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DPP-4 inhibitor therapy: new directions in the treatment of type 2 diabetes

Carolyn F Deacon[1], Richard D Carr[2], Jens J Holst[1]

[1]Department of Biomedical Sciences, Panum Institute, Blegdamsvej 3, DK-2200 Copenhagen N, Denmark ,[2]Merck Sharp & Dohme, Smedeland 8, DK-2600 Glostrup, Denmark

TABLE OF CONTENTS

1. ABSTRACT

Many patients with type 2 diabetes fail to achieve adequate glycaemic control with available treatments, even when used in combination, and eventually develop microvascular and macrovascular diabetic complications. Even intensive interventions to control glycaemia reduce macrovascular complications only minimally. There is, therefore, a need for new agents that more effectively treat the disease, as well as target its prevention, its progression, and its associated complications. One emerging area of interest is centred upon the actions of the incretin hormones glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP), which enhance meal-induced insulin secretion and have trophic effects on the beta-cell. GLP-1 also inhibits glucagon secretion, and suppresses food intake and appetite. Two new classes of agents have recently gained regulatory approval for therapy of type 2 diabetes; long-acting stable analogues of GLP-1, the so-called incretin mimetics, and inhibitors of dipeptidyl peptidase 4 (DPP-4, the enzyme responsible for the rapid degradation of the incretin hormones), the so-called incretin enhancers. This article focuses on DPP-4 inhibitors.

2. INTRODUCTION

Type 2 diabetes mellitus (T2DM) is characterised by insulin resistance, impaired glucose-induced insulin secretion and inappropriately elevated glucagon concentrations that eventually result in hyperglycaemia. It may be considered one component of the so-called metabolic syndrome, which comprises, in addition to T2DM or insulin resistance, a variety of disorders, including arterial hypertension, dyslipidaemia and obesity. Despite the range of oral agents targeting different facets of diabetes (metformin, thiazolidinedione [TZD] insulin sensitisers, sulphonylureas), available treatment paradigms are unsatisfactory, with many patients failing to achieve adequate glycaemic control, even when multidrug approaches are used, necessitating the eventual use of insulin therapy to control hyperglycaemia. While the United Kingdom Prospective Diabetes Study (UKPDS) indicated that intensive intervention to control glycaemia reduced the incidence of the microvascular (1) and macrovascular (2) complications of T2DM, subsequent reanalysis demonstrated that the reduction in risk of macrovascular disease was only of borderline significance

(3). There is, therefore, a need for new and more efficacious agents, targeted not only at treatment, but also at prevention of the disease, its progression and its associated complications.

One new approach is based upon the effects of the incretin hormones glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP). These are gastrointestinal peptides, released following food ingestion, that enhance meal-induced insulin secretion (4). In addition, GLP-1 has a spectrum of other effects thought to be desirable in an antidiabetic agent, including trophic effects on the beta-cell, inhibition of glucagon secretion and suppression of appetite and food intake (5). The native peptides cannot be used therapeutically because they are labile *in vivo* and are rapidly degraded by the enzyme dipeptidyl peptidase 4 (DPP-4) (6), resulting in loss of their insulinotropic activity.

Two approaches have been proposed to overcome this drawback; (i) development of long-acting stable analogues of GLP-1, the so-called incretin mimetics, and (ii) inhibition of DPP-4 using low molecular weight inhibitors, the so-called incretin enhancers, to elevate levels of the endogenously released active forms of both incretin hormones (7). Both approaches take advantage of the actions of GLP-1, and because both alpha- and beta-cell dysfunction are targeted, not only is insulin secretion enhanced, but also the disrupted insulin/glucagon ratio is improved. Since T2DM is characterised by progressive structural and functional beta-cell deterioration, this, together with the possible beta-cell trophic effects, may lead to improvements in long-term pancreatic islet health.

This article will focus on DPP-4 inhibition as a novel therapy of T2DM, and will describe the rationale behind this approach, the mechanism of action of this new drug class, particularly with respect to improvements in islet cell function, and research data on the efficacy and safety of drugs currently under investigation.

3. INCRETINS AND GLUCOSE REGULATION IN HEALTH AND DISEASE

3.1. Pancreatic islet cell mass and function

T2DM can be considered a disease of inappropriate pancreatic islet hormone secretion relative to prevailing blood glucose concentrations. The presence of insulin resistance leads to further progressive deterioration in islet cell function (8). Indeed, as the UKPDS demonstrated, beta-cell function is already reduced by ~50% at the time of diagnosis and continues to decline regardless of treatment (9). Overall beta-cell function is determined by both the health of the individual beta-cell and the number of functioning beta-cells. Regulation of beta-cell mass is a dynamic process that depends upon the balance between beta-cell replication and apoptosis as well as the development of new islets from exocrine pancreatic ducts (10). There is evidence that in humans, new beta-cells arise primarily as a result of new islet formation (10) rather than beta-cell replication (11, 12). Disruption of any of these processes could lead to reduced beta-cell mass, and, in the longer term, reduced functional capacity. In humans, abnormal glucose tolerance or frank diabetes develops if >50% of beta-cell are lost following hemipancreatectomy (13). Recent studies indicate that beta-cell volume in patients with T2DM is reduced compared with matched nondiabetic subjects, and even subjects with impaired fasting glucose (a group at risk of developing T2DM) have a deficit in relative beta-cell volume, suggesting that loss of beta-cell mass occurs early and is important in the development of T2DM rather than simply arising as a consequence of hyperglycaemia (11). The mechanism behind the loss appears to be mainly apoptosis, since this was increased in the diabetic subjects, whereas the rate of new islet formation was largely unaffected (11).

Although reduction in absolute beta-cell number may contribute to the pathogenesis of T2DM (11), there is evidence that changes in beta-cell function also occur early in disease development. Beta-cell responsiveness to glucose is already reduced in subjects with impaired glucose tolerance (IGT) compared with glucose-tolerant individuals (14). In identical twins discordant for diabetes, first-phase insulin secretion is reduced in the nondiabetic twin irrespective of whether glucose tolerance is normal or impaired. However, only the nondiabetic twin with IGT also had reductions in insulin sensitivity, providing evidence that impairment of beta-cell function can occur before insulin resistance is detectable (15). Similar findings have been reported in offspring of diabetic parents and in first-degree relatives of patients with T2DM, further supporting the notion that beta-cell dysfunction may already be present in glucose-tolerant subjects with a genetic predisposition to developing T2DM (16). This loss of the first-phase insulin response has been shown to be a powerful predictor for progression to overt T2DM, where the combination of insulin resistance and inability to increase insulin secretion in compensation leads to the development of hyperglycaemia (8).

Fewer studies have investigated alpha-cell mass, although it appears that alpha-cell area is increased (17) and alpha-cell number is disproportionately high (8) in T2DM. There are also defects in alpha-cell function, with fasting hyperglucagonaemia and defective postprandial suppression of glucagon secretion (18), and it is likely that this hyperglucagonaemia contributes to the hyperglycaemia (19). Thus, the combination of impaired insulin together with inappropriately high glucagon secretion results in profound changes in the portal insulin:glucagon ratio, leading to inappropriately elevated hepatic glucose production rates.

3.2. Incretin actions

GLP-1–induced insulin secretion is glucose dependent, meaning that the insulinotropic effect is potentiated at elevated blood glucose concentrations and declines as normoglycaemia is approached. This is of clinical significance because any risk of hypoglycaemia as a consequence of elevated GLP-1 concentrations is, therefore, practically eliminated. Furthermore, insulin gene expression and all steps of insulin biosynthesis are upregulated, ensuring continued availability of insulin for

secretion. GLP-1 also up-regulates the expression of other genes essential for beta-cell function, including those for glucokinase and the GLUT2 glucose transporter (20). In animal and *in vitro* studies, GLP-1 enhances beta-cell proliferation and differentiation and inhibits apoptosis, leading to expansion of beta-cell mass (21, 22) which is of clinical significance because T2DM is associated with progressive loss of functional beta-cell mass. Although these trophic actions of GLP-1 have yet to be demonstrated in humans, the possibility arises that GLP-1 may be able to halt the deterioration in beta-cell mass or even to give rise to new beta-cells in patients with an insufficient number of functioning cells.

In addition to its effects on beta-cells, GLP-1 influences the alpha-cells, such that glucagon secretion is strongly inhibited (23). In the context of T2DM, this is important because of the inappropriately high glucagon levels. Notably, the glucagonostatic effect of GLP-1 also is glucose dependent (24), meaning that elevated GLP-1 concentrations are unlikely to impair the glucagon counter-regulatory response to hypoglycaemia.

In the gastrointestinal tract, GLP-1 inhibits motility and secretion (25), delaying the supply of nutrients for absorption to reduce meal-induced glucose excursions, and in healthy subjects under normal physiological circumstances, this appears to outweigh its insulinotropic effect in terms of the contribution to lowering glucose excursions (26). In humans, GLP-1 has a satiating effect (27) which, in the longer term, leads to significant weight loss (28).

Finally, more recent studies have suggested that GLP-1 may have beneficial cardiovascular effects, which is of significance since cardiovascular disease is a major cause of mortality in T2DM. In rats, GLP-1 has direct effects (independent of effects on insulin and/or glucose) to protect against ischaemia/reperfusion injury (29), while left ventricular function improved following GLP-1 infusions in patients with chronic heart failure or after acute myocardial infarction (30, 31).

GIP has similar effects to GLP-1 on the beta-cell (21), but whereas GLP-1 strongly inhibits glucagon secretion, GIP has little effect on glucagon release (32). GIP appears to have no physiological effect on gastric emptying or food intake, but may have a role in lipid metabolism (33).

3.3. The incretin effect

Oral glucose elicits a much greater insulin response than when the rise in blood glucose is mimicked using intravenously infused glucose. This difference is known as the incretin effect, and is due to the oral glucose stimulating the release of peptides from the gastrointestinal tract, which then enhance the beta-cell response to glucose (34). In healthy humans, the incretin effect accounts for ~70% of the total amount of insulin released in response to a 75-g oral glucose load and can be entirely explained by the release of GLP-1 and GIP. Although GLP-1 is more potent than GIP in this respect (35), GIP circulates in higher concentrations, with the net effect that both hormones contribute almost equally to the incretin effect in healthy subjects (36).

In T2DM, the incretin effect is severely impaired, such that the (already impaired) action of glucose alone accounts for almost all of the insulin response to an oral glucose challenge (37), and it is probable that this defect contributes to the deficient insulin secretion that characterises T2DM. The deficient incretin effect in T2DM is characterised by (i) impaired postprandial secretion of GLP-1 (whereas secretion of GIP is normal or only slightly impaired) (18, 38); (ii) impaired beta-cell sensitivity to GLP-1, although its efficacy is at least partially preserved (39); and (iii) completely abolished effect of GIP on second-phase insulin secretion, although a first-phase response is present (40).

Numerous studies in patients with T2DM, in populations at high risk of developing the disease later in life, in subjects with diabetes of different aetiology, and in identical twins have investigated whether the defective incretin effect contributes to the development of T2DM or whether it arises subsequently as a consequence of the condition (41). GLP-1 secretion is normal in first-degree relatives of diabetic subjects (41) and in women with previous gestational diabetes (42), while in identical twins discordant for diabetes, GLP-1 secretion is reduced only in the diabetic twin (15), suggesting that impaired GLP-1 secretion does not precede development of diabetes. However, once glucose control begins to deteriorate, GLP-1 secretion may start to be affected, since both meal- and oral glucose–induced GLP-1 secretion may be modestly reduced in subjects with IGT (14, 18).

The insulinotropic effects of GIP were found to be impaired in 50% of healthy first-degree relatives of patients with T2DM, suggesting that defective GIP action may have a genetic component (43). However, another study examining patients with diabetes of different aetiologies from those of the classic obese patient with T2DM found that all groups displayed the same absent second-phase insulin response to GIP, suggesting that the GIP defect was a consequence of the diabetic state *per se*, rather than being genetically predetermined (40). Subsequent reinterpretation of the study in first-degree relatives (43) concluded that the GIP defect in the relatives is likely to be indicative of general impairments of beta-cell function that are not specific to GIP (41).

Beta-cell responsiveness to glucose itself is reduced in patients with T2DM (39), but this can be normalised by pharmacological infusions of GLP-1, in agreement with the finding of reduced beta-cell sensitivity, but preserved efficacy of GLP-1 (39). Interestingly, the reduced sensitivity to GLP-1 in T2DM may arise as a consequence of the elevated blood glucose levels, because correction of the hyperglycaemia helps improve beta-cell responsiveness to GLP-1 (44).

Whereas beta-cell sensitivity to GLP-1 is reduced in T2DM, nothing is yet known about alpha-cell sensitivity,

although the efficacy of GLP-1 in suppressing glucagon is preserved (32, 45). In agreement with this, infusion of GLP-1 reduces glucose levels also in patients with type 1 diabetes (46, 47). It is likely that the antihyperglycaemic actions of GLP-1 depend as much upon its inhibition of glucagon secretion as upon its insulinotropic effects.

3.4 The incretin receptors

The antihyperglycaemic activity of GLP-1 is exerted via its interaction with a specific membrane-located receptor belonging to the G protein–coupled receptor superfamily, which also includes receptors for glucagon, GIP, pituitary adenylate cyclase-activating polypeptide, secretin and vasoactive intestinal peptide, and which is expressed in the pancreatic beta-cell as well as in extra-pancreatic sites (21). Receptor activation leads to increases in intracellular cAMP with subsequent activation of protein kinase A, culminating in a series of events which alter ion channel activity and intracellular calcium handling and result in the stimulation of exocytosis of insulin-containing granules (21). Importantly, this cascade is glucose-dependent, *i.e*., a certain amount of glucose is a prerequisite for GLP-1 enhancement of insulin secretion. Moreover, it appears that GLP-1 receptor signalling is necessary to facilitate beta-cell responses to glucose itself, *i.e*., GLP-1 may act as a glucose sensitiser and impart glucose competence to the beta-cell (20).

The GIP receptor (GIPR) is also expressed in both pancreatic and extra-pancreatic sites. In general, GIPR signalling leads to increases in cAMP and intracellular calcium concentrations, which in the beta-cell culminates in insulin secretion (21).

4. BIOLOGY AND ACTIONS OF DPP-4

4.1. Enzymatic action

DPP-4, also known as the T-cell antigen CD26, is a serine peptidase found in numerous sites, including the kidney, intestinal brush-border membranes, hepatocytes and vascular endothelium, as well as in a soluble form in plasma (48). It cleaves an N-terminal dipeptide from susceptible peptides, and *in vitro* kinetic studies revealed that both GLP-1 and GIP were good substrates (49). Subsequently, the metabolites expected to be formed after DPP-4 cleavage were identified as endogenous circulating peptides in man (50, 51). A physiological role for DPP-4 in incretin hormone metabolism was demonstrated when DPP-4 inhibition was shown to prevent the N-terminal degradation of GLP-1 and GIP that normally occurs *in vivo* (52). Cleavage of GLP-1 in particular is very rapid, resulting in an apparent plasma half-life of only 1 to 2 minutes (53). A number of other peptides have been indicated as DPP-4 substrates from *in vitro* kinetic studies (see (48) for review), but for most of them, the physiological relevance of DPP-4 for their metabolism and biological activity *in vivo* has yet to be established (54).

DPP-4 contributes to T-cell activation and proliferation via interactions with other membrane-expressed antigens such as CD45 (55), but its presence may not be essential for normal immune function, with the evidence to date indicating that DPP-4's role in the immune system is independent of its enzymatic action and that its absence can be compensated for. Thus, animal models lacking DPP-4 are completely viable and seem to suffer no ill effects (56, 57). *In vitro* studies with highly selective DPP-4 inhibitors have demonstrated that the catalytic activity of DPP-4 is not required for T-cell activation or proliferation. However, non-selective inhibitors and inhibitors selective for the closely related enzymes, DPP-8 and DPP-9, do have an adverse impact, suggesting that the catalytic activity of these other enzymes may have a role in the immune system (58). Long-term studies with the DPP-4 inhibitors in clinical development have, to date, proved these to be safe and well tolerated and not to be associated with adverse immune effects.

4.2. DPP-4 and T2DM

GLP-1 concentrations are reduced in patients with diabetes (18, 38), raising the possibility that the impaired incretin effect in T2DM may be partly due to a greater degradation of GLP-1 (and possibly GIP) in the patients. However, elimination of intact (non-degraded) GLP-1 and GIP does not differ between healthy and diabetic subjects (53, 59). Nevertheless, because up to 80% of endogenous GLP-1 and ~50% of endogenous GIP circulate in the degraded form in humans (50, 51), inhibition of DPP-4 is likely to have a significant impact to enhance incretin hormone action by elevating levels of the endogenous active peptides into the range shown to be therapeutically useful (60).

5. DPP-4 INHIBITORS FOR TREATMENT OF T2DM

5.1. Rationale for the antidiabetic activity of DPP-4 inhibitors

Although GLP-1 has a unique profile considered highly desirable in any antidiabetic agent, its pharmacokinetic and pharmacodynamic profiles mean that the native peptide is not therapeutically useful. Thus, while GLP-1 normalises fasting and postprandial glucose concentrations when administered continuously to patients with T2DM (45, 61), single subcutaneous injections have short-lasting effects (62). The discovery of GLP-1's particular susceptibility to DPP-4 cleavage *in vivo* opened the possibility that inhibition of this process would raise levels of intact GLP-1 sufficiently to be able take advantage of its beneficial effects, and led to the first suggestion that DPP-4 inhibitors may have a therapeutic application in T2DM (7). It was subsequently shown that DPP-4 inhibition enhances levels of endogenously released GLP-1 and GIP (52), and is associated with improved glucose tolerance in animal models of insulin resistance, impaired glucose tolerance and type 2 diabetes (5).

One DPP-4 inhibitor was recently approved by the US and European regulatory authorities for treatment of T2DM and others are in late-stage clinical development (Figure 1). Most are competitive reversible inhibitors of DPP-4, with good oral bioavailability and a relatively long duration of action, such that once-daily dosing gives 70–90% inhibition of plasma DPP-4 activity over a 24-hour

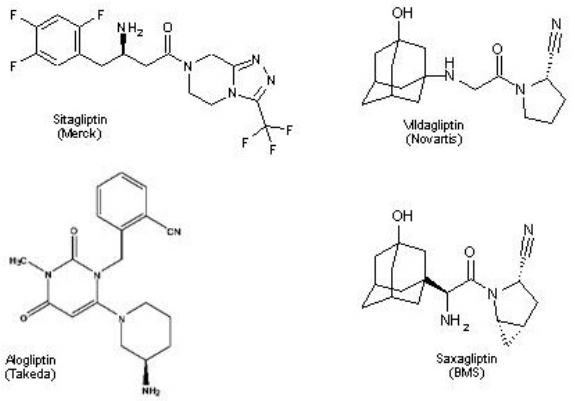

Figure 1. Structures of DPP-4 inhibitors. Data are taken from (63), sitagliptin; (64), vildagliptin; (68), saxagliptin and (69), alogliptin.

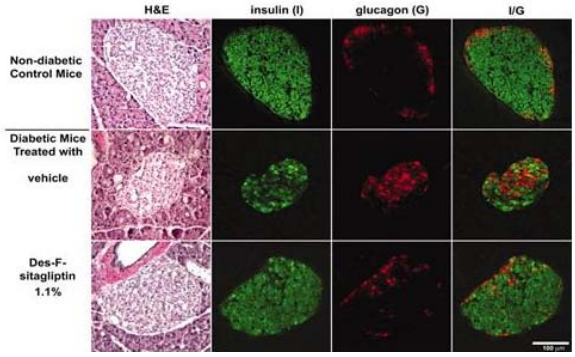

Figure 2. Effects of DPP-4 inhibition on beta-cell mass and islet architecture in a rodent model of type 2 diabetes, which included non-diabetic control mice, diabetic mice treated with vehicle, and diabetic mice treated with 1.1% des-F-sitagliptin. Consecutive pancreas sections were stained with hematoxylin and eosin (H&E), anti-insulin antibody (green), or anti-glucagon antibody (red). Shown are representative islets from each group with each staining and the overlay of the insulin and glucagon staining (I/G). Reprinted with permission from (73).

period (5). Most data are available for sitagliptin (63) (Januvia®, Merck & Co., Inc.) and vildagliptin (64) (Galvus®, Novartis AG). The recently approved sitagliptin, which is longer acting than vildagliptin (65), is rapidly absorbed; steady-state plasma concentrations are attained within 2 days after once-daily dosing. Sitagliptin is not appreciably metabolised *in vivo*, and ~90% of the dose is excreted renally, unchanged as the parent drug (66). Vildagliptin, which is pending regulatory approval, is a tight-binding inhibitor with a slow off-rate (67); it is rapidly absorbed and is suitable for both once- and twice-daily dosing. It has low protein binding; the predominant route of metabolism is hydrolysis to produce a pharmacologically inactive metabolite, with 85% of the dose being excreted as this metabolite in the urine (201). Saxagliptin (Bristol-Myers Squibb, phase III (68)), denagliptin (Redona®, GlaxoSmithKline, halted in phase III (202)), alogliptin (Takeda, phase III (69)) and BI 1356 (Boehringer-Ingelheim, phase II (70)) are also long-acting inhibitors designed for once-daily dosing. PSN9301 (formerly developed by Probiodrug under the name P93/01; Prosidion Ltd, phase II) takes a different approach, with a rapid onset and short duration of action; dosing is expected to be meal related (203). Inhibitor selectivity may be important, because inhibition of DPP-8 and DPP-9 is associated with severe toxicity and mortality in preclinical studies (58). The DPP-4 inhibitors in development are highly selective for DPP-4 (63, 67, 69), and although sitagliptin displays the greater selectivity, it is of note that neither sitagliptin nor vildagliptin (the only compounds where long-term clinical data are available) have been associated with adverse events of greater severity or incidence than placebo (5).

5.2. Animal model experience

Acute studies in normal and glucose-intolerant animal models confirming the antihyperglycaemic effectiveness of DPP-4 inhibition were rapidly followed by longer-term studies demonstrating durability in terms of improved glucose tolerance and beta-cell function with a variety of DPP-4 inhibitors (5), but relatively few preclinical studies have directly investigated whether DPP-4 inhibition has beta-cell trophic effects. Long-term DPP-4 inhibition increases total beta-cell number and the number of small islets in Wistar rats after beta-cell mass reduction using streptozotocin and in insulin-resistant, high-fat–fed mice (5). In other studies, vildagliptin treatment of neonatal rats for 3 weeks increased beta-cell replication and inhibited apoptosis, leading to increased beta-cell mass (71), while treatment of *db/db* mice with the DPP-4 inhibitor S 40010 for 34 days stimulated beta-cell neogenesis and led to an increase in beta-cell mass comparable to that obtained with exendin-4 (72). In a mouse model with impairments in insulin sensitivity and secretion arising from the combination of a high-fat diet together with beta-cell mass reduction using streptozotocin, treatment with a sitagliptin analogue for 3 months increased the number of insulin-positive beta-cells, so that beta-cell mass and the ratio of beta-cells to alpha-cells were normalised and normal islet architecture (beta- and alpha-cell distribution pattern) was restored (Figure 2) (73). Taken together, these studies suggest that DPP-4 inhibitors share the trophic effects of GLP-1 on the pancreatic islets, at least in rodents, but the extent to which similar effects may be achieved in humans remains unknown.

5.3. Clinical proof of concept

Clinical proof of concept for the utility of DPP-4 inhibitors as antidiabetic agents was published by Ahrén and coworkers, using the predecessor to vildagliptin, NVP-DPP728 (74), an inhibitor of relatively short duration. In this placebo-controlled study, patients with relatively mild T2DM (mean HbA1c, 7.4%) received NVP-DPP728 monotherapy (100 mg tid or 150 mg bid) for 4 weeks, resulting in lowered fasting and postprandial glucose levels and a fall in HbA1c levels to 6.9%. This study was followed by another 4-week study, using once-daily vildagliptin monotherapy (100 mg qd), with similar reductions in fasting and postprandial glucose concentrations and HbA1c levels (75). The mechanism of

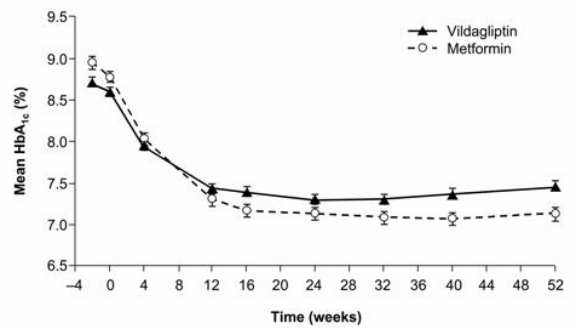

Figure 3. HbA1c levels in patients with type 2 diabetes after 52 weeks of vildagliptin monotherapy (50 mg bid) or metformin monotherapy (1000 mg bid). Reprinted with permission from (77).

action appeared to be GLP-1-mediated, since intact GLP-1 concentrations increased 2-fold, resulting in insulin secretion being maintained despite the improvements in glycaemia, and significant suppression of glucagon concentrations.

5.4. Efficacy as monotherapy

When given as monotherapy over 12 weeks, vildagliptin (25 mg bid) lowered fasting and postprandial glucose concentrations by 1.1 and 1.9 mmol/l, respectively. HbA1c levels were reduced from baseline (8%) to 7.4% at the end of the study, whereas they were unchanged with placebo treatment (76). Of note is the finding that patients with higher baseline HbA1c levels (8%-9.5%), reflecting poorer metabolic control, seemed to show the greatest improvements, with reductions averaging 1.2%, suggesting that benefits of DPP-4 inhibition may not be restricted to those patients with mild diabetes (76). These reductions in HbA1c concentrations are sustainable, as shown in a 52-week study with vildagliptin (50 mg bid) (Figure 3) (77). Once-daily vildagliptin for 12 weeks also has significant effects, reducing HbA1c levels at the 2 highest doses (50 and 100 mg qd) compared with placebo (78).

Similar results were obtained with sitagliptin. Thus, sitagliptin (5-50 mg bid for 12 weeks) dose-dependently reduced fasting plasma glucose (FPG) by up to 1.0 mmol/l and HbA1c levels from a baseline of 7.9% by up to 0.8% with the highest dose, compared with placebo (79). In another 12-week study, sitagliptin (100 mg qd) reduced HbA1c levels by 0.6% relative to placebo (baseline 7.8%), and as with vildagliptin, those patients with higher baseline HbA1c levels showed the greatest reductions (80). The efficacy of sitagliptin monotherapy has also been demonstrated in longer duration studies, giving reductions in HbA1c of 0.6% (baseline, 8.1%) and 0.8% (baseline, 8%) after 18 and 24 weeks, respectively, together with improvements in markers of beta-cell function (81, 82).

Less is known about the other inhibitors in clinical development. Saxagliptin (10 mg qd) is reported to reduce HbA1c concentrations by 1% after 8 weeks, with the reduction sustained over the following 4 weeks (204). Alogliptin is also said to have sustained efficacy to reduce blood glucose levels throughout the 24-hour period (69), and in a 2-week study, it dose-dependently reduced 4-hour postprandial glucose levels after breakfast, lunch and dinner after once daily dosing (25, 100 or 400 mg) (82). After 4 weeks treatment with BI 1356, placebo-corrected changes in HbA1c of -0.31, -0.37 and -0.28% were obtained with doses of 2.5, 5 and 10 mg, respectively (baseline 7%) (84). In a 14-day study, PSN9301 pharmacokinetics were dose-proportional and produced significant lowering of oral glucose–induced glucose excursions (85). Good tolerability of all of the inhibitors in clinical development, which appear to be weight neutral, is reported.

5.5. Efficacy as combination therapy

DPP-4 inhibitors have been investigated for their utility in combination therapy. The first of these studies examined vildagliptin (50 mg qd) as add-on therapy in patients with T2DM treated with metformin (≥1500 mg/d) in a double-blinded, placebo-controlled trial (86). HbA1c levels in subjects receiving placebo (i.e., metformin alone) began to deteriorate by week 12, reaching 8.3% at week 52 (baseline, 7.9%). In contrast, addition of vildagliptin to ongoing metformin treatment reduced FPG and postprandial glucose concentrations, leading to a placebo-subtracted reduction of 0.7% in HbA1c at week 12, which was maintained to the end of the study, giving a between-group difference of -1.1%. After 52 weeks, ~40% of patients receiving vildagliptin and metformin achieved HbA1c levels of <7% compared to only 10% of patients on metformin alone (86). Sitagliptin (100 mg qd) has also been used as add-on to metformin (≥1500 mg/d) in a 24-week study. Whereas placebo treatment (metformin alone) resulted in no significant change, by 24 weeks of combination treatment, HbA1c levels had fallen from baseline (8.0%) to 7.3%, with 47% of patients achieving target levels of <7%, and 17% reaching <6.5% (compared with 18% and 5%, respectively, of patients in the placebo arm) (87). Initial combination therapy with sitagliptin and metformin in drug-naive patients has also been demonstrated to give greater improvements in glycaemic control than either sitagliptin or metformin monotherapy (Figure 4), with even an open-label cohort (baseline HbA1c 11.2%) achieving reductions of 2.9% after 24 weeks of combination therapy (88). Saxagliptin (2.5, 5 or 10 mg qd) also gives improved glycaemic control when used in addition to on-going metformin (≥1500 mg/d) therapy, giving placebo-subtracted reductions in HbA1c of 0.73, 0.83 and 0.71% (baseline 8.0%) after 24 weeks (89) In these studies (86, 87, 88, 89), DPP-4 inhibitor treatment had a neutral effect on body weight.

The efficacy of DPP-4 inhibitors has also been examined when used in combination with TZDs. In a 24 week study in drug-naive patients, vildagliptin (100 mg qd) gave superior glycaemic control when given in initial combination with pioglitazone (30 mg qd), with HbA1c reductions of 1.9% from baseline (8.7%) compared to 1.4% for patients on pioglitazone alone, and FPG reductions of 2.8 mmol/l (versus 1.9 mmol/l). The combination was well tolerated (90). Furthermore, additional glycaemic control is obtained when vildagliptin is added on to pioglitazone in

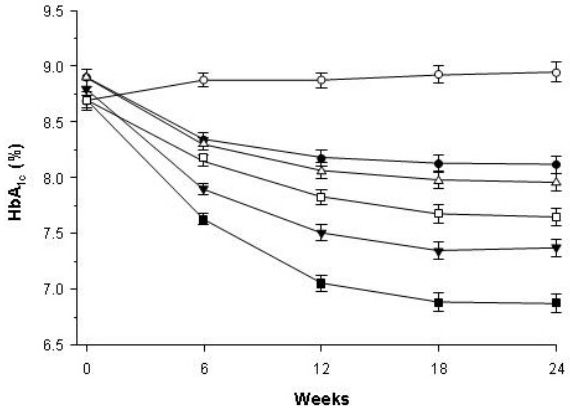

Figure 4. Change in HbA1c over time for patients treated with initial therapy of placebo (white circle), sitagliptin monotherapy 100 mg qd (black circle), metformin monotherapy 500 mg bid (white triangle) or 1000 mg bid (white square) or combination therapy with sitagliptin 50 mg + metformin 500 mg bid (black triangle) or sitagliptin 50 mg + metformin 1000 mg bid (black square). Reprinted with permission from (88).

patients inadequately controlled with TZD monotherapy (91). After 24 weeks, HbA1c was reduced by 1.0% with the combination versus 0.3% for placebo (baseline 8.7%). Likewise, sitagliptin (100 mg qd) resulted in significant improvements in glycaemic control when added to ongoing pioglitazone (30 or 45 mg/d) therapy. In a 24-week study, the combination therapy produced significant placebo-subtracted reductions in HbA1c (-0.70%, $p<0.001$) and FPG (-17.7 mg/dL, $p<0.001$), whereas there was no significant change in either parameter in the placebo (pioglitazone alone) arm (92). In this study, 45% and 24% of patients reached HbA1c levels below 7% and 6.5% respectively (versus 23% and 5% on placebo treatment). The combination was generally well tolerated, although there was a modestly higher incidence of gastrointestinal adverse effects compared with placebo. Again, addition of the DPP-4 inhibitor had no additional effect on body weight relative to pioglitazone alone, which caused a weight gain of ~1.5 kg (92).

DPP-4 inhibitors also provide additional glycaemic efficacy when added to existing sulphonylurea monotherapy. In a 24-week study, HbA1c levels were reduced by 0.6% from baseline (8.5%) when vildagliptin (50 mg qd or 50 mg bid) was added to ongoing glimepiride (4 mg/d) monotherapy, compared to a 0.1% increase with placebo (93). The addition of vildagliptin was not associated with increased hypoglycaemia (1.2% vs 0.6% for placebo), and was weight neutral. Sitagliptin has also been used together with ongoing glimepiride (≥ 4 mg/d) in patients with inadequate glycaemic control (94). After 24 weeks, sitagliptin (100 mg qd) reduced HbA1c by 0.57% relative to placebo (baseline 8.34%). This study also included a group receiving glimepiride plus metformin (≥ 1500 mg/d); in these patients, the addition of sitagliptin gave HbA1c reductions of 0.89% relative to placebo. At 24 weeks, 17.1% of patients on dual therapy achieved target HbA1c levels of < 7% (compared to 4.8% on placebo), while for those on triple therapy, 22.6% reached target (versus 1.0% on placebo). The use of sitagliptin in dual and triple therapy was generally well tolerated, although there was a higher incidence of hypoglycaemia in the sitagliptin groups. Thus, hypoglycaemia was reported by 7.5% of patients receiving sitagliptin plus glimepiride (vs 2.8% on glimepiride monotherapy), and by 16.4% on triple therapy (vs 0.9% on glimepiride plus metformin), but none was considered severe and most (73%) were said to have precipitating factors, such as missed meals or increased physical activity. Body weight increased modestly (+ 1.1 kg in each arm compared to placebo). (94)

A single study has looked at the combination of DPP-4 inhibitors with insulin treatment (>30 U/d). Vildagliptin (50 mg bid) added to insulin treatment (~80 U/d), reduced HbA1c levels by 0.5% (baseline 8.5%) versus a reduction of 0.2% with placebo. Interestingly, despite the improvements in glycaemic control, there were significantly fewer hypoglycaemic events in the patients receiving the combination therapy (95).

5.6. Comparison with existing therapies

It is of considerable interest how the efficacy of DPP-4 inhibitors compares with that of existing therapies. In an on-going head-to-head study comparing vildagliptin (50 mg bid) with metformin (1000 mg bid) in drug-naïve patients, HbA1c levels decreased over the first 12 weeks, and this effect was maintained over 52 weeks, giving reductions of 1.0% and 1.4% from baseline (8.7%) for vildagliptin and metformin, respectively (Figure 3). However, the between-group difference failed to establish noninferiority of vildagliptin to metformin (77). Preliminary 2-year data confirm this, with HbA1c reductions of 1.1% from baseline (8.7%) with vildagliptin versus 1.5% for metformin ($p < 0.05$) (205). There was no weight gain with vildagliptin (in contrast to a modest weight loss with metformin), and while the overall incidence of adverse effects was similar in both groups, the incidence of gastrointestinal adverse effects was significantly less in the vildagliptin-treated group (77).

Noninferiority of vildagliptin (50 mg bid) to rosiglitazone (8 mg qd) was established in a 24-week study in drug-naïve patients (baseline HbA1c, 8.7%), with reductions in mean HbA1c levels of 1.1% from baseline (96). In a subset of more poorly controlled patients (baseline HbA1c, >9%), both drugs were equally effective (reductions of 1.8% and 1.9% for vildagliptin and rosiglitazone, respectively). Lipid profiles were improved to a greater extent with vildagliptin, and in contrast to rosiglitazone, which caused weight gain, vildagliptin was weight neutral. The overall incidence of adverse effects was similar in both groups, although the incidence of oedema was greater with rosiglitazone (4.9%) than with vildagliptin (2.5%) (96).

Noninferiority to a sulphonylurea was demonstrated in a 1-year active comparator study, where sitagliptin (100 mg qd) or glipizide (5 or 10 mg qd) was added to ongoing metformin (≥1500 mg/d) therapy (97). Mean changes in HbA1c from baseline (7.5%) were the

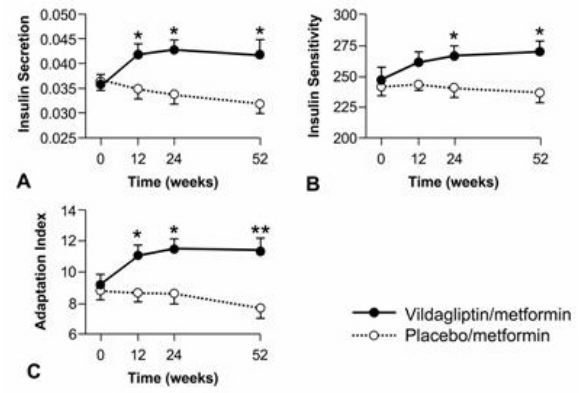

Figure 5. Effects of 52 weeks of therapy with vildagliptin (50 mg qd) as an add-on to metformin (1.5–3 g/day) on insulin secretion (pmol/L 30 min)/(mmol/L), dynamic insulin sensitivity (OGIS, mL • min^{-1} • m^{-2})and adaptation index ($nmol_{C\text{-}peptide}$ • $mmol_{glucose}^{-1}$ • mL^{-1} • m^{-2}) in patients with type 2 diabetes. Asterisks indicate probability level of random difference between groups: * $p<0.05$, ** $p<0.01$. Reprinted with permission from (107).

same in both arms (-0.7%), and this relationship remained true when patients were stratified according to starting baseline levels, with reductions ranging from ~0.2% (baseline, <7%) up to ~1.7% (baseline, >9%). After 1 year, ~60% of patients in each group achieved target HbA1c levels of <7%, but the incidence of hypoglycaemia was higher with glipizide (32%) than with sitagliptin (5%). Patients in the sitagliptin/metformin arm showed a tendency for modest weight loss while those in the glipizide/metformin arm had modest weight gain, leading to a 2.5-kg weight difference by the end of the study (97).

DPP-4 inhibitors have not yet been directly compared with the incretin mimetics. Exenatide (Byetta®, Amylin Pharmaceuticals, Inc./Eli Lilly and Company) entered the US market in June 2005, while liraglutide (Novo Nordisk A/S) is in phase III trials. Exenatide is used as add-on therapy in patients inadequately controlled with existing oral antidiabetic agents (metformin, a sulphonylurea, or both), and has proved efficacious in lowering HbA1c levels by ~1.0% from baseline (8.4%), with 44% of patients reaching levels of ≤7%. Body weight is also reduced significantly, and both weight loss and glycaemic improvements are sustained (98). Liraglutide monotherapy over 14 weeks also reduces HbA1c levels by up to 1.7% relative to placebo (baseline 8.1%-8.5%), with ~50% of patients achieving targets levels of ≤7% compared with only 8% of patients on placebo. Body weight is also reduced (99).

5.7. Mechanism of action

The principal mediators of the efficacy of DPP-4 inhibitors seem to be GLP-1 and GIP; it is noteworthy that the inhibitors' antidiabetic activity is lost in mice in which both incretin receptors have been deleted (100, 101). However, it remains uncertain how much GIP actually contributes, because the effects of GIP are severely impaired in T2DM. Preclinical studies indicate that incretin receptor expression is reduced by hyperglycaemia (102, 103), with recovery when glucose levels are normalised (103). Furthermore in patients with T2DM, beta-cell responsiveness to GLP-1 improves following antihyperglycaemic therapy (44), and there is evidence that GIP action may also improve following treatment to reduce FPG (104, 105). Therefore, the possibility exists that although GLP-1 is probably the primary mediator of the antidiabetic effects of DPP-4 inhibition (106), particularly in the early stages of treatment, once glucose levels begin to fall in the longer term, the insulinotropic actions of GIP may also play a role.

Improvements in islet cell function contribute to the antidiabetic effects of DPP-4 inhibitors. Thus, decreased proinsulin/insulin ratios following DPP-4 inhibition are indicative of better beta-cell function (82, 107). The insulinogenic index (a measure of assessing changes in insulin concentrations in relation to concomitant plasma glucose concentrations) was improved after 1 year of vildagliptin+metformin therapy (86). Insulin sensitivity (assessed by modelling glucose and insulin data during a meal test to estimate glucose clearance in relation to the prevailing insulin levels [the OGIS index of insulin sensitivity]), increased during the first 24 weeks when vildagliptin was added to metformin treatment, with the effect being maintained (Figure 5), although the mechanism (direct or secondary to improvements in glycaemia) responsible could not be determined (107).

In drug-naïve patients with T2DM treated with vildagliptin for 4 weeks, mathematical modelling demonstrated that the insulin secretory rate to glucose (insulin secretory tone) improved, and insulin sensitivity (OGIS) was increased (108). Similar findings were reported after analysis of data from phase III trials of 18 to 24 weeks duration with sitagliptin as monotherapy and as an add-on to metformin, showing improvements in beta-cell responsiveness to glucose under fasting and post-meal conditions (109). While effects on postprandial glucose and glucagon (reductions) and intact GLP-1 and GIP (increases) are seen on day 1 of treatment, changes in FPG and insulin sensitivity appear to require more time, suggesting that they may have been, at least partially, dependent on reductions in glucolipotoxicity and associated general improvements in metabolism (108).

In addition to the beta-cell effects, improvements in alpha-cell function also contribute to the antidiabetic effects of DPP-4 inhibition. Fasting and meal-related glucagon levels were reduced by vildagliptin in the 4-week monotherapy studies (75, 108), suggesting that glucagon suppression, leading to reduced hepatic glucose production, is an important mediator of the improvements in glucose tolerance. Indeed, when hepatic and peripheral glucose metabolism were directly assessed in patients with T2DM, endogenous glucose production was suppressed by vildagliptin, both in the postprandial and fasting (overnight) periods, and was positively correlated with reductions in FPG (110). This is likely to be an effect mediated via GLP-1 which is independent of its insulinotropic effects because, compared to placebo, vildagliptin treatment is also

associated with suppression of prandial glucagon levels in insulin-treated patients with type I diabetes (111)

6. PERSPECTIVE

Most existing antidiabetic agents target only one aspect of the pathology of T2DM, and notably do not tackle the progressive deterioration in beta-cell mass and function (9) or the hyperglucagonaemia that accompanies T2DM, although one recent paper reports that rosiglitazone reduces the incidence of T2DM in subjects with IGT or impaired fasting glucose (112). In contrast, the incretin approach is multifactorial (6), and unlike existing therapies, both alpha- and beta-cell dysfunction is targetted. There is, therefore, hope that an incretin-based therapy will address both the progressive loss of beta-cell mass and function as well as the inappropriate secretion of glucagon, and will restore the normal glucagon:insulin relationship, which is important for the regulation of hepatic glucose metabolism. The extent to which this will improve efficacy and durability remains to be seen. Because they rely on endogenous incretin hormone secretion to stimulate insulin secretion, and because beta-cell mass and function continue to decline with time, it could be speculated that DPP-4 inhibitors will have the greatest efficacy when therapy is initiated early in the course of the disease. This speculation is supported by the observation that HbA1c levels are lowered to a greater extent by sitagliptin in patients with a short duration of diabetes when compared subjects with more long-standing disease (81). Furthermore, although direct head-to-head comparisons between vildagliptin and metformin monotherapies failed to show non-inferiority of the DPP-4 inhibitor (77, 205), vildagliptin was equally as effective as the TZDs (96). Therefore, it may be unlikely that DPP-4 inhibitors will be widely used as first-line monotherapy, but there may still be a place for them as initial therapy in those patients in whom metformin is contraindicated or not tolerated. There may also be a possibility of using DPP-4 inhibitors as initial combination therapy, since a sitagliptin/metformin combination (88) and a vildagliptin/TZD combination (90) both showed greater efficacy than the respective monotherapies in drug-naïve patients with T2DM. In particular, the combination of a DPP-4 inhibitor with metformin seems particularly attractive in light of the finding that biguanide compounds, in addition to their other effects, actually stimulate GLP-1 secretion (113). Thus, the combination of metformin plus a DPP-4 inhibitor resulted in a greater increase in fasting intact GLP-1 levels in rats than either agent alone (113), while more recently, combined sitagliptin and metformin administration produced greater than additive increases in postprandial intact GLP-1 concentrations in healthy subjects (114). This complementary action helps explain the additive efficacy seen when DPP-4 inhibitors are used together with metformin (88), and may lead to this combination ultimately replacing metformin monotherapy as a first-line therapy. However, due to the progressive nature of T2DM, glycaemic control deteriorates with time, necessitating the introduction of additional agents. It is therefore highly relevant that the DPP-4 inhibitors appear to be well tolerated when administered together with metformin, TZDs, sulphonuylureas or insulin, and give additional benefits in terms of glycaemic control, even in patients with long-standing disease. There are apparently no pharmacokinetic drug–drug interactions between DPP-4 inhibitors and the sulphonylurea glibenclamide (115, 116), the TZDs pioglitazone or rosiglitazone (90, 117) or metformin (201), meaning that in the clinical setting, DPP-4 inhibitors can be added to these agents to improve glycaemic control without dose adjustment of either compound. Furthermore, the DPP-4 inhibitors have the advantage of simplicity compared to other oral agents, because they can be used across a broad spectrum of different patient groups without need for dose titration or adjustment (201, 206). As a once-daily oral therapy, DPP-4 inhibitors significantly improve glycaemic control, apparently irrespective of the severity of the diabetes. They seem to be equally effective regardless of body weight (i.e., over a large range of body mass index or age (effective in the elderly), with a low risk of hypoglycaemia, even in the fasting state or if meals are missed, and no body weight gain.

As yet, trophic effects on the beta-cells have only been demonstrated in animal and *in vitro* studies, but in studies with incretin mimetics and DPP-4 inhibitors, markers of alpha- and beta-cell function improve. However, it is important to stress that we still have to learn whether these islet effects are durable. One preliminary study with vildagliptin suggests that some of them may persist for several weeks after discontinuation of treatment (118). If this can be confirmed in studies of longer duration and lead to reduced incidence or delayed progression to secondary failure relative to other secretagogues, the incretin approach may have the potential to modify the disease process itself by delaying or even preventing the reduction in functional beta-cell mass, which is part of the natural progression of T2DM.

The fact that the DPP-4 inhibitors are orally available, coupled with presently available evidence indicating that they are well tolerated with an adverse effect profile resembling placebo, raises the possibility that they may be able to be used early, to delay or even prevent the development of T2DM in subjects at risk of developing the disease. Thus, a 12 week study in subjects with IGT showed that vildagliptin (50 mg qd) was effective at improving beta-cell function and decreasing glucose excursions (119). Similarly, 6 weeks of vildagliptin (100 mg qd) increased insulin sensitivity and beta-cell function and reduced meal-induced glucose excursions in subjects with impaired fasting glucose, although fasting glucose itself was not altered, and the effects were not sustained after discontinuation of treatment (120). Nevertheless, if confirmed in longer-term outcome trials, these two studies raise the hope that DPP-4 inhibition may be able to ameliorate the progression from prediabetes to overt T2DM.

Since the macrovascular complications of diabetes are a major cause of morbidity and premature mortality, it is of considerable interest whether the potential beneficial cardiovascular effects of GLP-1 are realised with an incretin-based therapy. By the very nature of the disease,

long-term trials will be needed to establish this; however, it is encouraging that early data suggest there may be a reduction in some cardiovascular risk factors in patients receiving incretin mimetics or DPP-4 inhibitors (121, 122, 123). In addition, it is important to keep in mind that weight loss (and the prevention of weight gain) may improve cardiovascular outcome.

As a class, DPP-4 inhibitors appear to be efficacious and safe, and in combined analysis of phase II and phase III trials, in which >3500 patients were exposed to vildagliptin (>600 for >1 year) and >1500 patients exposed to sitagliptin, tolerability has been good, with an adverse effects profile resembling placebo (201, 206). However, careful monitoring for any unexpected off-target adverse effects will be necessary to confirm the long-term safety, since safety issues may not always become apparent during the clinical trial phase of the establishment of a new drug class. The importance of this is illustrated by the fact that off-target inhibition of the related enzymes DPP-8 and DPP-9 by non-selective compounds results in severe toxicities in preclinical studies (58). It is notable that despite early concerns that adverse effects may arise because of the inhibition of an enzyme with apparently multiple substrates or because of interference with the immunomodulatory actions of DPP-4 (CD26), the inhibitors in clinical development have all been well tolerated, with an adverse effects profile similar to that of placebo. Additionally, while the compounds in clinical development are all selective for DPP-4, they are structurally diverse, so it must be recognised that compound-specific, as opposed to class-specific adverse effects may arise, and it is noteworthy that clinical development of denagliptin was recently put on hold following unfavourable preliminary data from pre-clinical long-term toxicity trials (206).

7. CONCLUSIONS

The DPP-4 inhibitors are a new class of oral antidiabetic agents with an exciting potential for the treatment of T2DM. They seem likely to be as efficacious as currently available oral antidiabetic agents, although further trials powered for efficacy will help determine their likely clinical success. By enhancing incretin hormone action, DPP-4 inhibitors help restore the natural physiology of glucose homeostasis, rectifying the impaired insulin and inappropriate glucagon secretion to correct the imbalance in the insulin:glucagon ratio, thereby improving glucose uptake and reducing hepatic glucose output. They target fasting and postprandial glucose concentrations, which are both believed to contribute to the development of many diabetic complications. As a class, the DPP-4 inhibitors appear to have an excellent safety profile, with little or no risk for hypoglycaemia, no weight gain, and the potential benefit of addressing the islet dysfunction that characterises T2DM. If the beta-cell–preserving potential of this drug class can also be demonstrated in humans, the DPP-4 inhibitors may be able to address one of the underlying causes of progression of T2DM; the gradual loss of beta-cell mass and function that precedes the development of insulin resistance and reduced glucose tolerance. Taking all these factors into consideration, the DPP-4 inhibitors may offer the unique possibility of being used not only to treat the symptoms of T2DM, but also as disease-modifying drugs. Finally, in the future, if the long-term safety of DPP-4 inhibitors is confirmed, there is the real possibility that this class of drugs will not be confined to treating only patients with established diabetes but may also be used to prevent the development or progression of T2DM in people with IGT or at high risk of developing the disease.

8. REFERENCES

1. Nasr C.E, B.J. Hoogwerf, C. Faiman & S.S. Reddy: United Kingdom Prospective Diabetes Study (UKPDS). Effects of glucose and blood pressure control on complications of type 2 diabetes mellitus. *Cleve Clin J Med* 66, 247-253 (1999)

2. Stratton I.M, A.I Adler, H.A. Neil, D.R. Matthews, S.E. Manley, C.A. Cull, D. Hadden, R.C. Turner & R.R. Holman: Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study. *BMJ* 321**,** 405-412 (2000)

3. Gaede P & O. Pedersen: Multi-targeted and aggressive treatment of patients with type 2 diabetes at high risk: what are we waiting for? *Horm Metab Res* 37(suppl 1), 76-82 (2005)

4. Holst J.J: On the physiology of GIP and GLP-1. *Horm Metab Res* 36, 747-754 (2004)

5. Deacon C.F & J.J. Holst: Dipeptidyl peptidase IV inhibitors: a promising new therapeutic approach for the management of type 2 diabetes. *Int J Biochem Cell Biol* 38, 831-844 (2006)

6. Deacon CF: Therapeutic strategies based on glucagon-like peptide-1. *Diabetes* 53, 2181-2189 (2004)

7. Deacon C.F, M.A Nauck, M. Toft-Nielsen, L. Pridal, B. Willms & J.J. Holst: Both subcutaneously and intravenously administered glucagon-like peptide I are rapidly degraded from the NH2-terminus in type II diabetic patients and in healthy subjects. *Diabetes* 44, 1126-1131 (1995)

8. Del Prato S & P. Marchetti: Beta- and alpha-cell dysfunction in type 2 diabetes. *Horm Metab Res* 36, 775-781 (2004)..

9. Holman R.R: Long-term efficacy of sulfonylureas: a United Kingdom Prospective Diabetes Study perspective. *Metabolism* 55(5 suppl 1), S2-S5 (2006)

10. Bonner-Weir S: Islet growth and development in the adult. *J Mol Endocrinol* 24, 287-302 (2000)

11. Butler A.E, J. Janson, S. Bonner-Weir, R. Ritzel, R.A. Rizza & P.C. Butler: Beta-cell deficit and increased beta-cell apoptosis in humans with type 2 diabetes. *Diabetes* 52, 102-110 (2003)

12. Tyrberg B, J. Ustinov, T. Otonkoski & A. Andersson: Stimulated endocrine cell proliferation and differentiation in transplanted human pancreatic islets: effects of the ob gene and compensatory growth of the implantation organ. *Diabetes* 50, 301-307 (2001)

13. Robertson R.P, K.J. Lanz, D.E. Sutherland & E.R. Seaquist: Relationship between diabetes and obesity 9 to 18 years after hemipancreatectomy and transplantation in donors and recipients. *Transplantation* 73, 736-741 (2002)

14. Muscelli E, A. Mari, A. Natali, B.D. Astiarraga, S. Camastra, S. Frascerra, J.J. Holst & E. Ferrannini: Impact of incretin hormones on β-cell function in subjects with normal or impaired glucose tolerance. *Amer J Physiol Endocrinol Metab* 291, E1144-E1150 (2006)
15. Vaag A.A, J.J. Holst, A. Volund & H.B. Beck-Nielsen: Gut incretin hormones in identical twins discordant for non-insulin-dependent diabetes mellitus (NIDDM)—evidence for decreased glucagon-like peptide 1 secretion during oral glucose ingestion in NIDDM twins. *Eur J Endocrinol* 135, 425-432 (1996)
16. Chiasson J.L & R. Rabasa-Lhoret: Prevention of type 2 diabetes. Insulin resistance and β-cell function. *Diabetes* 53 (suppl 3), S34-S38 (2004)
17. Clark A, C.A. Wells, I.D. Buley, J.K. Cruickshank, R.I. Vanhegan, D.R. Matthews, G.J. Cooper, R.R. Holman & R.C. Turner: Islet amyloid, increased A-cells, reduced B-cells and exocrine fibrosis: quantitative changes in the pancreas in type 2 diabetes. *Diabetes Res* 9, 151-159 (1988)
18. Toft-Nielsen M.B, M.B. Damholt, S. Madsbad, L.M. Hilsted, T.E.Hughes, B.K. Michelsen & J.J. Holst: Determinants of the impaired secretion of glucagon-like peptide-1 in type 2 diabetic patients. *J Clin Endocrinol Metab* 86, 3717-3723 (2001)
19. Shah P, A. Vella, A. Basu A, R. Basu, W.F. Schwenk & R.A. Rizza: Lack of suppression of glucagon contributes to postprandial hyperglycemia in subjects with type 2 diabetes mellitus. *J Clin Endocrinol Metab* 85, 4053-4059 (2000)
20. Holst J.J & J. Gromada: Role of incretin hormones in the regulation of insulin secretion in diabetic and nondiabetic humans. *Am J Physiol Endocrinol Metab* 287, E199-E206 (2004)
21. Drucker D.J: The biology of incretin hormones. *Cell Metab* 3, 153-165 (2006)
22. Doyle M.E & J.M. Egan: Mechanisms of action of glucagon-like peptide 1 in the pancreas. *Pharmacol Ther* 113, 546-593 (2007)
23. Ørskov C, J.J. Holst & O.V. Nielsen: Effect of truncated glucagon-like peptide-1 [proglucagon-(78-107) amide] on endocrine secretion from pig pancreas, antrum, and nonantral stomach. *Endocrinology* 123, 2009-2013 (1988)
24. Nauck M.A, M.M. Heimesaat, K. Behle, J.J. Holst, M.S. Nauck, R. Ritzel, M. Hufner & W.H. Schmiegel: Effects of glucagon-like peptide 1 on counterregulatory hormone responses, cognitive functions, and insulin secretion during hyperinsulinemic, stepped hypoglycaemic clamp experiments in healthy volunteers. *J Clin Endocrinol Metab* 87, 1239-1246 (2002)
25. Wettergren A, B. Schjoldager, P.E. Mortensen, J. Myhre, J. Christiansen & J.J. Holst: Truncated GLP-1 (proglucagon 78-107-amide) inhibits gastric and pancreatic functions in man. *Dig Dis Sci* 38, 665-673 (1993)
26. Nauck M.A, U. Niedereichholz, R. Ettler, J.J. Holst, C. Orskov, R. Ritzel & W.H. Schmiegel: Glucagon-like peptide 1 inhibition of gastric emptying outweighs its insulinotropic effects in healthy humans. *Am J Physiol* 273**,** E981-E988 (1997)
27. Flint A, A. Raben, A. Astrup & J.J. Holst: Glucagon-like peptide 1 promotes satiety and suppresses energy intake in humans. *J Clin Invest* 101, 515-520 (1998)
28. Zander M, S. Madsbad , J.L. Madsen & J.J. Holst: Effect of 6-week course of glucagon-like peptide 1 on glycaemic control, insulin sensitivity, and beta-cell function in type 2 diabetes: a parallel-group study. *Lancet* 359, 824-830 (2002)
29. Bose A.K, M.M. Mocanu, R.D. Carr, C.L. Brand & D.M. Yellon: Glucagon-like peptide 1 can directly protect the heart against ischemia/reperfusion injury. *Diabetes* 54, 146-151 (2005)
30. Nikolaidis L.A, S. Mankad, G.G. Sokos, G. Miske, A. Shah, D. Elahi & R.P. Shannon: Effects of glucagon-like peptide-1 in patients with acute myocardial infarction and left ventricular dysfunction after successful reperfusion. Circulation 109, 962-965 (2004)
31. Sokos G.G, L.A. Nikolaidis, S. Mankad, D. Elahi & R.P. Shannon: Glucagon-like peptide-1 infusion improves left ventricular ejection fraction and functional status in patients with chronic heart failure. J Card Fail 12, 694-699 (2006)
32. Vilsbøll T, T. Krarup, S. Madsbad & J.J. Holst: Defective amplification of the late phase insulin response to glucose by GIP in obese Type II diabetic patients. Diabetologia 45, 1111-1119 (2002)
33. Yip R.G & M.M. Wolfe: GIP biology and fat metabolism. Life Sci 66, 91-103 (2000)
34. Creutzfeldt W: The incretin concept today. *Diabetologia* 16, 75-85 (1979)
35. Nauck M.A, M.M. Heimesaat, C. Ørskov, J.J. Holst, R. Ebert & W. Creutzfeldt: Preserved incretin activity of glucagon-like peptide 1 [7-36 amide] but not of synthetic human gastric inhibitor polypeptide in patients with type-2 diabetes. *J Clin Invest* 91, 301-307 (1993)
36. Vilsbøll T, T. Krarup, S. Madsbad & J.J. Holst: Both GLP-1 and GIP are insulinotropic at basal and postprandial glucose levels and contribute nearly equally to the incretin effect of a meal in healthy subjects. Regul Pept 114, 115-121 (2003)
37. Nauck M, F. Stockmann, R. Ebert & W. Creutzfeldt: Reduced incretin effect in type 2 (non-insulin-dependent) diabetes. Diabetologia 29, 46-52 (1986)
38. Vilsbøll T, T. Krarup, C.F. Deacon, S. Madsbad & J.J. Holst: Reduced postprandial concentrations of intact biologically active glucagon-like peptide 1 in type 2 diabetic patients. Diabetes 50, 609-613 (2001)
39. Kjems L.L, J.J. Holst, A. Volund & S. Madsbad: The influence of GLP-1 on glucose-stimulated insulin secretion: effects on beta-cell sensitivity in type 2 and nondiabetic subjects. Diabetes 52, 380-386 (2003)
40. Vilsbøll T, F.K. Knop, T. Krarup, A. Johansen, S. Madsbad, S. Larsen, T. Hansen, O. Pedersen & J.J. Holst: The pathophysiology of diabetes involves a defective amplification of the late-phase insulin response to glucose by glucose-dependent insulinotropic polypeptide-regardless of etiology and phenotype. J Clin Endocrinol Metab 88, 4897-4903 (2003)
41. Meier J.J & M.A. Nauck: Incretins and the development of type 2 diabetes. Curr Diabetes Rep 6, 194-201 (2006)
42. Meier J.J, B. Gallwitz, M. Askenas, K. Vollmer, C.F. Deacon, J.J. Holst, W.E. Schmidt & M.A. Nauck: Secretion of incretin hormones and the insulinotropic effect of gastric inhibitory polypeptide in women with a history of gestational diabetes. *Diabetologia* 48, 1872-1881 (2005)
43. Meier J.J, K. Hucking, J.J. Holst, C.F. Deacon, W.H. Schmiegel & M.A. Nauck: Reduced insulinotropic effect of

gastric inhibitory polypeptide in first-degree relatives of patients with type 2 diabetes. *Diabetes* 50, 2497-2504 (2003)
44. Højberg P.V, M. Zander, T. Vilsbøll, F.K. Knop, T. Krarup, J.J. Holst & S. Madsbad: Effect of 4 weeks of near-normalization of blood glucose on beta-cell sensitivity to glucose and GLP-1 in type 2 diabetic patients. *Diabetes* 54:(suppl 1), A362 (Abstract) (2005)
45. Nauck M.A, N. Kleine, C. Ørskov, J.J. Holst, B. Willms & W. Creutzfeldt: Normalization of fasting hyperglycaemia by exogenous glucagon-like peptide 1 (7-36 amide) in type 2 (non-insulin-dependent) diabetic patients. *Diabetologia* 36, 741-744 (1993)
46. Gutniak M, C. Ørskov, J.J. Holst, B. Ahren & S. Efendic: Antidiabetogenic effect of glucagon-like peptide-1 (7-36)amide in normal subjects and patients with diabetes mellitus. *N Engl J Med* 326, 1316-1322 (1992)
47. Creutzfeldt W.O, N. Kleine, B. Willms, C. Orskov, J.J. Holst & M.A. Nauck: Glucagonostatic actions and reduction of fasting hyperglycemia by exogenous glucagon-like peptide I(7-36) amide in type I diabetic patients. *Diabetes Care* 19, 580-586 (1996)
48. Lambeir A-M, C. Durinx, S. Scharpé & I. De Meester: Dipeptidyl-peptidase IV from bench to bedside: An update on structural properties, functions, and clinical aspects of the enzyme DPPIV. *Crit Rev Clin Lab Sci* 40, 209-294 (2003)
49. Mentlein R, B. Gallwitz & W.E. Schmidt: Dipeptidyl peptidase IV hydrolyses gastric inhibitor peptide, glucagon-like peptide (7-36) amide, peptide histidine methionine and is responsible for their degradation in human serum. *Eur J Biochem* 214, 829-835 (1993)
50. Deacon C.F, A.H. Johnsen & J.J. Holst: Degradation of glucagon-like peptide-1 by human plasma *in vitro* yields an N-terminally truncated peptide which is a major endogenous metabolite *in vivo*. *J Clin Endocrinol Metab* 80, 952-957 (1995)
51. Deacon C.F, M.A. Nauck, J. Meier, K. Hücking & J.J. Holst: Degradation of endogenous and exogenous gastric inhibitory polypeptide in healthy and in type 2 diabetic subjects as revealed using a new assay for the intact peptide. *J Clin Endocrinol Metab* 85, 3575-3581 (2000)
52. Deacon C.F, S. Wamberg, P. Bie, T.E. Hughes & J.J. Holst: Preservation of active incretin hormones by inhibition of dipeptidyl peptidase IV suppresses meal-induced incretin secretion in dogs. J Endocrinol 172, 355-362 (2002)
53. Vilsbøll T, H. Agerso, T. Krarup & J.J. Holst: Similar elimination rates of glucagon-like peptide-1 in obese type 2 diabetic patients and healthy subjects. J Clin Endocrinol Metab 88, 220-224 (2003)
54. Deacon C.F, B. Ahrén & J.J. Holst: Inhibitors of dipeptidyl peptidase IV: a novel approach for the prevention and treatment of type 2 diabetes. Expert Opin Investig Drugs 13, 1091-1102 (2004)
55. Fleicher B: CD26: a surface protease involved in T-cell activation. Immunol Today 15, 180-184 (1994)
56. Pederson R.A, T.J. Kieffer, R. Pauly, H. Kofod, J. Kwong & C.H.S. McIntosh: The enteroinsular axis in dipeptidyl peptidase IV-negative rats. Metabolism 45, 1335-1341 (1996)
57. Marguet D, L. Baggio, T. Kobayashi, A.M. Bernard, M. Pierres, P.F. Nielsen, U. Ribel, T. Watanabe, D.J. Drucker & N. Wagtmann: Enhanced insulin secretion and improved glucose tolerance in mice lacking CD26. *Proc Natl Acad Sci USA* 97, 6874-6879 (2000)
58. Lankas G.R, B. Leiting, R.S. Roy, G.J. Eiermann, M.G. Beconi, T. Biftu, C.C. Chan, S. Edmondson, W.P. Feeney, H. He, D.E. Ippolito, D. Kim, K.A. Lyons, H.O. Ok, R.A. Pate, A.N. Petrov, K.A. Pryor, X. Qian, L. Reigle, A. Woods, J.K. Wu, D. Zaller, X. Zhang, L. Zhu, A.E. Weber & N.A. Thornberry: Dipeptidyl peptidase IV inhibition for the treatment of type 2 diabetes: potential importance of selectivity over dipeptidyl peptidases 8 and 9. *Diabetes* 54, 2988-2994 (2005)
59. Vilsbøll T, A. Agersø, T. Lauritsen, C.F. Deacon, K. Aaboe, S. Madsbad, T. Krarup & J.J. Holst: The elimination rates of intact GIP as well as its primary metabolite, GIP 3-42, are similar in Type 2 diabetic patients and healthy subjects. *Regul Pept* 137, 168-172 (2006)
60. Holst J.J & C.F. Deacon: Inhibition of the activity of dipeptidyl peptidase IV as a treatment for type 2 diabetes. *Diabetes* 47, 1663-1670 (1998)
61. Rachman J, B.A. Barrow, J.C. Levy & R.C. Turner: Near-normalisation of diurnal glucose concentrations by continuous administration of glucagon-like peptide-1 (GLP-1) in subjects with NIDDM. *Diabetologia* 40, 205-211 (1997)
62. Nauck M.A, D. Wollschläger, J. Werner, J.J. Holst, C. Orskov, W. Creutzfeldt & B. Willms: Effects of subcutaneous glucagon-like peptide 1 (GLP-1 [7-36 amide]) in patients with NIDDM. *Diabetologia* 39, 1546-1553 (1996)
63. Kim D, L. Wang, M. Beconi, G.J. Eiermann, M.H. Fisher, H. He, G.J. Hickey, J.E. Kowalchick, B. Leiting, K. Lyons, F. Marsilio, M.E. McCann, R.A. Patel, A. Petrov, G. Scapin, S.B. Patel, R.S. Roy, J.K. Wu, M.J. Wyvratt, B.B. Zhang, L. Zhu, N.A. Thornberry & A.E. Weber: (2R)-4-oxo-4-[3-(trifluoromethyl)-5,6-dihydro[1,2,4]triazolo[4,3-a]pyrazin-7(8H)-yl]-1-(2,4,5-trifluorophenyl)butan-2-amine: a potent, orally active dipeptidyl peptidase IV inhibitor for the treatment of type 2 diabetes. *J Med Chem* 48, 141-151 (2005)
64. Villhauer E.B, J.A. Brinkman, G.B. Naderi, B.F. Burkey, B.E. Dunning, K. Prasad, B.L. Mangold, M.E. Russell & T.E. Hughes: 1-[[(3-hydroxy-1-adamantyl)amino]acetyl]-2-cyano-(S)-pyrrolidine: a potent, selective, and orally bioavailable dipeptidyl peptidase IV inhibitor with antihyperglycemic properties. *J Med Chem* 46, 2774-2789 (2003).
65. Deacon C.F: MK-431 Merck. *Curr Opin Investig Drugs* 6, 419-426 (2005)
66. Herman G.A, A. Bergman & J.A. Wagner: Sitagliptin, a DPP-4 inhibitor: an overview of the pharmacokinetic (PK) profile and the propensity for drug-drug interactions (DDI). *Diabetologia* 49(suppl 1), 481 (Abstract) (2006)
67. Burkey B.F, M. Russell, K. Wang, J. Trappe & T.E. Hughes: Vildagliptin displays slow tight-binding to dipeptidyl peptidase (DPP)-4, but not DPP-8 or DPP-9. *Diabetologia* 49(suppl 1), 477 (Abstract) (2006)
68. Augeri D.J, J.A. Robl, D.A. Betebenner, D.R. Magnin, A. Khanna, J.G. Robertson, A. Wang, L.M. Simpkins, P. Taunk, Q. Huang, S.P. Han, B. Abboa-Offei, M. Cap, L. Xin, L. Tao, E. Tozzo, G.E. Welzel, D.M. Egan, J. Marcinkeviciene, S.Y. Chang, S.A. Biller, M.S. Kirby,

R.A. Parker& L.G. Hamann: Discovery and preclinical profile of saxagliptin (BMS-477118): a highly potent, long-acting, orally active dipeptidyl peptidase IV inhibitor for the treatment of type 2 diabetes. *J Med Chem* 48, 5025-5037 (2005)
69. Feng J, Z. Zhang, M.B. Wallace, J.A. Stafford, S.W. Kaldor, D.B. Kassel, M. Navre, L. Shi, R.J. Skene, T. Asakawa, K. Takeuchi, R. Xu, D.R. Webb & S.L. Gwaltney.: Discovery of alogliptin: A potent, selective, bioavailable, and efficacious inhibitor of dipeptidyl peptidase IV. *J Med Chem* 50, 2297-2300 (2007)
70. Heise T, R. Tiessen, S. Huettner, A. Ring, A. Ritzhaupt, U. Graefe-Mody & K.A. Dugi: Treatment with BI 1356, a novel and potent DPP-IV inhibitor, significantly reduces glucose excursions after an oGTT in patients with type 2 diabetes. *Diabetes* 56(Suppl 1): A156 (Abstract) (2007)
71. Dutteroy A, F. Voelker, X. Zhang, X. Ren, K. Merriam, L. Qui, S. Knight, H. Chen T. Hughes & B. Burkey: The DPP-4 inhibitor vildagliptin increases pancreatic beta cell mass in rodents. *Diabetologia* 48(suppl 1), A178 (Abstract) (2005)
72. Combettes M, C. Ilic, O. Broux, C. Kargar, O. Della-Zuana, A. Benoist, G. De Nanteuil & A Ktorza: S 40010, a potent DPP-IV inhibitor, improves long-term glycemic control in *db/db* mice and increases pancreatic β-cell mass and neogenesis. *Diabetes* 56(Suppl 1): A158 (Abstract) (2007)
73. Mu J, J. Woods, Y.P. Zhou, R.S. Roy, Z. Li, E. Zycband, Y. Feng, L. Zhu, C. Li, A.D. Howard, D.E. Moller, N.A. Thornberry & B.B. Zhang: Chronic inhibition of dipeptidyl peptidase-4 with a sitagliptin analog preserves pancreatic {beta}-cell mass and function in a rodent model of type 2 diabetes. *Diabetes* 55, 1695-1704 (2006)
74. Ahrén B, E. Simonsson, H. Larsson, M. Landin-Olsson, H. Torgeirsson, P.A. Jansson, M. Sandqvist, P. Bavenholm, S. Efendic, J.W. Eriksson, S. Dickinson & D. Holmes: Inhibition of dipeptidyl peptidase IV improves metabolic control over a 4-week study period in type 2 diabetes. *Diabetes Care* 25, 869-875 (2002)
75. Ahrén B, M. Landin-Olsson, P.A. Jansson, M. Svensson, D. Holmes & A. Schweizer.: Inhibition of dipeptidyl peptidase-4 reduces glycemia, sustains insulin levels, and reduced glucagon levels in type 2 diabetes. *J Clin Endocrinol Metab* 89, 2078-2084 (2004)
76. Pratley R.E, S. Jauffret-Kamel, E. Galbreath & D Holmes: Twelve-week monotherapy with the DPP-4 inhibitor vildagliptin improves glycemic control in subjects with type 2 diabetes. *Horm Metab Res* 38, 423-428 (2006)
77. Schweizer A, A. Couturier, J.E. Foley & S. Dejager: Comparison between vildagliptin and metformin to sustain reductions in HbA1c over 1 year in drug-naive patients with type 2 diabetes (T2DM). *Diabetic Med* 24, 955-961 (2007)
78. Ristic S, S. Byiers, J. Foley & D. Holmes: Improved glycaemic control with dipeptidyl peptidase-4 inhibition in patients with type 2 diabetes: vildagliptin (LAF237) dose response. *Diab Obes Metab* 7, 692-698 (2005)
79. Scott R, M. Wu, M. Sanchez & P. Stein: Efficacy and tolerability of the dipeptidyl peptidase-4 inhibitor sitagliptin as monotherapy over 12 weeks in patients with type 2 diabetes. *Int J Clin Pract* 61, 1-10 (2007)
80.Hanefeld, M. G.A. Herman, M. Wu, C. Mickel & M. Sanchez: Once daily sitagliptin, a dipeptidyl peptidase-4 inhibitor, for the treatmeny ofpatients with type 2 diabetes. *Curr Med Res Opin* Apr 30; [Epub ahead of print] (2007)
81. Raz I, M. Hanefeld, L. Xu, C. Caria, D. Williams-Herman & H. Khatami: Efficacy and safety of the dipeptidyl peptidase-4 inhibitor sitagliptin as monotherapy in patients with type 2 diabetes mellitus. *Diabetologia* 49, 2564-2571 (2006)
82. Aschner P, M. Kipnes, M. Lunceford, M. Sanchez, C. Mickel & D. Williams-Herman.: Effect of the dipeptidyl peptidase-4 inhibitor sitagliptin as monotherapy on glycemic control in patients with type 2 diabetes. *Diabetes Care* 29, 2632-2637 (2006)
83. Christopher R, P. Covington, M. Davenport, P. Fleck, Q. Mekki, E. Wann & A. Karim: Pharmacokinetics, pharmacodynamics, and tolerability of multiple doses of alogliptin benzoate (SYR-322), a dipeptidyl peptidase-IV inhibitor, in patients with type 2 diabetes. *Diabetes* 56(Suppl 1): A133 (Abstract) (2007)
84. Forst T, B. Uhlig-Laske, A. Ring, A. Ritzhaupt, U. Graeffe-Mody & K.A. Dugi: The novel, potent, and selective DPP-IV inhibitor BI 1356 significantly lowers HbA1c after only 4 weeks of treatment in patients with type 2 diabetes. *Diabetes* 56(Suppl 1): A157 (Abstract) (2007)
85. Rachman J, P. Jaehnig, G. Golor, N. Piwon, M. Kruse, J. Heins, F. Burger & M.S. Thomsen: Glucose lowering effects and pharmakokinetics of 14-day treatment with the prandial DP-IV inhibitor, PSN9301, in patients with type 2 diabetes. *Diabetes* 55(suppl 1), A130 (Abstract) (2006)
86. Ahrén B, R. Gomis, E. Standl, D. Mills & A. Schweizer: Twelve- and 52-week efficacy of the dipeptidyl peptidase IV inhibitor LAF237 in metformin-treated patients with type 2 diabetes. *Diabetes Care* 27, 2874-2880 (2004)
87. Charbonnel B, A. Karasik, J. Liu, M. Wu & G. Meininger: Efficacy and safety of the dipeptidyl peptidase-4 inhibitor sitagliptin added to ongoing metformin therapy in patients with type 2 diabetes inadequately controlled with metformin alone. *Diabetes Care* 29, 2638-2643 (2006)
88. Goldstein B.J, M.N. Feinglos, J.K. Lunceford, J. Johnson & D.E. Williams-Herman: Effect of initial combination therapy with sitagliptin, a dipeptidyl peptidase-4 inhibitor, and metformin on glycemic control in patients with type 2 diabetes. *Diabetes Care* 30, 1979-1987 (2007)
89. DeFronzo R.A, M. Hissa, M.B. Blauwet & R.S. Chen: Saxagliptin added to metformin improves glycemic control in patients with type 2 diabetes. *Diabetes* 56(Suppl 1): A74 (Abstract) (2007)
90. Rosenstock J, M.A. Baron, R.P. Camisasca, A. Couturier & S. Dejager: Efficacy and tolerability of initial combination therapy with vildagliptin and pioglitazone compared with component monotherapy in patients with type 2 diabetes. *Diab Obes Metab* 9, 175-185 (2007)
91. Garber A.J, A. Schweizer, M.A. Baron, E. Rochette & S. Dejager: Vildagliptin in combination with pioglitazone improves glycaemic control in patients with type 2 diabetes failing thiazolidinedione monotherapy: a randomized placebo-controlled study. *Diab Obes Metab* 9, 166-174 (2007)

92. Rosenstock J, R. Brazg, P. Andryuk, K. Lu & P. Stein: Efficacy and safety of the dipeptidyl peptidase-4 inhibitor sitagliptin added to ongoing pioglitazone therapy in patients with type 2 diabetes: a 24 week, multicenter, randomized, double-blind, placebo-controlled parallel-group study. *Clin Ther* 28, 1556-1568 (2006)
93. Garber A.J, R.P. Camisasca, S. Jauffret & M.A. Baron: Efficacy and tolerability of vildagliptin added to a sulfonylurea (SU) in patients with type 2 diabetes (T2DM). *Diabetes* 56(Suppl 1): A134 (Abstract) (2007)
94. Hermansen K, M. Kipnes, E. Luo, D. Fanurik, H. Khatami & P. Stein: Efficacy and safety of the dipeptidyl peptidase-4 inhibitor, sitagliptin, in patients with type 2 diabetes mellitus inadequately controlled on glimepiride alone or on glimepiride and metformin. *Diabetes Obes Metab* 9, 733-745 (2007)
95. Fonseca V, A. Schweizer, D. Albrecht, M.A. Baron, I. Chang & S. Dejager: Addition of vildagliptin to insulin improves glycaemic control in type 2 diabetes (T2DM). *Diabetologia* 50, 1148-1155 (2007)
96. Rosenstock J, M.A. Baron, S. Dejager; D. Mills & A. Schweizer: Comparison of vildagliptin and rosiglitazone monotherapy in patients with type 2 diabetes: a 24-week, double-blind, randomized trial. *Diabetes Care* 30, 217-223 (2007)
97. Nauck M, G. Meininger, D. Sheng, L. Terranella & P. Stein: Efficacy and safety of the dipeptidyl peptidase-4 inhibitor, sitagliptin, compared to the sulfonylurea, glipizide, in patients with type 2 diabetes inadequately controlled on metformin alone: A randomized, double-blind, non-inferiority trial. *Diab Obes Metab* 9, 194-205 (2007)
98. Riddle M.C, R.R. Henry, T.H. Poon, B. Zhang, S.M. Mac, J.H. Holcombe, D.D. Kim & D.G. Maggs: Exenatide elicits sustained glycaemic control and progressive reduction of body weight in patients with type 2 diabetes inadequately controlled by sulphonylureas with or without metformin. *Diabetes Metab Res Re.* 22, 483-491 (2006)
99. Vilsbøll T, M. Zdravkovic, T. Le-Thi, T. Krarup, O. Schmitz, J.P. Courreges, R. Verhoeven, I. Buganova & S. Madsbad S: Liraglutide, a long-acting human GLP-1 analog, given as monotherapy significantly improves glycemic control and lowers body weight without risk of hypoglycemia in patients with type 2 diabetes mellitus. *Diabetes Care* 30, 1608-1610 (2007)
100. Hansotia T, L.L. Baggio, D. Delmeire, S.A. Hinke, Y. Yamada, K. Tsukiyama, Y. Seino, J.J. Holst, F. Schuit & Drucker: Double incretin receptor knockout (DIRKO) mice reveal an essential role for the enteroinsular axis in transducing the glucoregulatory actions of DPP-IV inhibitors. *Diabetes* 53, 1326-1335 (2004)
101. Flock G, L.L. Baggio, C. Longuet & D.J. Drucker: The incretin receptors for GLP-1 and GIP are essential for the sustained metabolic actions of vildagliptin in mice. *Diabetes* Aug 23; (2007)
102. Lynn F.C, S.A. Thompson, J.A.Pospisilik, J.A. Ehses, S.A. Hinke, N. Pamir, C.H. McIntosh & R.A. Pederson: A novel pathway for regulation of glucose-dependent insulinotropic polypeptide (GIP) receptor expression in beta cells. *FASEB J* 17, 91-93 (2003)
103. Xu G, H. Kaneto, D.R. Laybutt, V.F. Duvivier-Kali, N. Trivedi, K. Suzuma, G.L. King, G.C. Weir & S. Bonner-Weir: Downregulation of GLP-1 and GIP receptor expression by hyperglycemia: Possible contribution to impaired incretin effects in diabetes. *Diabetes* 56, 1551-1558 (2007)
104. Meneilly G.S, M. Bryer-Ash & D. Elahi: The effect of glyburide on beta-cell sensitivity to glucose-dependent insulinotropic polypeptide. *Diabetes Care* 16, 110-114 (1993)
105. Højberg PV, T. Vilsbøll, F.K. Knop, M. Bache, S. Madsbad, T. Krarup & J.J. Holst: Four weeks of near-normalization of blood glucose restores the insulin response to GIP and improves the insulin response to GLP-1 in patients with type 2 diabetes. *Diabetes* 56(suppl 1): A373 (Abstract) (2007)
106. Holst J.J & C.F. Deacon: Glucagon-like peptide-1 mediates the therapeutic actions of DPP-IV inhibitors. *Diabetologia* 48, 612-615 (2005)
107. Ahrén B, G. Pacini, J.E. Foley & A. Schweizer A: Improved meal-related beta-cell function and insulin sensitivity by the dipeptidyl peptidase-IV inhibitor vildagliptin in metformin-treated patients with type 2 diabetes over 1 year. *Diabetes Care* 28, 1936-1940 (2005)
108. Mari A, W.M. Sallas, Y.L. He, C. Watson, M. Ligueros-Saylan, B.E. Dunning, C.F. Deacon, J.J. Holst & J.E. Foley: Vildagliptin, a dipeptidyl peptidase IV-inhibitor improves model-assessed beta-cell function in patients with Type 2 diabetes. *J Clin Endocrinol Metab* 90, 4888-4894 (2005)
109. Xu L, C. Dalla Man, C. Cobelli, D. Williams-Herman, G. Meininger, H. Khatami & P. Stein: Sitagliptin, a dipeptidyl peptidase-4 inhibitor, improved β cell function in patients with type 2 diabetes: a model-based approach. *Diabetologia* 49(suppl 1), 396 (Abstract) (2006)
110. Balas B, M. Baig, C. Watson, B.E. Dunning, M. Ligueros-Saylan, Y. Wang, Y.L. He, C. Darland, J.J. Holst, C.F. Deacon, K. Cusi, A. Mari, J.E. Foley & R.A. DeFronzo: The dipeptidyl peptidase IV inhibitor vildagliptin suppresses endogenous glucose production and enhances islet function after single-dose administration in type 2 diabetic patients. *J Clin Endocrinol Metab* 92, 1249-1255 (2007)
111. Jones-Leone A, T. Yu, D. Barilla, Y.L. He, Y. Ho, M. Ligueros-Saylan, J. Foley & D.E. Kelley: Evidence for insulin independent suppression of glucagon secretion by LAF237. *Diabetologia* 47(Suppl. 1): A289 (Abstract) (2004)
112. DREAM (Diabetes Reduction Assessment with ramipril and rosiglitazone Medication) Trial Investigators: Effect of rosiglitazone on the frequency of diabetes in patients with impaired glucose tolerance or impaired fasting glucose: a randomised controlled trial. *Lancet* 368, 1096-1105 (2006)
113. Yasuda N, T. Inoue, T. Nagakura, K. Yamazaki, K. Kira, T. Saeki & I. Tanaka: Enhanced secretion of glucagon-like peptide 1 by biguanide compounds. *Biochem Biophys Res Commun* 298: 779-784 (2002)
114. Migoya E.M, J. Miller, P. Larsen, M. Tanen, D. Hilliard, C. Deacon, M. Gutierrez, A. Stoch, G.A. Herman, P. Stein, J.J. Holst & J.A Wagner: Sitagliptin, a selective DPP-4 inhibitor, and metformin have complementary effects to increase active gLP-1 concentrations. *Diabetes* 56(Suppl 1): A74 (Abstract) (2007)

115. Barilla D, Y.L. He, S. Balez, J. Bullock, Y. Ho, M. Guiterrez & M. Ligueros-Saylan: No pharmacokinetic interactions or acute clinical safety issues preclude combination of the DPP-4 inhibitor LAF237 with glyburide. *Diabetes* 53(suppl 2), A470 (Abstract) (2004)
116. Ruddy M.K, A.J. Bergman, W. Zheng, D. Hreniuk, M. Zinny, J.A. Wagner & G.A. Herman: Sitagliptin, a DPP-4 inhibitor, does not inhibit the pharmacokinetics of the sulfonylurea glyburide. *Diabetes* 55(suppl 1), A133 (Abstract) (2006)
117. Mistry G, A. Bergman, W.L. Luo, C. Cilissen, W. Haazen, M.J. Davies, K.M. Gottesdiener, J.A. Wagner & G.A. Herman: Multiple-dose administration of sitagliptin, a dipeptidyl peptidase-4 inhibitor, does not alter the single-dose pharmacokinetics of rosiglitazone in healthy subjects. *J Clin Pharmacol* 47, 159-164 (2007)
118. Foley J.E, M. Ligueros-Saylan, C.A. Watson, Y.L. He, B.E. Dunning, R.E. Pratley & D.A. D'Alessio.: Differential effects of vildagliptin on islet function in patients with type 2 diabetes receiving no additional agent or concomitant metformin. *Diabetologia* 49(suppl 1), 397 (Abstract) (2006)
119. Rosenstock J, M.S.Rendell, M. Landin-Olsson, J.E. Foley, E. Rochette & M.A. Baron: Effects of vildagliptin in subjects with IGT. *Diabetes* 56(Suppl 1): A135 (Abstract) (2007)
120. Utzschneider K.M, J. Tong, J. Udayasank, F. Gerchman, B. Montgomery, C.E. Watson, M.A. Ligueros-Saylan, J.E. Foley & S.E. Kahn. The dipeptidyl peptidase-4 (DPP-4) inhibitor vildagliptin improves insulin sensitivity and β-cell function in subjects with impaired fasting glucose. *Diabetes* 56(Suppl 1): A137 (Abstract) (2007)
121. Blonde L, E.J. Klein, J. Han, B. Zhang, S.M. Mac, T.H. Poon, K.L. Taylor, M.E. Trautmann, D.D. Kim & D.M. Kendall: Interim analysis of the effects of exenatide treatment on A1C, weight and cardiovascular risk factors over 82 weeks in 314 overweight patients with type 2 diabetes. *Diabetes Obes Metab* 8, 436-447 (2006)
122. Matikainen N, S. Manttari, A. Schweizer, A. Ulvestad, D. Mills, B.E. Dunning, J.E. Foley & M.R. Taskinen: Vildagliptin therapy reduces postprandial intestinal triglyceride-rich lipoprotein particles in patients with type 2 diabetes. *Diabetologia* 49, 2049-2057 (2006)
123. Nathwani A, A. Lebeaut, S. Byiers, C. Gimpelewicz & I.H. Chang: Reduction in blood pressure in patients treated with vildagliptin as monotherapy or in combination with metformin for type 2 diabetes. *Diabetes* 55(suppl 1), A113 (2006)
201. Nathwani A: The use of vildagliptin for treatment of patients with type 2 diabetes. Late-breaking clinical studies, 66th Scientific sessions, American Diabetes Association Washington, 2006, http://webcasts.prous.com/ada2006_CME/article.asp?AID=164&CLID=2&CID=Y.
202. GSK 3rd quarter results. http://www.gsk.com/investors/reports/gsk_q32006/q32006pdf.
203. Prosidion http://www.osip.com/PSN9301
204. Gregg R.E: Bristol-Meyers-Squibb Investors Community Meeting, November 2004 [WWW webpage]. http://www.bms.com/investors/speeches_and_events/content/data/gregg.pdf. (2004)
205. Nathwani A: Novartis pipeline event, CMV Franchise overview, London, November 2006, [WWW webpage].http://www.novartis.com/downloads/investors/events/pipeline-update/2006/04_Nathwani_Print_Web.pdf
206. Stein P: Sitagliptin, a novel dipeptidyl peptidase-4 inhibitor, for the treatment of patients with type 2 diabetes. Late-breaking clinical studies, 66th Scientific sessions, American Diabetes Association Washington, 2006. http://webcasts.prous.com/ada2006_CME/article.asp?AID=166&CLID=2&CID=Y.

Abbreviations: DPP-4: dipeptidyl peptidase-4, GLP-1: glucagon-like peptide-1, GIP: glucose-dependent insulinotropic polypeptide, T2DM: type 2 diabetes mellitus, TZD: thiazolidinedione, UKPDS: United Kingdom Prospective Diabetes Study, IGT, impaired glucose tolerance, GIPR: GIP receptor, FPG: fasting plasma glucose

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Send correspondence to: Dr CF Deacon, Department of Biomedical Sciences, Panum Institute, Blegdamsvej 3, DK-2200 Copenhagen N, Denmark, Tel: 45-3532-7523, Fax: 45-3532-7537, E-mail: deacon@mfi.ku.dk

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