HbA1c (%)</th>
<th>Change in HbA1c by vildagliptin (%)</th>
<th>n</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Monotherapy (100 mg QD)</td>
<td>4</td>
<td>7.2</td>
<td>-0.53</td>
<td>18</td>
<td>[19]</td>
</tr>
<tr>
<td>Monotherapy (100 mg QD)</td>
<td>12</td>
<td>7.64</td>
<td>-0.53</td>
<td>63</td>
<td>[39]</td>
</tr>
<tr>
<td>Monotherapy (25 mg BID)</td>
<td>12</td>
<td>8.0</td>
<td>-0.26</td>
<td>70</td>
<td>[40]</td>
</tr>
<tr>
<td>Monotherapy</td>
<td>24</td>
<td>8.4</td>
<td>-0.7</td>
<td>83</td>
<td>[41]</td>
</tr>
<tr>
<td>Monotherapy (50 mg QD)</td>
<td>24</td>
<td>8.4</td>
<td>-0.8</td>
<td>163</td>
<td>[42]</td>
</tr>
<tr>
<td>Monotherapy</td>
<td>24</td>
<td>8.4</td>
<td>-0.8</td>
<td>152</td>
<td>[42]</td>
</tr>
<tr>
<td>Monotherapy (100 mg QD)</td>
<td>24</td>
<td>8.4</td>
<td>-0.9</td>
<td>157</td>
<td>[42]</td>
</tr>
<tr>
<td>Monotherapy</td>
<td>52</td>
<td>8.7</td>
<td>-1.0</td>
<td>526</td>
<td>[44]</td>
</tr>
<tr>
<td>Monotherapy</td>
<td>104</td>
<td>8.6</td>
<td>-0.82</td>
<td>396</td>
<td>[45]</td>
</tr>
<tr>
<td>Monotherapy</td>
<td>12</td>
<td>7.6</td>
<td>-0.95</td>
<td>188</td>
<td>[46]</td>
</tr>
<tr>
<td>Monotherapy</td>
<td>24</td>
<td>8.6</td>
<td>-1.4</td>
<td>441</td>
<td>[47]</td>
</tr>
<tr>
<td>Monotherapy</td>
<td>24</td>
<td>8.6</td>
<td>-1.1</td>
<td>300</td>
<td>[50]</td>
</tr>
<tr>
<td>Metformin</td>
<td>52</td>
<td>7.7</td>
<td>-0.6</td>
<td>56</td>
<td>[49]</td>
</tr>
<tr>
<td>Metformin</td>
<td>24</td>
<td>7.5</td>
<td>-1.1</td>
<td>185</td>
<td>[50]</td>
</tr>
<tr>
<td>Initial Metformin (500 mg BID)</td>
<td>24</td>
<td>8.6</td>
<td>-1.6</td>
<td>290</td>
<td>[50]</td>
</tr>
<tr>
<td>Initial Metformin (1000 mg BID)</td>
<td>24</td>
<td>8.7</td>
<td>-1.3</td>
<td>295</td>
<td>[50]</td>
</tr>
<tr>
<td>Metformin</td>
<td>52</td>
<td>7.3</td>
<td>-0.44</td>
<td>1396</td>
<td>[51]</td>
</tr>
<tr>
<td>Metformin</td>
<td>52</td>
<td>8.4</td>
<td>-0.9</td>
<td>295</td>
<td>[53]</td>
</tr>
<tr>
<td>Glimepiride (50 mg QD)</td>
<td>24</td>
<td>8.5</td>
<td>-0.58</td>
<td>132</td>
<td>[54]</td>
</tr>
<tr>
<td>Glimepiride</td>
<td>24</td>
<td>8.6</td>
<td>-0.63</td>
<td>132</td>
<td>[54]</td>
</tr>
<tr>
<td>Glimepiride</td>
<td>12</td>
<td>7.9</td>
<td>-1.0</td>
<td>102</td>
<td>[55]</td>
</tr>
<tr>
<td>Pioglitazone (50 mg QD)</td>
<td>24</td>
<td>8.6</td>
<td>-0.8</td>
<td>147</td>
<td>[56]</td>
</tr>
<tr>
<td>Pioglitazone</td>
<td>24</td>
<td>8.7</td>
<td>-1.0</td>
<td>158</td>
<td>[56]</td>
</tr>
<tr>
<td>Insulin</td>
<td>24</td>
<td>8.4</td>
<td>-0.5</td>
<td>144</td>
<td>[57]</td>
</tr>
</tbody>
</table>

Dosage of vildagliptin is 50 mg BID unless otherwise stated. Duration of therapy, baseline HbA1c, change in HbA1c from baseline by vildagliptin and number (n) of patients in the vildagliptin arm of the various trials are shown.
placebo-adjusted reduction in HbA1c of 0.7% during the initial 12 weeks and of 1.1% after the entire 52 week study period. Furthermore, in a larger 24-week study, vildagliptin reduced HbA1c by 1.1% from a baseline of 7.5% when added to metformin [50], and an initial combination with vildagliptin plus metformin reduced HbA1c by 1.6–1.7% (depending on metformin dose) from baseline of 8.6% after 24 weeks [48]. These studies thus show potent efficacy of the combination of vildagliptin and metformin.

One long-term (52-week) study compared the add-on to metformin of vildagliptin versus glimepiride [52]. The main results of this study are shown in Figure 2. The study showed that the two compounds similarly reduced HbA1c similarly (by 0.4 and 0.5%, respectively, from the baseline of 7.3%) whereas adverse events were markedly different in the groups in favor of vildagliptin [51]. This difference in degree of hypoglycemia and body weight between vildagliptin and glimepiride persisted throughout a second year extension of this study [52]. Another study compared vildagliptin with pioglitazone as add-on to metformin in patients with mean HbA1c 8.4% and showed reduction in HbA1c by 0.9% by vildagliptin and by 1.0% by pioglitazone [53]. There was no difference in the overall number of adverse events between the two groups but body weight increased by pioglitazone (by 2.6 kg) but not by vildagliptin (+0.2 kg).

**Vildagliptin: clinical experience in combination with sulphonylurea, thiazolidinedione or insulin**

Vildagliptin improves glycemia when added to on-going therapy with sulphonylurea. Thus, in a 24-week study, vildagliptin, added to on-going therapy with glimepiride, the placebo-adjusted HbA1c was reduced by 0.6% by vildagliptin at 50 mg once daily and 0.76% at 50 mg twice daily [54]. Another study investigated the effects and tolerability of vildagliptin when added to on-going therapy with glimepiride in Japanese patients with type 2 diabetes having a mean HbA1c of 7.9% [55]. During the 12-week study period, vildagliptin reduced HbA1c by 1.0% with no significant change in HbA1c (-0.1%) in the placebo-treated group which continued with glimepiride therapy. There was no difference in adverse events between the two treatment arms; hypoglycemia was observed in only three of the 202 patients: two in the vildagliptin group and one in the placebo group.

Vildagliptin also improved glycemia when added to on-going therapy with pioglitazone in a 6-month study in patients with a mean baseline HbA1c of 8.6% [56]. Vildagliptin reduced HbA1c by 1.1% (50 mg BID) versus 0.3% in the placebo given pioglitazone alone. One study has evaluated the add-on of vildagliptin to insulin in subjects type 2 diabetes mean baseline HbA1c 8.9% over 24 weeks [57]. HbA1c was reduced by vildagliptin by 0.5% versus 0.2% in the group given insulin alone. This was associated with a reduced risk for hypoglycemia.

**Vildagliptin: clinical experience in very elderly patients & in patients with renal impairment**

A recent publication undertook a meta-analysis of patients treated with vildagliptin in seven monotherapy studies (baseline HbA1c 8.3%) and in three studies on add-on to metformin (baseline HbA1c 8.5%) in patients >75 years old (mean age 77 years) to report efficacy and safety
of the treatment in this patient group [58]. The results showed that vildagliptin reduces HbA1c by 0.9% in monotherapy and by 1.1% when used as add-on to metformin. This was associated by small reduction in body weight (by 0.9 kg) in the monotherapy studies with no change in body weight when studied as add-on to metformin. No hypoglycemia occurred in the studies and adverse events were reported by the same degree in vildagliptin treated patients and controls. It was therefore concluded that vildagliptin is safe and efficacious also in very elderly patients with type 2 diabetes.

One study examined the 24-week safety, tolerability and efficacy of vildagliptin when used in patients with type 2 diabetes having moderate (n=165; baseline HbA1c 7.9%; GFR 30–50 ml/min) or severe (n=97; baseline HbA1c 7.7%; GFR <30 ml/min) renal impairment [59]. The patients continued with their background antidiabetic medication (in most cases insulin) and vildagliptin (50 mg QD) or placebo was added. Compared to placebo vildagliptin reduced HbA1c by 0.5–0.6% without any increased risk for adverse events or worsening of renal impairment. Hence, vildagliptin may be an option for the antihyperglycemic management of patients with type 2 diabetes and renal impairment, and because vildagliptin is eliminated by the kidney [14], it has been approved for use in patients with GFR <50 ml/min at the dose of 50 mg QD.

Vildagliptin: experience on safety & tolerability
As evident from the large number of clinical trials, vildagliptin is well tolerated, and the number of adverse effects is low, and in fact not different from numbers of adverse events seen in placebo groups [60]. This relates to all types of reported adverse events, such as for example urinary tract or respiratory infections or headache. Furthermore, retrospective analyses of clinical trials has neither shown any increased risk for fractures, cancer or cardiovascular events during treatment with vildagliptin or other DPP-4 inhibitors [61–63]. A large meta-analysis has also been undertaken to examine the cardiovascular safety of vildagliptin in relation to other therapies. The study was a pooled analysis of 25 Phase III-studies using vildagliptin as mono- or combination therapy for more than 12 weeks and the study comprised more than 6 000 patients. A subgroup analysis also examined the cardiovascular safety in patients who have a higher risk, mainly in those with a preceding cardiovascular event. It was found that the relative risk for a major acute cardiovascular event for vildagliptin (50 mg BID) compared with other comparators was 0.84% with a confidence interval of 0.62–1.14, that is, no significantly increased risk compared with comparators [64]. The cardiovascular safety of vildagliptin is also reinforced by a study on effects of vildagliptin on cardiac repolarization and conduction in 101 healthy volunteers given vildagliptin consecutively for 5 days [65]. The study showed that vildagliptin did not prolong the QT interval on ECG or affected cardiac conductivity showing no deleterious effects on cardiac repolarization and conductivity in healthy subjects.

It has been discussed whether incretin-based therapies increase the risk of pancreatitis [66], since pancreatitis has occurred during this treatment. There are also clinical reports of acute pancreatitis in patients treated with vildagliptin [67]. However, there does not seem to be any
increased risk for acute pancreatitis in patients treated with vildagliptin when compared with the generally increased risk for pancreatitis in type 2 diabetes, as shown in pooled analyses [60]. This pooled analyses of more than 7000 subject-years of exposure to vildagliptin and 6 500 subject-years of exposure to comparators showed that the odds ratio for pancreatitis with vildagliptin compared with comparators was 0.70 with a confidence interval of 0.26–1.88, that is, no significant difference. A meta-analysis of all clinical trials with all DPP-4 inhibitors arrived at the same conclusion [63]. Nevertheless, it is important for longer follow-up periods and postmarketing surveillance in regard to long-term safety, but the experience of today suggest a high tolerability with no additional risk for adverse events with vildagliptin or the other DPP-4 inhibitors.

In an earlier meta-analysis of clinical trials it was found that when vildagliptin was administered at 100 mg QD, a small increase in liver transaminases occurred when compared with the clinically recommended dosing of 50 mg BID, although this was not related to any increased risk for hepatic adverse events [60]. Liver function tests are therefore recommended before and regularly during treatment with vildagliptin.

Vildagliptin & potential effects on diabetes complications

It has been demonstrated that GLP-1 receptors are widely expressed and therefore that there is a potential that GLP-1 affects a number of different organs in the body, such as the heart, bones, kidney and the nervous system [68]. It is therefore possible that DPP-4 inhibitors have also extra-pancreatic effects which may be beneficial for patients treated with these agents. During recent years, potential cardiovascular benefits of incretin-based therapy has been discussed. Both the heart and endothelial cells express GLP-1 receptors, and administration of GLP-1 has been shown to be cardioprotective and to improve endothelial function in different conditions [69]. Improvement of cardiovascular morbidity is therefore a possibility in the long-term treatment with incretin-based therapy [70]. Several long-term cardiovascular outcome studies have therefore been initiated; results from those are expected from the year 2014 and following years. Presently, therefore, no evidence for this has been presented in controlled clinical studies. However, a meta-analysis of clinical trials has examined the risk for major cardiovascular events during treatment with any of several different DPP-4 inhibitors in 40 different clinical trials. This analysis showed a trend for each of the DPP-4 inhibitors (sitagliptin, vildagliptin, saxagliptin and alogliptin) towards a lower cardiovascular risk compared with comparators [63]. This trend did not, however, reach significance for any of the individual DPP-4 inhibitors, but if all 40 studies were analysed together, there was a significantly reduced risk for major acute cardiovascular diseases during clinical trials in patients treated with DPP-4 inhibitors than with comparators. The widespread expression of GLP-1 receptors in vascular cells also may suggest that incretin based therapy may improve also microvascular complications, which has not yet been studied in detail [71].

Vildagliptin: clinical positioning

Since vildagliptin improves islet function and therefore targets the key pathophysioligic defects in type 2 diabetes, it may be used both in early and in late stages of the disease. A preferential positioning of vildagliptin is as add-on to metformin, sulphonylurea or thiazolidinediones in subjects with inadequate glycaemic control on these therapies alone. Vildagliptin also holds promises as monotherapy in subjects in whom metformin is contraindicated or unsuitable, and as add-on to insulin therapy in subjects to improve glycemia and at the same time reduce the risk for hypoglycemia and/or weight gain. It should also be emphasized that vildagliptin is efficient across all age groups and in patients with low and high BMI, as well as in patients with renal impairment. Vildagliptin will therefore be of particular importance in the treatment of elderly patients and of patients with renal impairment, where several of the other therapies are undesirable. Finally, the low risk for hypoglycemia with vildagliptin also suggests that it may be used in patients where hypoglycemia is undesirable. Vildagliptin, toether with the other DPP-4 inhibitors, therefore offer a well documented glucose-lowering option in the treatment of Type 2 diabetes.

Future perspective

Vildagliptin has been characterized in detail in regard to chemistry and binding characteristics, pharmacokinetics, pharmacodynamics and clinical effects and possibilities. What is now important to study is long-term durability and effects
on long-term end points over two years, which are the time period for the so far longest studies. Furthermore, for exact clinical positioning in relation to other therapy it will also be important to undertake head-to-head comparison with other DPP-4 inhibitors, to allow guidelines to be more specific. Comparisons between DPP-4 inhibitors and GLP-1 receptor agonists are also of interest; two already reported comparisons have shown that GLP-1 receptor agonists (liraglutide or exenatide) have better effects on HbA1c and lowering of body weight that DPP-4 inhibition (sitagliptin) and this is supported by meta-analysis [38,72,73]. Widening the indication also to Type 1 diabetes is another future possibility for DPP-4 inhibitors, as recently was suggested for vildagliptin based on results of a four week study period [74]. Finally, there are also interesting future perspectives for the incretin therapy field as a whole, including development of novel approaches, such as combining DPP-4 inhibitors with GLP-1 secretagogues as a therapy [75].

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