

# A Review of Incretin-Based Therapies for Type 2 Diabetes Treatment

Continuous, subcutaneous administration of native GLP-1 to type 2 diabetes patients has been shown to lower fasting and postprandial glucose and A1C, as well as promote satiety and weight loss.

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**G**lucagon-like peptide 1 (GLP-1), an incretin hormone, stimulates insulin release<sup>1</sup> and plays a major role in glucose metabolism.<sup>2,3</sup> Unlike the other incretin hormone, glucose-dependent insulinotropic polypeptide (GIP), GLP-1 retains its glucose-regulatory actions in patients with diabetes. According to a report in *Nature Reviews Endocrinology* (2009;5:262–269), these findings led to the creation of distinct GLP-1 receptor (GLP-1R) agonists, which mimic the actions of GLP-1 in vivo in humans.<sup>2-4</sup> When investigators were able to elucidate the role of dipeptidyl peptidase 4 (DPP-4) in the inactivation of bioactive GLP-1 and GIP<sup>5,6</sup> orally available DPP-4 inhibitors were developed. DPP-4 stabilizes both incretin hormones at physiologically active levels. The following is a summary of Drs. Lovshin and Drucker's original review.

## INTRODUCTION

GLP-1 is secreted at low basal rates in the fasting state and increases after eating. GLP-1 binds to GLP-1R, a receptor expressed on pancreatic beta cells, increasing beta cells' sensitivity to glucose. GLP-1 has been shown to protect rodent and human pancreatic beta cells from apoptotic cell death, and in other animal experiments, triggers proliferative pathways that lead to expansion of beta-cell mass. GLP-1 also suppresses glucagon from pancreatic alpha cells, resulting in a decrease in hepatic glucose production and a delay in nutrients traveling from the stomach to the duodenum through inhibition of gastric emptying.<sup>7</sup> GLP-1 promotes satiety, often resulting in weight loss. In healthy individuals, glucose-dependent insulinotropic peptide (GIP)

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exerts incretin-like effects on beta-cells, however, its actions are impaired in type 2 diabetes patients thus limiting its potential as a clinical therapy.<sup>8,9</sup>

Continuous, subcutaneous administration of native GLP-1 to type 2 diabetes patients with type 2 diabetes has been shown to lower fasting and postprandial glucose and A1C, as well as promote weight loss.<sup>10</sup> Based on these findings, two drug classes have emerged: peptide-based, degradation-resistant GLP-1R agonists (administered by subcutaneous injection) and oral DPP-4 inhibitors.<sup>4</sup> The glucose regulatory effects of both classes of agents occur through GLP-1, but there are differences in their mechanisms of action. Both act on pancreatic islets to stimulate insulin secretion and inhibit glucagon secretion. GLP-1R agonists, however, also inhibit gastric emptying and promote satiety. DPP-4 inhibitors stabilize bioactive GIP levels, so these agents may lower glucose levels in part through GIP-mediated stimulation of insulin secretion.<sup>9</sup>

The first GLP-1R agonist to be introduced was exenatide (Byetta, Eli Lilly and Amylin) and the first DPP-4 inhibitor was sitagliptin (Januvia, Merck). Now several of these drugs are either commercially available or have reached late stages of clinical development.

## GLP-1R AGONISTS

**Exenatide.** Exenatide is a synthetic form of the naturally occurring *Heloderma suspectum* peptide exendin. It exhibits about 50% amino acid identity with human GLP-1 and is a potent agonist of human GLP-1R. It is resistant to degradation by DPP-4 and therefore has increased circulating half-life in vivo. Three 30-week, pivotal, phase 3 clinical trials examined the efficacy of twice-daily injections of 5 or 10  $\mu\text{g}$  exenatide in patients with type 2 diabetes who were inadequately controlled with a sulfonylurea and/or metformin.<sup>11-13</sup> Substantial benefits on A1C levels and modest reductions in body weight were observed. Exenatide lowered fasting (FPG) and postprandial glucose (PPG) concentrations, and was generally well tolerated; mild nausea and vomiting were the most common adverse effects. Nausea dissipated over time in most patients.

The US Food and Drug Administration approved exenatide in 2005, and the European Medicines Agency granted subsequent approval in November 2006. Exenatide is indicated an adjunct to metformin, sulfonylurea, or both, in patients with type 2 diabetes. A 16-week study examining the efficacy of exenatide plus thiazolidinediones (TZDs) found that exenatide-treated patients had substantial reductions in FPG (about 1.69 mmol/L), A1C (0.98%) and weight (1.5 kg).<sup>14</sup> Exenatide was then approved for use with a TZD, with or without metformin.

Exenatide's efficacy has been assessed in head-to-head comparison trials with insulin glargine in combination with metformin or a sulfonylurea. An open-label study revealed similar improvements in blood glucose control in both treatment groups. Insulin therapy, however, generally led to gain weight, whereas exenatide was associated with weight loss. The incidence of hypoglycemia was comparable between the two groups, but gastrointestinal malaise and drop-out rates were higher among patients taking exenatide.<sup>15</sup> Similar results were observed in a 52-week, open-label study.<sup>16</sup> Exenatide represents a reasonable alternative to insulin therapy in patients suboptimally controlled with oral agents, particularly with regard to weight-gain concerns, based on these studies.

**Liraglutide.** Liraglutide (Victoza, Novo Nordisk) is a modified form of human GLP-1 that has a prolonged half-life in vivo. Liraglutide has been shown to mimic the expected actions of GLP-1, and nausea and diarrhea are the most commonly reported adverse events.<sup>17</sup> Several phase 3 clinical trials have investigated liraglutide's efficacy—as monotherapy or in combination—compared with oral agents, exenatide, or insulin. Liraglutide was found to be at least as efficacious in lowering A1C as comparator treatments and was often associated with weight loss. Add-on therapy with liraglutide among patients inade-

quately controlled with metformin and rosiglitazone caused a mean A1C reduction of 1.5%, from a baseline value of 8.6%, as well as weight loss of about 2 kg and a reduction in systolic blood pressure.<sup>18</sup> Nausea, vomiting and diarrhea were the most common adverse events and the principal reasons for withdrawal from the study. A 52-week study that compared monotherapy with glimepiride or liraglutide showed that liraglutide was more effective for A1C lowering. Liraglutide-treated patients also experienced weight loss and blood pressure reduction, whereas glimepiride-treated patients gained weight.<sup>19</sup> Liraglutide was also more effective than rosiglitazone in producing additional reductions in FPG and A1C over 26 weeks. Rosiglitazone was associated with weight gain and liraglutide was not.<sup>20</sup>

Additive glimepiride was compared with liraglutide in a 26-week study of patients inadequately controlled with metformin.<sup>21</sup> Liraglutide was as effective as glimepiride in reducing A1C, was associated with fewer episodes of minor hypoglycemia, a slight reduction in blood pressure, and an increase in heart rate, and more nausea versus glimepiride. Body weight decreased in liraglutide-treated patients but increased with glimepiride.<sup>21</sup> Liraglutide produced a greater reduction in

A1C and body weight versus insulin glargine on a background therapy of metformin and glimepiride. Liraglutide also improved the proinsulin:C-peptide ratio and reduced systolic blood pressure; however, some liraglutide patients had episodes of major hypoglycemia ( $n = 5$ ), whereas no episodes were seen in the insulin patients.<sup>22</sup>

A US new drug application was filed for liraglutide in May 2008. Liraglutide is also being investigated obesity treatment in nondiabetic patients at doses of up to 3 mg daily.

**Modified exenatide.** Ave0010 (Sanofi-Aventis) is a modified exendin-4 molecule. A dose-ranging, placebo-controlled phase 2b study looked at 542 type 2 diabetes patients inadequately controlled with metformin monotherapy.<sup>23</sup> After 13-week treatment with escalating doses of Ave0010 (5  $\mu\text{g}$ , 10  $\mu\text{g}$ , 20  $\mu\text{g}$ , or 30  $\mu\text{g}$ ). Patients had reductions in A1C from baseline with once-daily (0.28–0.57%) and twice-daily (0.47–0.69%) Ave0010, as well as decreases in body weight. This agent is in phase 3 clinical trials.

A long-acting, once-weekly formulation of exenatide was evaluated at two doses, 0.8 mg and 2 mg, in type 2 diabetes patients who were also treated with diet and exercise and/or metformin for 15 weeks. Both groups had marked reductions in A1C, however, only the 2-mg exenatide-treated patients lost weight.<sup>24</sup> A clinical trial compared the efficacy of 10  $\mu\text{g}$  exenatide twice daily with 2 mg exenatide once weekly in 300 patients who were

TABLE 1. INCRETIN-BASED THERAPIES

Agent	Dose	Status
<i>GLP-1R agonists (subcutaneous injection)</i>		
Exenatide	5–10 µg twice daily	A
Liraglutide	1.2–1.8 mg once daily	F
AvA0010	5–30 µg once or twice daily	I
Exenatide QW	2 mg once weekly	I
Taspoglutide	20–30 mg once weekly	I
Albiglutide	30–50 mg once weekly	I
CJC-1134-PC	1.5–3 mg once or twice weekly	I
NN9535	0.1–1.6 mg once weekly	I
LY2189265	0.25–3 mg once weekly	I
LY2428757	0.5–17.6 mg once weekly	I
<i>DPP-4 inhibitors (oral)</i>		
Sitagliptin	25–100 mg once daily	A
Vildagliptin	50 mg twice daily	A
Alogliptin	12.5–25 mg once daily	F
Saxagliptin	5–10 mg once daily	F
Linagliptin	2.5–5 mg once daily	I
Dutogliptin	200–400 mg once daily	I

*QW = once weekly; A = approved; F = filed for regulatory approval; I = being investigated.*

*Courtesy of Nature Reviews Endocrinology (2009;5:262–269).*

either not treated with oral agents or who were receiving one or two oral agents for 30 weeks.<sup>24</sup> Both groups experienced significant reductions in A1C. More patients assigned to once-weekly exenatide achieved target A1C <7% versus those who received twice-daily exenatide (77% versus 61%, respectively). Weight loss was similar in both treatment groups (3.6–3.9 kg). Once-weekly treatment was associated with a greater reduction in plasma glucagon and FPG versus the twice-daily dose. Twice-daily exenatide was a more potent suppressor of postprandial glycemic excursions, the investigators noted. Nausea and vomiting were the most commonly reported adverse effects.

**Albiglutide.** Albiglutide (Syncria, GlaxoSmithKline) is a long-acting, recombinant GLP-1R agonist. It allows sustained action and once-weekly administration. Preclinical rodent studies showed that it activates GLP-1R and reproduces many GLP-1 actions, including inhibition of gastric emptying and satiety following acute administration.<sup>25</sup> This agent entered phase 3 clinical studies in the first quarter of 2009.

**Taspoglutide.** Taspoglutide (Roche/Ipsen) is a GLP-1-based molecule that is resistant to DPP-4 degradation. A zinc-based formulation of taspoglutide allows once-

weekly dosing. A randomized, placebo-controlled, phase 2 trial investigated the efficacy and safety of weekly or biweekly taspoglutide in 306 type 2 diabetes patients inadequately controlled with metformin.<sup>26</sup> Both taspoglutide regimens reduced A1C after 8 weeks, and dose-dependent reductions in body weight were observed in both groups. Taspoglutide therapy was associated with nausea and vomiting, and some patients developed antipeptide antibodies. A second phase 2 study examined taspoglutide dosing regimens in 133 metformin-treated patients who were randomized to placebo or 20 mg taspoglutide once weekly for 4 weeks, followed by a second 4-week treatment period with 20 mg, 30 mg or 40 mg once weekly. All patients had improved glucose control, and nausea was the most commonly reported adverse event.<sup>27</sup> This drug is being evaluated in phase 3 studies.

**Other long-acting GLP-1R agonists.** CJC1134 (ConjuChem) was shown to exert a broad range of GLP-1-receptor-dependent glucose-regulatory actions in preclinical studies.<sup>28</sup> Several once-weekly GLP-1 therapies are under clinical investigation in phase 1 or 2 studies (Table 1.)

**Adverse effects of GLP-1R agonists.** Nausea and vom-

iting are the most commonly reported diverse events associated with GLP-1R agonists. Incidence and severity seems to be related to maximum doses and the time taken to reach this concentration. Although nausea and vomiting are usually mild, transient, and diminish over time, some patients will not be able to tolerate the therapy.

Exenatide is linked to induction of antiexenatide antibodies.<sup>29</sup> Antiexenatide antibodies do not seem to impact the agents effectiveness for most patients, however, a small subset of individuals with high titers of antibodies (>1:625) may have diminished benefits.

Understanding the potential relationship between incretin-based therapies and pancreatic inflammation is clinically important.

Pancreatitis has been reported in some exenatide patients<sup>30</sup> and in several participants during the liraglutide clinical trials.<sup>19</sup> Concerns are emerging surrounding new onset or possible exacerbation of pancreatitis, but data are limited regarding pancreatitis among exenatide-treated patients versus those using other therapies. It is known that GLP-1 or exendin-4 alone can cause or exacerbate pancreatitis, and many patients who are treated with GLP-1R agonists have occasional abdominal discomfort. This complicates the diagnosis of pancreatitis. Nevertheless, understanding the potential relationship between these therapies and pancreatic inflammation is clinically important.

## DPP-4 INHIBITORS

**Sitagliptin and vildagliptin.** Sitagliptin was approved for US use in October 2006, followed by approval in other countries. Vildagliptin (Galvus, Novartis) was subsequently approved for use in Europe and other countries but not in the United States. DPP-4 inhibitors may be administered orally, once daily (sitagliptin) or twice daily (vildagliptin), they do not influence body weight, and are well tolerated.

Sitagliptin has been approved for US use as monotherapy or in combination with metformin, a sulfonyleurea, or a TZD.<sup>31-36</sup> DPP-4 inhibitors are approved for use in combination with metformin for patients with early type 2 diabetes who are assigned combination therapy. Many patients treated with this combination achieved target A1C. Similar results have been observed with vildagliptin.<sup>37-39</sup>

**Alogliptin and saxagliptin.** Alogliptin (Takeda) has

been studied in phase 3 trials as monotherapy or in combination with other oral antidiabetic agents (metformin, sulfonyleurea, or TZD). It has also been evaluated as monotherapy for 26 weeks in patients with poorly controlled diabetes at doses of 12.5 mg or 25 mg daily. Patients experienced reductions in A1C, and the agent appeared to be well tolerated.<sup>40</sup> Alogliptin, at doses of 12.5 mg and 25 mg once daily, also reduced blood glucose levels when added to existing therapy in patients responding inadequately to metformin monotherapy.<sup>41</sup> Alogliptin and vildagliptin have been successfully used in combination with insulin.<sup>42</sup> An NDA for alogliptin was filed December 2007. In June 2008, an NDA was filed for saxagliptin, a once-daily selective DPP-4 inhibitor investigated in phase 3 trials. It is not known to what extent alogliptin or saxagliptin will exhibit unique antidiabetic properties or if the safety profile will be different from that seen with other DPP-4 inhibitors. Additional DPP-4 inhibitors in late-stage testing (Table 1) include linagliptin (BI-1356, Boehringer Ingelheim) and dutogliptin tartrate (PHX1149, Phenomix).<sup>43</sup>

## UNANSWERED QUESTIONS

Preclinical study evidence shows that GLP-1R activation, and, to a lesser extent, GIP-receptor activation, promotes expansion of beta-cell mass through cell proliferation and apoptosis inhibition. Incretin-based therapies have disease-modifying biological potential due to their effects on the beta cell,<sup>3</sup> however clinical studies have not shown much evidence suggesting a regenerative or protective effect of these agents on beta-cell function in diabetes patients. Exenatide has been suggested as a possible treatment for patients with type 1 diabetes following islet transplantation.<sup>44,45</sup>

Cardiovascular safety of antidiabetic agents is of great interest, however, information is limited about the cardiovascular actions of GLP-1R agonists in humans. They may be associated with weight loss, blood pressure reductions, and improvements in plasma lipid profiles. These agents are not likely to increase CVD risk in diabetes patients.<sup>46</sup> Preliminary data indicate that native GLP-1 may have beneficial effects on heart failure<sup>47</sup> or following myocardial infarction.<sup>48</sup> Less is known about the actions of DPP-4 on the cardiovascular system, and DPP-4-inhibitor therapy is not associated with significant reduction in body weight or blood pressure.

## CONCLUSIONS

New diabetes treatments are increasing important due to the rising prevalence of type 2 diabetes around the world. Emerging incretin-based therapies are expensive, and physician and patient experience with these new

agents is limited. As incretin therapies gain wider acceptance and new agents come to market, interest will continue to increase. There are several advantages associated with the use of incretin drugs, such as their glucose-dependent mechanism of action and no risk of weight gain, their long-term efficacy, safety, and durability of effect continues to be elucidated. Incretin-based agents represent an important option in the fight against diabetes, but they should be fully scrutinized. ■

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- Kreymann B, Williams G, Ghatei MA, Bloom SR. Glucagon-like peptide-17–36: a physiological incretin in man. *Lancet*. 1987;2:1300–1304.
- Deacon CF. Therapeutic strategies based on glucagon-like peptide 1. *Diabetes*. 2004;53:2181–2189.
- Drucker D J. The biology of incretin hormones. *Cell Metab*. 2006;3:153–165.
- Drucker, DJ, Nauck MA. The incretin system: glucagon-like peptide-1 receptor agonists and dipeptidyl peptidase-4 inhibitors in type 2 diabetes. *Lancet*. 2006;368:1696–1705.
- Deacon CF, Johnsen AH, Holst JJ. Degradation of glucagon-like peptide-1 by human plasma in vitro yields an N-terminally truncated peptide that is a major endogenous metabolite in vivo. *J Clin Endocrinol Metab*. 1995;80:952–957.
- Kieffer T J, McIntosh C H, Pederson RA. Degradation of glucose-dependent insulinotropic polypeptide and truncated glucagon-like peptide 1 in vitro and in vivo by dipeptidyl peptidase iv. *Endocrinology*. 1995;136:3585–3596.
- Cervera A, et al. Mechanism of action of exenatide to reduce postprandial hyperglycemia in type 2 diabetes. *Am J Physiol Endocrinol Metab*. 2008;294:e846–e852.
- Nauck MA. Preserved incretin activity of glucagon-like peptide 17–36 amide but not of synthetic human gastric inhibitory polypeptide in patients with type-2 diabetes mellitus. *J Clin Invest*. 1993;91:301–307.
- Højberg, P. v. et al. Four weeks of nearnormalisation of blood glucose improves the insulin response to glucagon-like peptide-1 and glucose-dependent insulinotropic polypeptide in patients with type 2 diabetes. *Diabetologia*. 2008;52:199–207.
- Zander M, Madsbad S, Madsen JL, Holst JJ. 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*. 2002;359:824–830.
- Buse, J. B. et al. effects of exenatide (exendin-4) on glycemic control over 30 weeks in sulfonylurea-treated patients with type 2 diabetes. *Diabetes Care*. 2004;27:2628–2635.
- DeFronzo RA. Effects of exenatide (exendin-4) on glycemic control and weight over 30 weeks in metformin-treated patients with type 2 diabetes. *Diabetes Care*. 2005;28:1092–1100.
- Kendall DM. effects of exenatide (exendin-4) on glycemic control over 30 weeks in patients with type 2 diabetes treated with metformin and a sulfonylurea. *Diabetes Care*. 2005;28:1083–1091.
- Zinman B. The effect of adding exenatide to a thiazolidinedione in suboptimally controlled type 2 diabetes: a randomized trial. *Ann Intern Med*. 2007;146:477–485.
- Heine RJ. Exenatide versus insulin glargine in patients with suboptimally controlled type 2 diabetes: a randomized trial. *Ann Intern Med*. 2005;143:559–569.
- Nauck MA. A comparison of twice-daily exenatide and biphasic insulin aspart in patients with type 2 diabetes who were suboptimally controlled with sulfonylurea and metformin: a non-inferiority study. *Diabetologia*. 2007;50:259–267.
- Vilsbøll T. 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*. 2007;6:160–610.
- Zinman B. Efficacy and safety of the human GLP-1 analog liraglutide in combination with metformin and TZD in patients with type 2 diabetes mellitus (LeAD-4 Met + TZD). Presented at the 44th Annual Meeting of the European Association for the Study of Diabetes. September 7–11, 2008. Rome.
- Garber A. Liraglutide versus glimepiride monotherapy for type 2 diabetes (LeAD-3 Mono): a randomised, 52-week, phase iii, double-blind, parallel-treatment trial. *Lancet*. 2009;373:473–481.
- Marre M. Liraglutide, a once-daily human GLP-1 analogue, added to a sulphonylurea over 26 weeks produces greater improvements in glycaemic and weight control compared with adding rosiglitazone or placebo in subjects with type 2 diabetes (LeAD-1 sU). *Diabetic Medicine*. 14 Jan doi: 10.1111/j.1464-5491.2009.
- Nauck M. Efficacy and safety comparison of liraglutide, glimepiride, and placebo, all in combination with metformin in type 2 diabetes mellitus (LeAD-2 Met). *Diabetes Care*. 2008;32:84–90.
- Russell-Jones D. Significantly better glycemic control and weight reduction with liraglutide, a once-daily human GLP-1 analog, compared with insulin glargine: all as add-on to metformin and a sulfonylurea in type 2 diabetes. Presented at the 68th Annual meeting of the American Diabetes Association. June 6–10, 2008. San Francisco.
- Ratner RE. A dose-finding study of the new GLP-1 agonist Ave0010 in type 2 diabetes insufficiently controlled with metformin. Presented at the 68th Annual meeting of the American Diabetes Association. June 6–10, 2008. San Francisco.
- Kim D. effects of once-weekly dosing of a long-acting release formulation of exenatide on glucose control and body weight in subjects with type 2 diabetes. *Diabetes Care*. 2007;30:1487–1493.
- Baggio LL. A recombinant human glucagon-like peptide (GLP)-1-albumin protein (albugon) mimics peptidergic activation of GLP-1 receptor-dependent pathways coupled with satiety, gastrointestinal motility, and glucose homeostasis. *Diabetes*. 2004;53:2492–2500.
- Balena R. Eight weeks of treatment with the long acting, human GLP-1 analogue r1583 improves glycemic control and lowers body weight in subjects with type 2 diabetes mellitus (T2DM) treated with metformin: a double-blind placebo-controlled phase 2 study. Presented at the 68th Annual Meeting of the American Diabetes Association. June 6–10, 2008. San Francisco.
- Ratner R. Safety and tolerability of high doses of the long acting, human GLP-1 analogue r1583 in diabetic subjects treated with metformin: a double-blind, placebo-controlled phase 2 study. Presented at the 68th Annual Meeting of the American Diabetes Association. June 6–10, 2008. San Francisco.
- Baggio LL. The long-acting albumin-exendin-4 GLP-1r agonist CJC-1134 engages central and peripheral mechanisms regulating glucose homeostasis. *Gastroenterology*. 2008;134:1137–1147.
- Drucker DJ. Exenatide once weekly versus twice daily for the treatment of type 2 diabetes: a randomised, open-label, noninferiority study. *Lancet*. 2008;372:1240–1250.
- Ahmad SR, Swann J. Exenatide and rare adverse events. *N Engl J Med*. 2008;358:1970–1972.
- Aschner P. Effect of the dipeptidyl peptidase-4 inhibitor sitagliptin as monotherapy on glycemic control in patients with type 2 diabetes. *Diabetes Care*. 2006;29:2632–2637.
- Charbonnel B. 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*. 2006;29:2638–2643.
- Rosenstock J. 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*. 2006;28:1556–1568.
- Goldstein BJ. 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*. 2007;30:1979–1987.
- Scott R. Efficacy and safety of sitagliptin when added to ongoing metformin therapy in patients with type 2 diabetes. *Diabetes Obes Metab*. 2008;10:959–969.
- Raz I. Efficacy and safety of sitagliptin added to ongoing metformin therapy in patients with type 2 diabetes. *Curr Med Res Opin*. 2008;24:537–550.
- Pi-sunyer FX. Efficacy and tolerability of vildagliptin monotherapy in drug-naive patients with type 2 diabetes. *Diabetes Res Clin Pract*. 2007;76:132–138.
- Rosenstock J. Comparison of vildagliptin and rosiglitazone monotherapy in patients with type 2 diabetes: a 24-week, double-blind, randomized trial. *Diabetes Care*. 2007;30:217–223.
- Bolli G. Efficacy and tolerability of vildagliptin vs. pioglitazone when added to metformin: a 24-week, randomized, double-blind study. *Diabetes Obes Metab*. 2008;10: 82–90.
- DeFronzo RA. Efficacy and safety of the dipeptidyl peptidase-4 inhibitor alogliptin in patients with type 2 diabetes mellitus and inadequate glycemic control: a randomized, double-blind, placebo-controlled study. *Diabetes Care*. 2008;31:2315–2317.
- Nauck, M. A. et al. efficacy and safety of adding the dipeptidyl peptidase-4 inhibitor alogliptin to metformin therapy in patients with type 2 diabetes inadequately controlled with metformin monotherapy: a multicentre, randomised, double-blind, placebo-controlled study. *Int J Clin Pract*. 2009;63:46–55.
- Fonseca V. Addition of vildagliptin to insulin improves glycaemic control in type 2 diabetes. *Diabetologia*. 2007;50:1148–1155.
- Garcia-soria G. The dipeptidyl peptidase-4 inhibitor PHX1149 improves blood glucose control in patients with type 2 diabetes mellitus. *Diabetes Obes Metab*. 2008;10: 293–300.
- Ghofilai KA. Effect of exenatide on  $\beta$ -cell function after islet transplantation in type 1 diabetes. *Transplantation*. 2007;83:24–28.
- Froud, T. et al. The use of exenatide in islet transplant recipients with chronic allograft dysfunction: safety, efficacy, and metabolic effects. *Transplantation*. 2008;86: 36–45.
- Inzucchi SE, McGuire DK. New drugs for the treatment of diabetes: part ii: incretin-based therapy and beyond. *Circulation*. 2008;117:574–584.
- Sokos GG. Glucagon-like peptide-1 infusion improves left ventricular ejection fraction and functional status in patients with chronic heart failure. *J Card Fail*. 2006;12: 694–699.
- Nikolaïdis LA. Effects of glucagon-like peptide-1 in patients with acute myocardial infarction and left ventricular dysfunction after successful reperfusion. *Circulation*. 2004;109:962–965.