

CLINICAL RESEARCH AND EXPERIENCE WITH
INCRETIN-BASED THERAPIES*

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ABSTRACT

Despite proven lifestyle recommendations and the availability of a range of oral antidiabetic agents, many patients with type 2 diabetes fail to achieve adequate glycemic control. Patients with poorly controlled type 2 diabetes may be exposed to considerable complications, including elevated cardiovascular risk. New therapeutic strategies have been under investigation to improve glycemic control and avoid some of the adverse effects associated with available antidiabetic agents, most notably weight gain, while improving cardiovascular health. This review will discuss incretin mimetics and their potential role in improving diabetes management. (*Adv Stud Med.* 2008;8(11):387-392)

GLP-1 AND ITS ROLE IN DIABETES THERAPY

Glucagon-like peptide-1 (GLP-1) is secreted in response to food intake, and usually begins even before eating due to neurologic cues, such as the look and smell of the food that is about to be eaten. This secretion of GLP-1 causes an enhancement in glucose-

dependent insulin secretion from β cells, as well as a suppression of glucagon secretion, which results in decreased hepatic glucose output.^{1,2} Research has also confirmed that GLP-1 reduces the gastric emptying rate, and investigators predicted that GLP-1 would have the potential to induce weight loss.³ Exenatide, an incretin mimetic that is delivered by subcutaneous injection, acts in a similar manner as GLP-1 and causes glucose-dependent insulin secretion in β cells. Sulfonylureas cause glucose-dependent insulin secretion by binding to adenosine triphosphate-dependent potassium channel (K_{ATP}) receptors on the β cell, resulting in a depolarization of the β cell and continuous stimulation of insulin secretion. In contrast, GLP-1 acts through a cyclic adenosine monophosphate-dependent channel that is independent of the K_{ATP} pathway. This implies that sulfonylurea therapy and GLP-1 may have an additive effect on insulin secretion. In fact, as demonstrated in recent clinical studies, this ongoing stimulation of insulin secretion with concomitant sulfonylurea therapy and exenatide can result in hypoglycemia.^{4,5}

Although the combination of exenatide and sulfonylurea therapy has been shown to induce hypoglycemia, clinical studies have confirmed that the use of incretin mimetic therapy alone does not cause hypoglycemia. One study of exenatide infusion demonstrated a reduction in glucose through an increase in insulin secretion and glucagon suppression. As glucose levels returned to a normal range or trended toward hypoglycemia, insulin secretion stopped and glucagon levels returned to normal, thus decreasing the risk of hypoglycemia (Figure 1).⁶ Another placebo-controlled study induced hypoglycemia in individuals with the use of a euglycemic clamp, and found that exenatide administration resulted in a more

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robust glucagon response than placebo.⁷ These data suggest that exenatide may enhance the ability to recover from hypoglycemia, as opposed to sulfonylureas or insulin therapy.

**ENHANCING GLP-1:
GLP-1 ANALOGUES VERSUS DPP-4 INHIBITORS**

Glucagon-like peptide-1 analogues are just one class of agents that are being investigated for their role in the enhancement of GLP-1 action. Another class, known as dipeptidyl peptidase-4 (DPP-4) inhibitors, increase physiologic levels of GLP-1 by blocking the DPP-4 enzyme that is responsible for breaking down GLP-1, as well as other incretins, such as gastric inhibitory peptide (GIP). The DPP-4 inhibitors include sitagliptin, which is currently available in the United States, as well as vildagliptin, saxagliptin, and alogliptin. All of the DPP-4 inhibitors are oral agents that increase GLP-1 levels.

EXENATIDE IN DIABETES

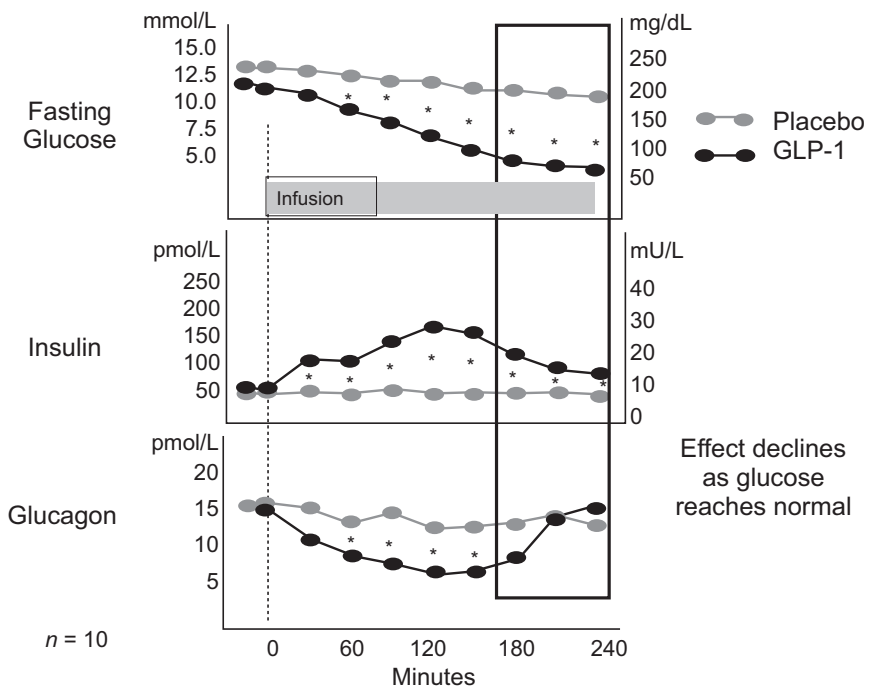
Glucagon-like peptide-1 enhancement with exenatide has demonstrated multiple beneficial effects in patients with diabetes. In 3 major pivotal trials, exenatide effectively reduced glycosylated hemoglobin (A_{1c}), and resulted in some degree of weight loss.^{4,5,8} Although the weight loss achieved with exenatide was modest in most cases, these data demonstrated that unlike other agents used to improve glycemic control, exenatide does not result in weight gain. In a 3-year extension study of pivotal exenatide trials, individuals realized sustained reductions in A_{1c}, 46% of subjects achieved and maintained the therapeutic target of A_{1c} of 7% or lower, and weight loss was progressive over the course of the study without a plateau effect.⁹ Overall, a mean weight loss of 5.3 kg was achieved from baseline to the end of the study ($P < .0001$) with exenatide. However, clinicians should note that the patients treated in this 3-year extension study were following on from a randomized trial and during that study, those patients who did

not adequately respond to exenatide or did not experience weight loss may have discontinued the drug.

Recent data presentations confirm the likely benefits of exenatide in diabetes. A pooled analysis comparing results from trials of exenatide and insulin therapy confirmed the findings in direct comparator trials, including improved glycemic control without a risk of hypoglycemia.¹⁰ Another trial compared the twice-daily exenatide formulation with an extended-release once-weekly exenatide formulation (exenatide long-acting release [LAR]), reporting that exenatide LAR resulted in a slightly greater drop in A_{1c}.¹¹ It is unclear whether these findings were related to a greater potency with exenatide LAR or greater compliance achieved with once-weekly dosing.

Exenatide can be associated with several adverse events. For instance, approximately 40% of subjects enrolled in pivotal trials with exenatide experienced nausea, and a small number of these patients had nausea severe enough that they discontinued treatment.

Figure 1. GLP-1 Actions Are Glucose Dependent in Patients with Type 2 Diabetes



* $P < .05$.
GLP-1 = glucagon-like peptide-1.
Reprinted with permission from Nauck et al. *Diabetologia*. 1993;36:741-744.⁶

Likewise, another small percentage of patients discontinued treatment in these trials due to vomiting. Importantly, pancreatitis has been reported with exenatide, and has prompted the US Food and Drug Administration (FDA) to require additional warnings in the exenatide label. The results from current trials should further clarify the risk of pancreatitis with exenatide therapy.

There have been postmarketing reports of acute pancreatitis in individuals receiving exenatide, resulting in FDA alerts recommending the discontinuation of exenatide in patients with symptoms consistent with pancreatitis—namely severe persistent abdominal pain, with or without vomiting—and if pancreatitis is confirmed, exenatide should not be restarted.¹² No patient characteristics have been identified that predict which patients may be at greater risk of suffering from pancreatitis.

CHOOSING BETWEEN INSULIN AND EXENATIDE

An important outstanding issue with the introduction of exenatide has been the most appropriate clinical setting for the regular use of this agent, and eventually other incretin mimetics or DPP-4 inhibitors, as opposed to established oral antidiabetic drugs (OADs). Obviously, patients with diabetes who do not respond to OAD therapy now have the choice between initiating insulin therapy or exenatide, both of which are administered by injection. A 26-week, open-label extension study reported by Heine et al found that both exenatide and insulin glargine, a long-acting basal insulin analogue, resulted in equivalent glycemic control as measured by A_{1c} (7.1% and 7.2%, respectively).¹³ Importantly, the insulin glargine dose used in this study was lower than doses used in previous glargine studies, and the insulin glargine regimen required only 1 daily dose, whereas the exenatide regimen required twice-daily injections.

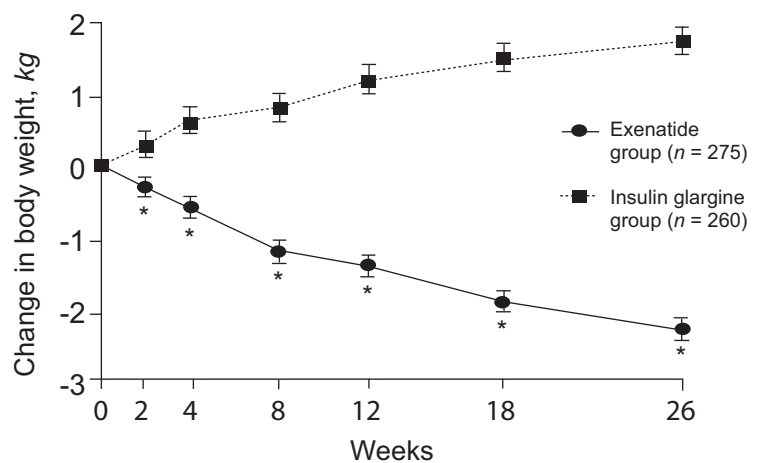
Overall, postprandial glucose was lower with exenatide therapy, whereas fasting glucose was improved with insulin glargine. However, changes in weight differed considerably between treatment groups. Subjects in the insulin glargine group gained a mean of 1.8 kg, whereas those receiving exenatide experienced a mean weight loss of 2.3 kg (Figure 2).¹³ Based on these findings, it is possible for clinicians to rationally choose between exenatide and insulin therapy as they balance between their desire to impact fasting glucose, postprandial glucose, and weight.

NEW INCRETIN MIMETIC OPTIONS

In addition to exenatide, new incretin mimetic agents that have the potential to impact diabetes care are under development. As mentioned previously, an extended-release version of exenatide, exenatide LAR, is under development and will allow for once-weekly injectable dosing due to a long half-life. Liraglutide, another GLP-1 analogue, is also being investigated in the Liraglutide Effect and Action in Diabetes (LEAD) series of clinical trials, which has been comparing the effects of liraglutide with those achieved with standard OAD therapy in patients with type 2 diabetes who are inadequately controlled on standard therapy.¹⁴⁻¹⁹ Similar to detemir insulin, a long-acting basal insulin analogue derived from recombinant human DNA that is bound to albumin to extend its half-life, liraglutide consists of human GLP-1 that is bound to albumin, resulting in a prolonged half-life. Unlike exenatide, the extended half-life of liraglutide allows for effective once-daily dosing.

Analyses comparing the actions of exenatide and liraglutide in patients with diabetes have reported a great deal of similarity in the action of the 2 drugs. Importantly, both agents resulted in reduced postprandial glucose and weight loss, without a risk of

Figure 2. Changes in Body Weight



* $P < .0001$ compared with insulin glargine measure at the same time point. Reprinted with permission from Heine et al. *Ann Intern Med.* 2005;143:559-569.¹³

hypoglycemia when used as monotherapy.¹⁵ A trial with exenatide LAR likewise revealed similar findings.²⁰ In addition, GLP-1 analogues, including exenatide and liraglutide, also may offer benefits beyond glycemic control by attenuating important cardiovascular risk factors in patients with diabetes.²¹ Ongoing studies continue to probe the effects of GLP-1 on the heart and vasculature, which is known to have GLP-1 receptors.

In contrast to exenatide therapy, both exenatide LAR and liraglutide resulted in lower rates of nausea, which could be the result of a pharmacokinetic effect with these extended-release agents, because lower drug levels are needed than with twice-daily exenatide due to the shorter half-life. Exenatide does result in a higher level of antibody production than liraglutide,²⁰ possibly because liraglutide is derived from a human version of GLP-1.

Liraglutide monotherapy has also demonstrated the ability to improve A_{1c} and postprandial glucose, in addition to fasting glucose, possibly due to the long half-life of the drug. Meanwhile, a 15-week trial of exenatide LAR also demonstrated effective A_{1c} reduction, but only those receiving the higher dose of the drug experienced meaningful weight loss. However, the brief duration of this study may have limited the ability to demonstrate an impact on weight with the lower dose. Liraglutide has also been compared with OAD therapy, including glimepiride, and in combination with metformin. Overall, liraglutide has demonstrated a dose-dependent drop in A_{1c} , which is most pronounced with doses of once-daily liraglutide 1.8 mg. Liraglutide has demonstrated a reasonable degree of weight loss, low rates of hypoglycemia, and lower rates of nausea when compared with findings from exenatide trials.²²

Liraglutide has also been compared with insulin glargine. Similar to previous trials comparing liraglutide with insulin glargine, liraglutide therapy resulted in effective reductions in A_{1c} and modest weight loss, whereas insulin glargine caused modest weight gain.²³

CLINICAL BENEFITS OF DPP-4 INHIBITORS

As mentioned previously, DPP-4 inhibition results in greater physiologic levels of GLP-1, in addition to GIP. These circulating peptides act on both α cells and β cells, resulting in increased insulin, decreased glucagon, and improved glycemic control. In one

study of the DPP-4 inhibitor sitagliptin along with metformin as first-line therapy in patients with type 2 diabetes, the combination regimen resulted in effective reductions in A_{1c} , suggesting the possibility of a synergistic effect between sitagliptin and metformin.²⁴ Researchers have demonstrated that metformin independently increases GLP-1, and although some initially thought that this was due to DPP-4 inhibition with metformin, it has been confirmed that metformin actually stimulates GLP-1 secretion in the gut. With the addition of a DPP-4 inhibitor such as sitagliptin, this effect is prolonged.

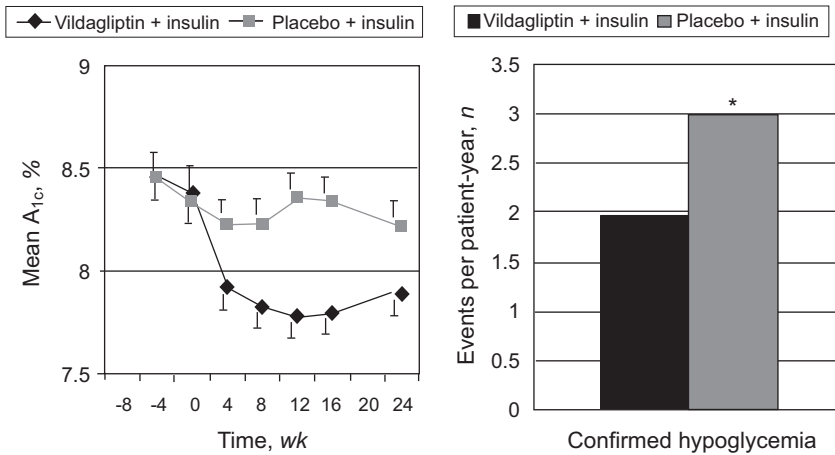
In another 24-week, randomized, placebo-controlled study, sitagliptin 100-mg daily therapy in patients receiving ongoing pioglitazone resulted in a mean reduction in A_{1c} of 0.7% ($P < .001$). The percentage of individuals reaching the target A_{1c} of 7% or lower was 45.4% and 23% in those receiving sitagliptin and placebo, respectively.²⁵ When evaluating the available data with sitagliptin as a whole, sitagliptin therapy, either alone or in combination with other antidiabetic agents, results in a mean A_{1c} reduction of approximately 0.7%. Unlike GLP-1 analogues, sitagliptin has demonstrated a weight-neutral effect, with less than 1-kg weight loss, on average.²²

In addition to sitagliptin, other DPP-4 inhibitors are under development. In one brief, 12-week study of saxagliptin monotherapy in patients with type 2 diabetes, A_{1c} was reduced by up to 0.9%.²⁶ Vildagliptin has also been studied in the clinical setting, demonstrating an effective reduction in postprandial glucose.²⁷ In patients failing to achieve effective glycemic control with the combination of metformin and rosiglitazone, the addition of sitagliptin has been shown to reduce A_{1c} by approximately 0.9%.²⁸

For patients already receiving insulin for diabetes and who have failed to achieve effective glycemic control, GLP-1 analogues or DPP-4 inhibitors may likewise play a role in helping many patients reach their therapeutic goals. Preliminary data have demonstrated that vildagliptin, in combination with insulin, improved A_{1c} in poorly controlled patients while reducing the rate of confirmed hypoglycemia (Figure 3).²⁹ However, it should be noted that the use of incretin mimetics or DPP-4 inhibitors in addition to insulin is not an FDA-approved therapeutic option due to the lack of high-quality data in this setting.

Adverse events most commonly reported with DPP-4 inhibitors have included nasal pharyngitis and

Figure 3. Vildagliptin + Insulin Improves Glycemic Control and Reduces Hypoglycemia Over 24 Weeks



* $P < .001$.

Patients randomized to sitagliptin received 50 mg twice daily.

A_{1c} = glycosylated hemoglobin.

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urinary tract infections. Although these events have not occurred at excessive rates, these findings suggest a possible effect on the immune system that needs to be evaluated in long-term studies.

CONCLUSIONS

A wealth of data are available that demonstrate the benefits of incretin mimetics in improving glycemic control. Both GLP-1 analogues and DPP-4 inhibitors have been shown to improve glycemic control by stimulating insulin secretion and suppressing glucagon, and GLP-1 analogues also achieve effective postprandial glycemic control. Although DPP-4 inhibitors are generally weight neutral, GLP-1 analogues are associated with weight loss, which may contribute to improvements in cardiovascular risk markers that have been reported in clinical trials. Although incretin mimetics may represent a promising alternative to other antidiabetic agents in individuals who fail to achieve glycemic control, the long-term safety of these agents still remains to be established, and clinicians should carefully weigh the risks and benefits of switching therapy in patients responding well to current antidiabetic regimens.

REFERENCES

1. Larsson H, Holst JJ, Ahren B. Glucagon-like peptide-1 reduces hepatic glucose production indirectly through insulin and glucagon in humans. *Acta Physiol Scand*. 1997;160:413-422.
2. Nauck MA, Heimesaat MM, Behle K, et al. Effects of glucagon-like peptide 1 on counter-regulatory hormone responses, cognitive functions, and insulin secretion during hyperinsulinemic, stepped hypoglycemic clamp experiments in healthy volunteers. *J Clin Endocrinol Metab*. 2002;87:1239-1246.
3. Flint A, Raben A, Ersbøll AK, et al. The effect of physiological levels of glucagon-like peptide-1 on appetite, gastric emptying, energy and substrate metabolism in obesity. *Int J Obes Relat Metab Disord*. 2001;25:781-792.
4. Buse JB, Henry RR, Han J, 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.
5. DeFronzo RA, Ratner RE, Han J, et al. 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.
6. Nauck MA, Kleine N, Orskov C, et al. Normalization of fasting hyperglycaemia by exogenous glucagon-like peptide 1(7-36 amide) in type 2 (non-insulin-dependent) diabetic patients. *Diabetologia*. 1993;36:741-744.
7. Degen KB, Brock B, Juhl CB, et al. Effect of intravenous infusion of exenatide (synthetic exendin-4) on glucose-dependent insulin secretion and counterregulation during hypoglycemia. *Diabetes*. 2004;53:2397-2403.
8. Kendall DM, Riddle MC, Rosenstock J, et al. 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.
9. Klonoff DC, Buse JB, Nielsen LL, et al. Exenatide effects on diabetes, obesity, cardiovascular risk factors and hepatic biomarkers in patients with type 2 diabetes treated for at least 3 years. *Curr Med Res Opin*. 2008;24:275-286.
10. Bunck MC, Diamant M, Corner A, et al. Exenatide improves postprandial hyperglycemia and dyslipidemia in metformin treated patients with type 2 diabetes. *Diabetes*. 2008;57(suppl 1):109-OR.
11. Loh J, Clement SC. Efficacy of exenatide therapy over two years in a "real world" setting. *Diabetes*. 2008;57(suppl 1):105-OR.
12. US Food and Drug Administration Center for Drug Evaluation and Research. Information for Healthcare Professionals: Exenatide (marketed as Byetta). Available at: <http://www.fda.gov/CDER/drug/InfoSheets/HCP/exenatide2008HCP.htm>. Accessed December 13, 2008.
13. Heine RJ, Van Gaal LF, Johns D, et al. Exenatide versus insulin glargine in patients with suboptimally controlled type 2 diabetes: a randomized trial. *Ann Intern Med*. 2005;143:559-569.
14. Blonde L, Rosenstock J, Sesti G, et al. Liraglutide: superior

- glycemic control versus exenatide when added to metformin and/or sulphonylurea in type 2 diabetes (LEAD-6). Poster presented at: Canadian Diabetes Association Congress; October 15-18, 2008; Montreal, Canada.
15. Garber A, Henry R, Ratner R, et al. Liraglutide versus glimepiride monotherapy for type 2 diabetes (LEAD-3 Mono): a randomised, 52-week, phase III, double-blind, parallel-treatment trial. *Lancet*. 2008. [Epub ahead of print].
 16. Nauck MA, Brandle M, Vaag A, et al. The once-daily human GLP-1 analog liraglutide substantially reduces HbA_{1c} in subjects with type 2 diabetes, irrespective of HbA_{1c} at baseline. *Diabetes*. 2008;57(suppl 1):2148-PO.
 17. Marre M, Shaw JE, Brandle M, et al. Liraglutide, a once-daily human GLP-1 analog, added to a sulphonylurea (SU) offers significantly better glycemic control and favorable weight change compared with rosiglitazone and SU combination therapy in subjects with type 2 diabetes. *Diabetes*. 2008;57(suppl 1):13-OR.
 18. Zinman B, Gerich J, Buse J, et al. Effect of the GLP-1 analogue liraglutide on glycaemic control and weight reduction in patients on metformin and rosiglitazone: a randomized double-blind placebo-controlled trial. *Diabetologia*. 2008;51(suppl 1):S359.
 19. Russell-Jones D, Shaw JE, Brandle M, et al. The once-daily human GLP-1 analog liraglutide reduces body weight in subjects with type 2 diabetes, irrespective of body mass index at baseline. *Diabetes*. 2008;57(suppl 1):2147-PO.
 20. Kim D, MacConell L, Zhuang D, et al. 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.
 21. Vilsbøll T, Zdravkovic M, Le-Thi T, et al. Liraglutide, a long-acting human glucagon-like peptide-1 analog, given as monotherapy significantly improves glycemic control and lowers body weight without risk of hypoglycemia in patients with type 2 diabetes. *Diabetes Care*. 2007;30:1608-1610.
 22. Nauck MA, Schmidt WE, Meier JJ. The incretin modulators— incretin mimetics (GLP-1 receptor agonists) and incretin enhancers (DPP-4 Inhibitors). In: Mogensen CE, ed. *Pharmacotherapy of Diabetes: New Developments*. New York, NY: Springer Science + Business Media, LLC; 2007. Available at: <http://www.springerlink.com/content/x48756/?p=962d3b67d33c4dffa5be6048aef2e832&pi=0>. Accessed December 1, 2008.
 23. Russell-Jones D, Vaag A, Schmitz O, et al. 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 sulphonylurea in type 2 diabetes. *Diabetes*. 2008;57(suppl 1):536-P.
 24. Migoya EM, Miller J, Larson P, et al. Sitagliptin, a selective DPP-4 inhibitor, and metformin have complementary effects to increase active GLP-1 concentrations. *Diabetes*. 2007;56(suppl 1):0286-OR.
 25. Rosenstock J, Brazg R, Andryuk PJ, et al. 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.
 26. Rosenstock J, Sankoh S, List JF. Glucose-lowering activity of the dipeptidyl peptidase-4 inhibitor saxagliptin in drug-naive patients with type 2 diabetes. *Diabetes Obes Metab*. 2008;10:376-386.
 27. Rosenstock J, Foley JE, Rendell M, et al. Effects of the dipeptidyl peptidase-IV inhibitor vildagliptin on incretin hormones, islet function, and postprandial glycemia in subjects with impaired glucose tolerance. *Diabetes Care*. 2008;31:30-35.
 28. Dobs A, Goldstein BJ, Wieczorek L, et al. Triple combination therapy with sitagliptin, metformin, and rosiglitazone improves glycemic control in patients with type 2 diabetes. *Diabetes*. 2008;57(suppl 1):2152-PO.
 29. Fonseca V, Schweizer A, Albrecht D, et al. Addition of vildagliptin to insulin improves glycemic control in type 2 diabetes. *Diabetologia*. 2007;50:1148-1155.