

# How incretin-based therapies address the spectrum of physiologic disturbance in type 2 diabetes

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## Citation

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## Abstract

Blood glucose-lowering agents that exert their therapeutic effect through the incretin hormone system are emerging as effective and well-tolerated therapies for type 2 diabetes. Due to their glucose-dependent mode of action these agents are associated with minimal hypoglycemic risk, and do not cause weight gain, thus avoiding limitations associated with many existing treatments that may threaten treatment adherence. Of the two classes of incretin therapies currently available, the GLP-1 receptor agonists have shown the ability to decrease HbA1c to a greater extent than DPP-4 inhibitors, and GLP-1 agonists may also reduce cardiovascular risk through modification of certain known risk factors, including via weight loss. This article explains the rationale behind using incretin-based therapies, summarizes key data from clinical trials of the GLP-1 agonists exenatide and liraglutide, and licensed DPP-4 inhibitors including sitagliptin and saxagliptin, and provides practical guidance on the use of these agents in clinical practice.

## INTRODUCTION

Diabetes mellitus is currently a foremost public health concern, with the most recent data indicating that 23.6 million people in the United States (7.8% of the population) have a diagnosis of diabetes (1). Despite continuous advances in treatment, approximately 44% of patients in 2003–2004 were still failing to reach the hemoglobin A1c (HbA1c) target of <7% currently recommended by the American Diabetes Association (2,3).

Despite the wide range of treatment options available, a solution to the inevitable decline in beta cell function that underpins the progression of type 2 diabetes remains elusive, and treatment intensification, including the addition of insulin, becomes necessary in many patients (4). While insulin is essential in patients with insufficient beta cell reserve, its use is associated with increased risk of hypoglycemia and weight gain, both of which can reduce treatment adherence (5,6). Despite the fact that weight gain itself is a recognized risk factor for type 2 diabetes, emphasis on weight management is often trumped by the need to prioritize glycemic control. Importantly however, weight loss of just 5–10% can reduce HbA1c by 0.5% (7). Since weight loss can improve glycemic control, reduce cardiovascular risk and reduce the use of medications (8), it remains an essential goal of treatment.

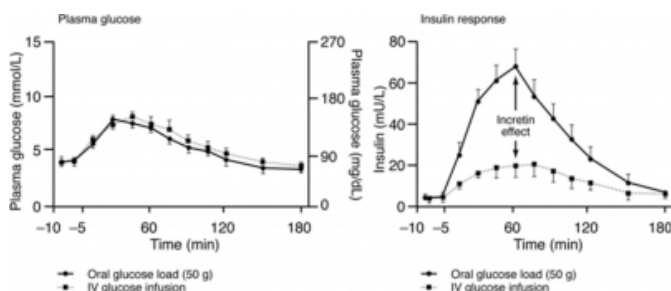
The ideal diabetes treatment would therefore provide effective, sustained glycemic control with negligible risk of hypoglycemia, while improving cardiovascular risk and avoiding weight gain. The crowning glory would be the ability to modify the disease trajectory by forestalling the decline in beta cell mass. With these concerns in mind, incretin-based therapies offer a practical strategy for glucose control, with many associated metabolic benefits, for patients with sufficient beta cell reserve.

### The physiology of the incretin system

Insulin secretion is greater following oral glucose intake than after an intravenous glucose bolus (the incretin effect) (Figure 1; 9,10), an effect mediated by incretin hormones that may be responsible for up to 70% of the insulin response to a meal (9).

**Figure 1**

Figure 1. The incretin effect: insulin response is greater after an oral glucose load than after intravenous (IV) glucose injection (9).



As a result there has been increased focus on the incretin hormones, and most notably glucagon-like-peptide 1 (GLP-1), in glucose homeostasis. Due to the glucose-dependent insulin-secreting action of GLP-1, therapeutic approaches based on enhancing its effects, including the use of GLP-1 receptor agonists, and GLP-1 analogs, are associated with a low risk of hypoglycemia (11,12). Further to its effects on glucose control (increased insulin synthesis; increased beta-cell glucose sensitivity; and glucose-dependent inhibition of glucagon secretion) (13,14), GLP-1 demonstrates the capacity to lower body weight due to increased feelings of satiety, reduced food intake (15) and delayed gastric emptying (16,17). Some experts are also cautiously optimistic about the ability of GLP-1 to modify disease progression through beta cell preservation, as animal models have shown the potential to increase beta cell mass (18,19).

Rationale for use of incretin-based therapies in the management of diabetes

GLP-1 secretion may be reduced in type 2 diabetes (20,21), and intravenous replacement improves glucose homeostasis (13). However, administration of GLP-1 itself is not a therapeutic option since the native hormone is rapidly degraded by the enzyme dipeptidyl peptidase-4 (DPP-4), reducing its in vivo half-life to approximately 2 min (22). Drug development efforts have therefore focused either on enhancing the physiological effects of GLP-1 through GLP-1 receptor agonism (synthetic exendin-based therapies such as exenatide, and the human GLP-1 analog liraglutide) or by inhibiting GLP-1 degradation (through DPP-4 inhibitors: sitagliptin, vildagliptin and saxagliptin).

### **GLP-1 RECEPTOR AGONISTS: EXENATIDE AND LIRAGLUTIDE EXENATIDE**

The GLP-1 receptor agonist, exenatide (Byetta®, Amylin

Pharmaceuticals Inc., San Diego, CA, USA), is a synthetic form of exendin-4, a salivary gland hormone from the Gila monster lizard. Exenatide is approved in Europe and the US for use in combination with metformin (Met), a sulfonylurea (SU), a thiazolidinedione (TZD), and in triple combination with Met + SU or Met + TZD, in patients with type 2 diabetes. The amino acid structure of exenatide shows 53% structural similarity to native GLP-1 but, since it is not a substrate for DPP-4, exenatide has a longer half-life than endogenous GLP-1 (23,24). The current formulation requires twice-daily subcutaneous injection 0–60 minutes before breakfast and dinner using a pen device, although a long-acting release (LAR) formulation is being developed that may require only once-weekly dosing.

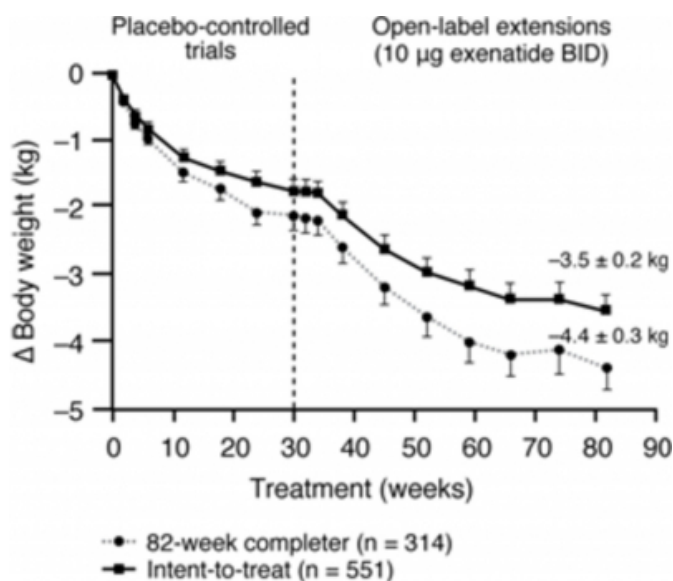
The pivotal clinical data for exenatide come from the three AC-2993: Diabetes Management for Improving Glucose Outcomes (AMIGO) studies, which investigated the addition of exenatide in patients with type 2 diabetes who were inadequately controlled on Met (25); a SU (26); or both (27). During each of the 30-week trials, patients received subcutaneous exenatide, 5 or 10 µg, twice daily. HbA1c decreased by 0.8% and 0.9% in the lower and higher exenatide dose groups respectively (p < 0.002 versus placebo), compared with a reduction of only 0.1% in the placebo group (24-26). In a separate 16-week study, the addition of exenatide in 233 patients inadequately controlled on a TZD with or without Met, reduced mean HbA1c by 0.9% (28).

Fasting plasma glucose (FPG) levels decreased by 10.8 mg/dL from baseline in the AMIGO studies, and by as much as 32.4mg/dL when exenatide was added to a TZD (28) while post-prandial glucose (PPG) concentrations were statistically significantly lower than baseline in both exenatide dose groups in a subset of patients poorly controlled on Met alone, or Met + SU (25,27). Weight loss ranged between 1.6 kg (26,27) and 2.8 kg (25).

In two 52-week extension studies, one in 150/183 patients who continued exenatide (10 µg) + Met (29), and the other in 314 patients taking exenatide + SU ± Met (30), HbA1c decreased 1.1–1.3% from baseline. There was progressive weight loss (Figure 2; 30), as well as improvement in multiple lipid parameters, these being most marked in patients who lost the most weight, although this correlation with weight conflicts with more recent data (31).

**Figure 2**

Figure 2. In an uncontrolled 52-week exenatide +SU ±MET treatment extension study, weight loss continued to decline throughout the course of the study (30).



In a longer-term pooled analysis of data from 283 patients who completed any one of the AMIGO studies and continued receiving exenatide beyond 82 weeks, HbA1c reduction at 30 weeks was maintained after 2 years (1.1%;  $p < 0.05$  versus baseline) (32), at which time FPG had decreased by 25.2 mg/dL. Weight loss increased to 4.7 kg ( $p < 0.001$  versus baseline), an encouraging finding since improved glycemic control is usually achieved at the expense of weight gain. Further cardiovascular benefit was suggested in the mean reduction in blood pressure (-2.6 mmHg systolic and -1.9 mmHg diastolic from baseline;  $p = 0.003$  and  $p < 0.001$ , respectively). Significant improvement in homeostasis model assessment-B (HOMA-B), a measure of beta cell function ( $p < 0.01$  versus baseline), was also observed. Sustained improvements in glycemic and lipid parameters and blood pressure after 3 years of exenatide treatment have recently been demonstrated (33).

Mild to moderate nausea, vomiting and diarrhea were the most frequent adverse events (AEs). Nausea occurred in 40–50% of patients receiving 5 µg or 10 µg exenatide in the AMIGO trials, although the incidence declined after 8 weeks and withdrawals due to nausea were infrequent (2–4%). Diarrhea was reported by 10–18% of all patients. The most serious, albeit uncommon, gastrointestinal AE was acute pancreatitis, which occurred in 8 of the approximately 2,000 patients in the phase IIIa program, a frequency less than that seen in the general population (34). Nonetheless, the FDA requested revisions to the exenatide product label in late

2007, advising discontinuation in patients with symptoms consistent with pancreatitis pending confirmation of their etiology, and termination of treatment in cases of proven pancreatitis with no other known cause. A subsequent safety update was issued in 2008 after postmarketing reports referenced six deaths in patients with pancreatitis, of which two were believed to have been related to pancreatitis (34). No severe hypoglycemic events occurred in any AMIGO trial, although the overall risk of hypoglycemia is increased by the combined use of exenatide with SUs. Low titers of antibodies to exenatide were detected in up to 50% of patients in the AMIGO trials (25–27); at present the implications of this are unknown, but low titers appear to be of no clinical significance. High antibody titers were found in 6% with half of these individuals having an attenuated glycemic response to exenatide; if this situation arises, alternative treatment should be initiated (35).

Exenatide has also been compared with biphasic insulin aspart 70/30 (36,37), and insulin glargine (38). Each agent resulted in equivalent reduction in HbA1c, but exenatide offered superior PPG control. These results should be interpreted with caution since insulin titration was not optimized, and the findings may not hold during more aggressive insulin use.

Exenatide has demonstrated the potential to improve beta cell function in vitro by reducing beta cell apoptosis (39,40), and in vivo by enhancing first and second-phase insulin response to a glucose challenge (41), both of which are impaired in type 2 diabetes.

### EXENATIDE-LAR

The initial clinical data on exenatide-LAR includes a 15-week randomized, placebo-controlled study in 45 patients (42). Once-weekly exenatide-LAR, 0.8 mg or 2.0 mg, reduced mean HbA1c by 1.4% and 1.7%, respectively, ( $p < 0.0001$  versus placebo for both doses). HbA1c  $\leq 7\%$  was achieved by 36% and 86% of exenatide-LAR-treated patients (0.8 mg or 2 mg, respectively), compared with zero patients taking placebo. FPG decreased by 43.2 and 39.6 mg/dL ( $p < 0.001$  for both 0.8 mg or 2 mg, versus placebo). The higher dose of exenatide reduced body weight by 3.8 kg ( $p < 0.05$ ). Injection site bruising occurred more frequently with exenatide-LAR (13% and 7% in lower and higher dose groups respectively) than placebo (0%). In addition, while nausea was the most frequently reported AE, the same proportion of patients in the lower dose group experienced gastroenteritis, which also occurred in 13% of patients

taking the higher dose.

Recent data from a randomized, open-label study in 295 patients managed with diet/exercise and/or oral antidiabetics (OADs) demonstrated a significantly greater reduction in HbA1c using 2 mg exenatide-LAR once weekly (-1.9%) compared with 10 µg twice daily (-1.5%,  $p = 0.002$ ) as well as greater FPG reductions (42 versus 25 mg/dL;  $p < 0.0001$ ) after 30 weeks (43). Weight loss of approximately 4 kg was noted in both treatment groups. Although both exenatide regimens resulted in significant improvement in several quality of life (QoL) measures from baseline, there were no significant differences in treatment satisfaction between the once-weekly and twice-daily exenatide groups (44,45).

### LIRAGLUTIDE

The human GLP-1 analog, liraglutide has been approved in Europe and is currently under review by regulatory agencies in the US. By virtue of its half-life of 13 hours (46), liraglutide requires only once-daily subcutaneous injection with a pen device.

The most substantial liraglutide data come from the recently completed Liraglutide Effect and Action in Diabetes (LEAD) program, a series of randomized, controlled, double-blind studies, including approximately 3,800 patients with inadequately controlled type 2 diabetes. Study designs are presented in Table 1. The LEAD program investigated liraglutide as a monotherapy or in combination with one or more OADs. While different dose levels were investigated (0.6 mg, 1.2 mg, 1.8 mg); only the results for liraglutide 1.8 mg daily are presented here.

**Figure 3**

Table 1: Design of LEAD study program for liraglutide

	Liraglutide monotherapy (LEAD-3)	Liraglutide + metformin (LEAD-2)	Liraglutide + glimepiride (LEAD-1)	Liraglutide + metformin + rosiglitazone (LEAD-4)	Liraglutide + metformin + glimepiride (LEAD-5)	Liraglutide versus exenatide + OADs (LEAD-6)
Description	Effect of liraglutide in monotherapy	Effect of liraglutide in combination with metformin	Effect of liraglutide in combination with glimepiride	Effect of liraglutide in combination with metformin + rosiglitazone	Effect of liraglutide in combination with metformin and glimepiride	Effect of liraglutide in combination with metformin, glimepiride or both
Comparator	Glimepiride	Glimepiride/placebo	Rosiglitazone/placebo	Placebo	Insulin glargine/placebo	Exenatide
Background medication	None	Metformin	Glimepiride	Metformin + rosiglitazone	Metformin + glimepiride	Metformin + glimepiride
Overall inclusion criterion	Subjects with type 2 diabetes on diet/exercise or OAD	Subjects with type 2 diabetes treated with OAD(s)	Subjects with type 2 diabetes treated with OAD(s)	Subjects with type 2 diabetes treated with OAD(s)	Subjects with type 2 diabetes treated with OAD(s)	Subjects with type 2 diabetes treated with OAD(s)
N	702	1026	1026	492	570	464
Duration	12 months + 12-month extension	6 months + 18-month extension	6 months	26 weeks	26 weeks	26 weeks + 14-week extension
Primary endpoint	HbA1c	HbA1c	HbA1c	HbA1c	HbA1c	HbA1c
Clinicaltrials.gov identifier	NCT00294723	NCT00318461	NCT00318422	NCT000333151	NCT00331851	NCT00518882

OAD = oral antidiabetic; HbA1c = Hemoglobin A1c

Liraglutide monotherapy was examined in 746 drug-naïve or OAD monotherapy patients in the LEAD-3 study (47). In this 52-week trial liraglutide lowered HbA1c to a greater degree than glimepiride (-1.1 versus -0.5%, respectively;  $p < 0.0001$ ), and allowed more patients to reach HbA1c  $< 7.0\%$  (51% versus 28% respectively;  $p < 0.01$ ), with greater reduction in PPG (-37.8 versus -25.2 mg/dL;  $p < 0.05$ ).

When liraglutide was examined in combination with an OAD, liraglutide + Met reduced HbA1c to a greater extent than MET alone (mean reduction: -1.0% versus +0.1%;  $p < 0.0001$ ) with a placebo-level incidence of minor hypoglycemia that compared favorably to that with glimepiride ( $p < 0.001$ ) (48). In a second study, greater reduction in HbA1c was achieved with liraglutide (-1.1%) than rosiglitazone (-0.4%) when each was combined with glimepiride (49). The 28.6 mg/dL reduction in FPG seen at 26 weeks also compared favorably with that seen with rosiglitazone (reduction of 15.8 mg/dL;  $p < 0.006$ ), as did the decrease in PPG (-48.6 versus -32.4 mg/dL;  $p < 0.05$ ).

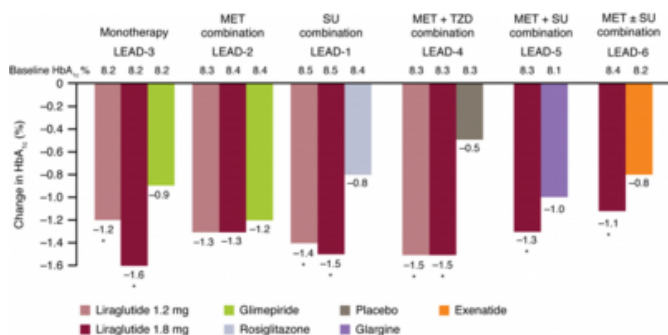
When evaluated in combination with two OADs, the addition of liraglutide to Met + rosiglitazone (50), or to Met + glimepiride (51) reduced HbA1c by 1.4% and 1.3%, respectively. Additional benefits were observed for FPG (-43.2 with liraglutide + Met + rosiglitazone versus -7.2 mg/dL with placebo) and PPG (-48.6 with liraglutide + Met + rosiglitazone versus -14.4 mg/dL with placebo). When liraglutide or insulin glargine was combined with MET + glimepiride, liraglutide lowered HbA1c to a greater extent (-1.3 versus -1.1%;  $p < 0.0001$ ) (51) and allowed more

patients to achieve HbA1c < 6.5% than insulin glargine (37.1 versus 23.6%;  $p < 0.05$ ), although insulin titration was not optimized.

Pooled LEAD data show that liraglutide lowered HbA1c irrespective of baseline value, with the greatest reductions in patients with HbA1c in the highest quartile at the outset. Individuals who received liraglutide +Met + rosiglitazone experienced the greatest HbA1c benefit (-2.3% for those in the highest HbA1c quartile) (52). Figure 3 summarizes the HbA1c data from all LEAD studies (48–50,52–54).

**Figure 4**

Figure 3: Change in HbA1c from baseline for overall population (LEAD 4,5) add-on to diet and exercise failure (LEAD 3); or add-on to previous oral antidiabetic monotherapy (LEAD 2,1).Data originally presented as LEAD 1 (49), LEAD 2 (48), (LEAD 3) (53), LEAD 4 (52), LEAD 5 (50), and LEAD 6 (54) \* significant difference versus comparator.



LEAD data measuring the effects of liraglutide on conditions associated with chronic hyperglycemia are also encouraging. Liraglutide generally reduced weight by 1.8–2.8 kg from baseline and sustained this over 1 year (53); the greatest benefits were seen in patients with baseline body mass index  $\geq 35$  kg/m<sup>2</sup> (55) and those not taking an SU. Furthermore, SBP was reduced by 2.3–5.6 mmHg.

The first and only direct comparison between liraglutide and exenatide (LEAD-6) was recently reported. In this 26-week open-label trial in 464 patients inadequately controlled using Met  $\pm$  SU, liraglutide lowered HbA1c to a significantly greater degree than exenatide in combination with Met and SU (-1.1% versus -0.8% respectively;  $p < 0.0001$ ) (54) and allowed more patients to reach HbA1c < 7% (54% versus 43%;  $p = 0.002$ ). Greater reduction in FPG was also observed with liraglutide (-29.0 mg/dL versus -10.8 mg/dL respectively;  $p < 0.0001$ ). Both insulins reduced body weight by approximately 3 kg. HOMA-B levels indicated greater improvement in beta cell function with liraglutide ( $p < 0.0001$ ). Minor hypoglycemia occurred less frequently with

liraglutide ( $p = 0.01$ ) and although nausea initially occurred in a similar proportion of patients in each group, symptoms resolved more rapidly with liraglutide such that after 5, 10 and 26 weeks of treatment, nausea was reported by 8%, 4% and 3% of liraglutide patients compared with 18%, 13% and 10% of exenatide patients, respectively.

As with exenatide, adverse effects in the LEAD studies were predominantly gastrointestinal and the overall incidence of nausea was higher in the liraglutide (7–40%) than non-liraglutide groups (1–9%). However, <0.1% of patients withdrew due to nausea in any study. Serious AEs occurred in <5% of LEAD patients and pancreatitis in only 5 out of 2,420 patients, a frequency lower than that seen in the general population (34) and somewhat lower than that with exenatide. There were almost no major, and only a few minor, hypoglycemic events; the few major events that occurred were in patients taking an SU. Antibodies to liraglutide were detected in a mean of 8.6% of patients across all LEAD trials.

In support of data from studies in animal models, there is increasing evidence that liraglutide improves beta cell function in human subjects (56–58), in part, by preventing beta cell apoptosis and possibly by inducing beta cell proliferation (59).

**DPP-4 INHIBITORS**

The reduction in HbA1c that can be achieved with the DPP-4 inhibitors as monotherapy, typically -0.6 to -0.8% (placebo-corrected), is less marked than that achieved with the GLP-1 receptor agonists and analogs, probably reflecting the lower serum concentrations of GLP-1 achieved by inhibition of DPP-4 as opposed to through delivery of pharmacologic levels of GLP-1. However, greater reduction in HbA1c may be possible when these agents are used as combination therapy (60–62) In contrast to exenatide and liraglutide, weight loss is negligible during DPP-4 inhibitor monotherapy (63,64); only when combined with Met has weight reduction been shown (1.5 kg versus baseline over 52 weeks) (65).

DPP-4 inhibitors are generally well tolerated: the incidence of gastrointestinal side effects is only marginally increased, and severe hypoglycemic events have not been reported. However, certain adverse events have raised concern, including the relative increase in infections compared with similar treatments (66), and occasional but serious hypersensitivity and allergic reactions that necessitate treatment discontinuation, including anaphylaxis,

angioedema, and exfoliative skin conditions. Comparative data for many of the key incretin-based therapy trials are presented in Table 2 (25,26–28,36,47,48,49,50,52,53,61,63,65,67–73).

**Figure 5**

Table 2: Core data from some of the clinical trials of incretin-based therapies. \* change from baseline; □ versus placebo

Treatment	Mean Δ HbA1c (%)	Mean Δ FPG (mg/dL)	Mean Δ weight (kg)	Reference
<b>MONOTHERAPY</b>				
Liraglutide*	-1.1*	-25.6*	-2.5*	47
Sitagliptin*	-0.6	-19.8	-	63
Vildagliptin*	-0.7 to -1.1*	-23.4*	-0.3*	67,68
<b>COMBINATION WITH MET</b>				
Exenatide	-0.8*	-10.8*	-2.8*	25
Liraglutide	-1.0*	-30.4*	-2.8*	48
Sitagliptin*	≥ -0.7	-10.1 to -25.2	-0.6	61,65,69
Vildagliptin*	-1.1	-30.6	+1.2	70
<b>COMBINATION WITH SU</b>				
Exenatide 10 µg*	-0.9	-10.8	-1.6	26
Liraglutide 1.8mg*	-1.1	-28.6	-0.2	49
Sitagliptin 100mg*	-0.7	-20.1	+0.8	71
<b>COMBINATION WITH TZD</b>				
Exenatide 10 µg*	-0.9	-28.6	-1.8	28
Sitagliptin*	-0.7	-17.7	+0.2	72
Vildagliptin	-1.0*	-19.8*	+1.3*	53
Vildagliptin + pio high-dose combination therapy in treatment-naive patients*	-1.9	-50.4	+2.1	73
<b>COMBINATION WITH MET+TZD</b>				
Liraglutide 1.8mg*	-1.5	-43.2	-2.1	52
<b>COMBINATION WITH MET+SU</b>				
Exenatide 10 µg*	-0.8	-10.8	-1.6	27
Exenatide 10 µg 1 year follow up*	-1.0	-32.4	-2.5	36
Liraglutide 1.8mg*	-1.3	-27.9	-1.8	50

MET = metformin, SU = sulphonylurea, TZD = thiazolidinedione, FPG = fasting plasma glucose

**SITAGLIPTIN AND VILDAGLIPTIN**

Sitagliptin (Januvia®, Merck & Co., Inc, Whitehouse Station, NJ, USA), the first oral DPP-4 inhibitor to reach the market, is licensed for use at a dose of 100mg/day, either as monotherapy or as initial or add-on combination therapy with Met, pioglitazone or glimepiride +/- Met.

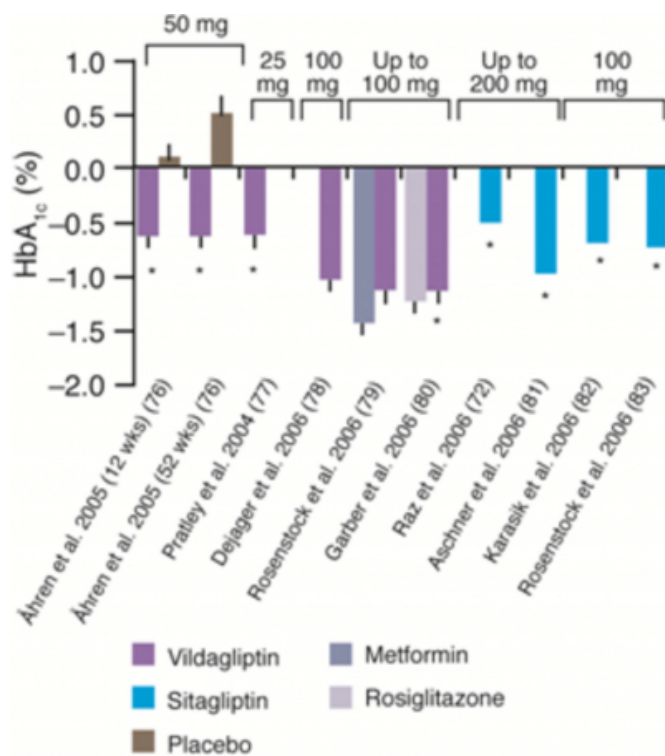
Sitagliptin reduces DPP-4 activity by over 80%, resulting in a 2–3-fold increase in endogenous GLP-1 levels 2 hours after an oral glucose load (74,75). Similar results have been obtained with vildagliptin (Galvus®, Novartis Pharmaceuticals, East Hanover, NJ, USA) (76,77), which is currently licensed in Europe. Its release in the US has been suspended indefinitely due to potentially immune-mediated

dermatological side effects observed in toxicology studies; data on vildagliptin are therefore not included in this article.

Randomized trials of sitagliptin monotherapy, 100mg daily, have shown reductions in HbA1c of 0.6–1.2% versus placebo and placebo-subtracted FPG reductions of -18 to -19.8 mg/dL (p ≤ 0.001 for both), over 12–24 weeks (63,64). Combination therapy with Met reduced HbA1c by 0.7% versus placebo and increased the proportion of patients with HbA1c < 7% to nearly 50% at 24 weeks (Figure 4; 63,69,78–85). Sitagliptin +Met sustained improvement in glycemic control over 52 weeks in a study in >1000 patients in which HbA1c was reduced by 0.7% compared with Met monotherapy (65). Similar results were obtained when combining sitagliptin with pioglitazone: the combination resulted in an FPG reduction of 17.7 mg/dL versus placebo (60). As a result of the synergy between sitagliptin and metformin, a twice-daily combination product was recently licensed that combines sitagliptin 50 mg and metformin 500 mg, or 1000 mg (Janumet™, Merck & Co., Inc, Whitehouse Station, NJ, USA).

**Figure 6**

Figure 4. Effect of DPP-IV inhibitors on HbA1c. \* indicates significant difference versus placebo or comparator drug. If no comparator is shown, results are placebo-subtracted (69).



**SAXAGLIPTIN**

The recently licensed DPP-4 inhibitor, saxagliptin

(Onglyza®, Bristol-Myers Squibb Company, New York, New York, USA), has demonstrated dose-dependent reductions in HbA1c of 0.6-1.7% when administered at a daily dose of 2.5-10 mg in trials of up to 24 weeks duration in drug-naïve subjects (62,86,87). Associated reductions in FPG and PPG were in the range 14-31 mg/dL, and 24-106 mg/dL, respectively and, in line with other DPP-4 inhibitors, saxagliptin was weight-neutral. Greater reduction in HbA1c, of up to 2.5%, was possible when saxagliptin was combined with metformin (62). These improvements in glycemia were statistically significantly superior to either agent as monotherapy.

### When and how to use incretin-based agents

Due to their mode of action, the GLP-1-based therapies are indicated where beta cell function remains sufficient to allow the full potential of these agents to be realized. The clinical trial data presented above support the use of incretin-based agents in the treatment of patients with type 2 diabetes either as a first-line monotherapy, or in addition to one or more OADs, as well as prior to initiating basal insulin in patients who are not achieving glycemic control following treatment with two or more OADs. Diabetes authorities such as the American Diabetes Association (ADA), the American Association of Clinical Endocrinologists (AACE) and the European Association for the Study of Diabetes (EASD) now fully recognize the value of incretin-based therapies (88,89), and have included them as Tier 2 therapies in recent guidelines, to be used in patients whose HbA1c remains above 7%, despite lifestyle modification and Met (88). There is currently no indication to use any incretin agent in combination with insulin, although research is underway.

### DOSING FOR THE INCRETIN-BASED THERAPIES

Exenatide is injected twice daily, within the 60-min period before morning and evening meals. To improve tolerability, dosing is initiated at 5 µg twice daily; after 1 month the dose may be increased to 10 µg if necessary. Due to renal metabolism, exenatide should be avoided in patients with severe renal impairment or end-stage renal disease. No dose adjustment is necessary in individuals with hepatic impairment and there are no drug–drug interactions (90–92), although since exenatide delays gastric emptying, patients are advised to separate the times at which they take exenatide and any other medications administered in association with food (93).

In the LEAD trials, liraglutide was administered, as either a

monotherapy or in combination with 1 or 2 OADs, once daily without regard to meals, and without the need for dose adjustment in patients with renal (94) or hepatic impairment (95). Nausea was limited, or even avoided, by starting at a dose of 0.6 mg liraglutide for at least 1 week then, assuming good tolerability, increasing the dose to 1.2 mg. If necessary to achieve greater efficacy, the dose may be further increased after another week to 1.8 mg, the highest dose tested. No clinically relevant drug–drug interactions were identified during the development program (96).

The standard dose of sitagliptin is 100 mg once daily, taken without regard to food. Dose reduction to 50 mg or 25 mg daily is necessary in patients with moderate or severe renal impairment, respectively (97). Dose adjustment is unnecessary in mild or moderate hepatic impairment; there are no data in patients with severe hepatic disease. There are no known drug–drug interactions with sitagliptin that require dose adjustment (98). The sitagliptin/metformin combination is contraindicated in patients with hepatic and renal dysfunction (99); the warning regarding allergic and hypersensitivity reactions observed with sitagliptin is retained in the combined preparation. The most serious potential adverse reaction with the combined product is lactic acidosis due to metformin accumulation, which has proven fatal in half of all cases; regular monitoring of renal function is therefore necessary, and the drug should be immediately discontinued in suspected cases.

Saxagliptin is administered as a dose of 2.5 mg or 5 mg, taken once daily regardless of meals. The lower dose is advised in patients with moderate or severe renal impairment, or end-stage renal disease (100). Dose adjustments due to hepatic impairment (101), age, or gender (102) are not necessary.

### Convenience and quality of life with incretin therapies

Exenatide and liraglutide are both injected therapies, although they remain free from many of the complications associated with other injectables. Self-monitoring of blood glucose is not required for safety or dose titration, so the need for educational input from the diabetes care team — associated with added cost — is reduced, and patients are expected to feel less overwhelmed by the prospect of daily treatment. Indeed, patients completing a self-administered questionnaire reported significantly greater QoL and psychiatric wellbeing after 52 weeks of liraglutide treatment (1.8 mg/day; total n = 746), as well as improved image/concern regarding their weight, compared with those

receiving glimepiride ( $p < 0.01$  for all parameters) (103). Both exenatide and liraglutide are delivered using pre-filled pens, thereby simplifying delivery and reducing potential dosing errors, while allowing treatment to remain discreet and portable. The DPP-4 inhibitors are orally administered, once daily, with or without food. Renal function should be monitored periodically to determine the potential need for dose adjustment.

### CONCLUSIONS

Despite advances in diabetes management, there remains a need for agents that effectively lower HbA1c without undue risk of hypoglycemia. The incretin system has been shown to be a successful target for therapeutic intervention, with robust data supporting the therapeutic and safety benefits of the GLP-1 receptor agonists exenatide and liraglutide, and the DPP-4 inhibitors sitagliptin and saxagliptin as monotherapy and in combination with other OADs. In addition to blood glucose-lowering efficacy, these agents are associated with negligible risk of hypoglycemia, and improved fasting and PPG control, and are well tolerated. Only exenatide and liraglutide offer the potentially cardioprotective benefits of reductions in blood pressure as well as reliable weight loss; and in animal models liraglutide has demonstrated somewhat greater improvement in beta cell function. Further research is necessary to determine the full potential of these agents.

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