



Incretin Mimetics and Dipeptidyl Peptidase-4 Inhibitors in the Treatment of Type 2 Diabetes

a report by

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Clinical studies evaluating two novel incretin-based therapies – dipeptidyl-peptidase-4 (DPP-4) inhibitors and the incretin mimetic exenatide – have been reported. DPP-4 inhibitor and exenatide therapy effectively lower glycated haemoglobin (HbA_{1c}) levels in patients with diabetes. Although HbA_{1c} reductions are similar with both incretin-based treatments, the results of clinical studies need to be put into perspective considering that the cited studies have different study populations and study designs. For example, exenatide has been shown to reduce HbA_{1c} levels in patients with a longer duration of type 2 diabetes (4.9–9.9 years). In addition, exenatide is associated with a mean reduction in body weight (1.3–2.8kg), whereas DPP-4 inhibitors are not associated with weight loss. Head-to-head comparisons between DPP-4 inhibitors and exenatide are lacking. In this manuscript, clinical studies published to date for the DPP-4 inhibitors sitagliptin and vildagliptin and for exenatide were evaluated with respect to study population, study design and effectiveness.

Introduction

Diabetes is associated with long-term microvascular and macrovascular complications and is widely recognised as one of the leading causes of mortality and morbidity. Population growth, ageing, urbanisation, the prevalence of obesity and a sedentary lifestyle are all factors associated with the dramatically growing type 2 diabetes epidemic.¹ Progressive beta-cell dysfunction and insulin resistance are the two core defects in the complex disease process of type 2 diabetes. When beta-cells fail to increase insulin secretion to compensate for the rising need of insulin to maintain euglycaemia in the setting of insulin resistance, type 2 diabetes occurs. However, besides insulin, glucagon is an important regulator of glucose metabolism and is responsible for the stimulation of glucose production by the liver. In type 2 diabetes, plasma glucagon concentrations are often elevated, leading to an increase in hepatic glucose output. Insulin and glucagon secretion are influenced by the incretin hormone glucagon-like peptide-1 (GLP-1), which is secreted by the L-cells of the intestinal mucosa after a meal. GLP-1 stimulates insulin secretion after a meal and suppresses glucagon secretion. In this way, GLP-1 helps to maintain normoglycaemia. In type 2 diabetes, exogenous GLP-1 can normalise blood glucose.²

Two innovative therapeutic options based on the incretin concept are now available for the management of type 2 diabetes mellitus: the first, incretin mimetic (exenatide) and the second, DPP-4 inhibitors (sitagliptin and vildagliptin). While sitagliptin has already been authorised for marketing, vildagliptin is still under review.^{3–6} The basis for these therapeutic modalities is the utilisation of the physiological properties of the incretin hormones, in particular GLP-1. GLP-1 not only stimulates insulin secretion under hyperglycaemic conditions and inhibits glucagon secretion, but also slows gastric emptying and acts as a mediator of

satiety in the central nervous system. In animal studies and *in vitro*, it increases the beta-cell mass and improves beta-cell function.⁴ As GLP-1 itself is not feasible for therapeutic purposes because of its short biological half-life, two approaches were developed as a means of utilising the favourable effects of GLP-1 in treating type 2 diabetes through the use of elevated concentrations of GLP-1 receptor ligands. One approach is to use long-acting incretin mimetics for subcutaneous administration. Exenatide is the first incretin mimetic to be authorised, and others are under development. The second therapeutic option is inhibition of incretin degradation by blockade of the DPP-4 enzyme. Unlike subcutaneously administered incretin mimetics, DPP-4 inhibitors are effective when taken orally.^{4,5}

DPP-4, also known as CD26, is an ubiquitous enzyme that degrades GLP-1 and gastric inhibitory polypeptide (GIP) as well as numerous other peptide hormones with the amino acid alanine or proline in position 2 of the N-terminus.⁷ In Europe, sitagliptin was authorised in March 2007 as a combination therapy with either metformin or a thiazolidinedione. A second DPP-4 inhibitor (vildagliptin) has been submitted for approval.⁹

Exenatide is the synthetic version of exendin-4, a naturally occurring 39 amino acid peptide, which exhibits 50% sequence identity to GLP-1. Its longer half-life makes it suitable for twice-daily subcutaneous injection in therapeutic use. Exenatide is termed an 'incretin mimetic' because it mimics several of the incretin effects of the natural peptide. The peptide sequence of exenatide is not derived from GLP-1's primary sequence. In contrast, the sequences of GLP-1 peptide analogues are derived from GLP-1's primary sequence. GLP-1 analogues have targeted alterations in the N-terminal region that are resistant to DPP-4. In Europe, exenatide is



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Table 1: Exenatide Clinical Trials

Prior Medication	Mean Diabetes Duration (years)	Baseline HbA _{1c}	Trial Duration (weeks)	Wash-out Phase	Treatment	Change in HbA _{1c} (%)	Weight Effect	References
Sulphonylurea (SU)	6.6	8.6%	30	None	Exenatide 10µg BID	-0.86	-1.3kg	Buse et al. ¹²
Metformin (≥1500mg)	4.9	8.2%	30	None	Exenatide 10µg BID	-0.78	-2.8kg	De Fronzo et al. ¹³
Metformin+SU	8.7	8.5%	30	None	Exenatide 10µg BID	-0.77	-1.6kg	Kendall et al. ¹⁴
Metformin+SU	9.8	8.6%	52	None	Exenatide 10µg BID	-1.04	-2.5kg	Nauck et al. ¹⁷
	10.0	8.6%			Premixed insulin aspart	-0.89	+2.9kg	
Metformin+SU	9.9	8.2%	26	None	Exenatide 10µg BID	-1.11	-2.3kg	Heine et al. ¹⁶
	9.2	8.3%			Insulin glargine	-1.11	+1.8kg	

licensed for the treatment of type 2 diabetes in combination with metformin and/or sulphonylurea.

To date, the clinical efficacy of incretin mimetics and DPP-4 inhibitors has not been directly compared in a type 2 diabetes patient population. Currently, a comparison of these two new therapeutic options can be made only indirectly. However, comparisons based exclusively on the HbA_{1c} effect are of little relevance in terms of estimating practical clinical benefit, as populations and designs differ between studies.

The aim of this paper is therefore to assess the existing clinical phase III trials on exenatide, sitagliptin and vildagliptin in terms of their study population and study design, efficacy (measured on the basis markers of glycaemia and body weight developments) and safety markers such as hypoglycaemia and adverse events.

Methods

Fourteen phase III clinical trials on the drugs exenatide, sitagliptin and vildagliptin were evaluated in terms of study population, study design,

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effectiveness (based on glycaemic control and weight) and safety. The differences between the patient cohorts investigated in the studies were analysed and compared in respect to disease duration and previous antidiabetic medication, in order to possibly identify those patients most likely experiencing benefit from these new treatment options.

To provide a basis for classifying the efficacy of the new treatment options, changes in HbA_{1c} effect in relation to baseline and to HbA_{1c} effect of the respective reference drug were taken. In accordance with standard international procedure, results from the intention-to-treat (ITT) population were used in investigating these efficacy markers. This review includes only phase III trials with a fully published manuscript (cut-off date: 28 February 2007). Clinical trials published only as an abstract were not included because the information given in abstracts may be incomplete, especially with regard to study population and design.

Three exenatide placebo-controlled trials and two non-inferiority studies with exenatide, four sitagliptin placebo-controlled trials and one sitagliptin non-inferiority study, and two vildagliptin trials and two vildagliptin non-inferiority studies were included in the analysis. The evaluation was based in each case on the doses at which the drugs will be marketed, i.e. sitagliptin 100mg per os (p.o.) once daily, vildagliptin 100mg p.o. once daily and exenatide 10µg subcutaneously (s.c.) two times daily (after a four-week run-in period with 5µg s.c. two times daily).

Exenatide

Exenatide shares similar glucoregulatory activities with the incretin hormone GLP-1, having multiple mechanisms of action that improve glycaemic control.¹⁰ Exenatide, which is primarily metabolised in the kidney, exhibits a half-life of approximately 2.5 hours and can be found in the circulation six to 10 hours after a single dose.¹⁰ Recently, intravenous infusion of exenatide has been shown to restore first- and second-phase insulin secretion after glucose challenge in patients with type 2 diabetes.¹¹ These results suggest that short-term intravenous administration of exenatide can acutely improve pancreatic beta-cell function in patients with type 2 diabetes.

The efficacy of glycaemic control with exenatide in patients with type 2 diabetes treated with metformin, a sulphonylurea or both has been investigated in three triple-blind, placebo-controlled, phase III clinical trials.^{12–14} The addition of exenatide to baseline oral antidiabetic (OAD) therapies significantly improved glycaemic control in patients with type 2 diabetes. The duration of treatment with study drug was 30 weeks in each case, preceded by a four-week placebo run-in period. Baseline HbA_{1c} in these studies was 8.2–8.6% and the mean duration of diabetes was 4.9–8.7 years. Mean HbA_{1c}, fasting plasma glucose and post-prandial glucose excursions were significantly reduced by 30-week subcutaneous injection of 10µg exenatide twice daily (BID). The HbA_{1c} reduction achieved from baseline was -0.77% to -0.86%, respectively, compared with a 0.1–0.2% increase in placebo groups.^{12–14} Furthermore, there were progressive reductions in mean bodyweight in subjects treated with 10µg exenatide and concomitant therapy: with sulphonylurea, 1.3kg; with sulphonylurea and metformin, 1.6kg; and with metformin, 2.8kg.^{12–14} Exenatide was generally well tolerated and there were no severe adverse drug effects, other than one case of severe hypoglycaemia in combination with metformin and sulphonylurea. The most common adverse effect was nausea (45–51%). The incidence of nausea was the greatest when the exenatide dose was titrated from 5 to 10µg during the initiation phases of the trials, from weeks four to eight in the 30-week placebo-controlled trials. Incidence of nausea declined in patients with continuous exposure to exenatide. In all the trials, episodes of

Table 2: Vildagliptin Clinical Trials

Prior Medication	Mean Diabetes Duration (years)	Baseline HbA _{1c} (%)	Trial Duration (weeks)	Wash-out Phase	Treatment	Change in HbA _{1c} (%)	Weight Effect	References
Metformin (≥1500mg)	5.8	8.4	24	None	Vildagliptin 100mg	-0.9	none	Bosi et al. ²²
None	2.1	8.3	24	None	Vildagliptin 10 mg	-0.8	none	Pi-Sunyer et al. ²³
None	2.3	8.7	24	None	Vildagliptin 100mg	-1.1	-0.3kg	Rosenstock et al. ²⁴
	2.7	8.7			Rosiglitazone 8mg	-1.3	+1.6kg	
None	1.9	8.6	24	None	Vildagliptin 100mg	-1.1	none	Rosenstock et al. ²⁵
	2.2	8.7			Pioglitazone 30mg	-1.4	+1.5kg	
	2.0	8.8			Vildagliptin + Pioglitazone (100/30mg)	-1.9	+2.1kg	
	2.0	8.8			Vildagliptin + Pioglitazone (50/15mg)	-1.7	+1.4kg	

hypoglycaemia were generally mild to moderate in intensity. No increase in the incidence of hypoglycaemia was observed in the combination therapy of exenatide and metformin. However, the incidence of hypoglycaemia in exenatide-treated patients increased when sulphonylurea was co-administered. In one of the three placebo-controlled phase III trials, it was observed that reducing the sulphonylurea dose decreased the incidence of hypoglycaemia in exenatide-treated patients.¹⁴ In addition, the same trial showed that a baseline HbA_{1c} level close to 7% was associated with a higher incidence of hypoglycaemia. Low-titre antiexenatide antibodies and, in a few cases, high-titre antiexenatide antibodies were detected in some exenatide-treated patients; however, the presence of those antibodies had no predictive effect on glycaemic control or the incidence of adverse events.¹⁵

In two other exenatide studies, patients taking a metformin-sulphonylurea combination therapy were treated with two different types of insulin (glargine and biphasic insulin aspart) or exenatide. The duration of diabetes in the study patients was 9.8 and 9.9 years, respectively. These studies did not incorporate a washout period for the oral pre-treatment.^{16,17} According to the inclusion criteria, enrolment was limited to patients receiving an optimally tolerated dose of OAD agents. Hence, this was a patient population that met European Association for the Study of Diabetes and American Diabetes Association criteria for initiation of insulin treatment.¹⁸

In a 26-week open-label, randomised, controlled trial involving 551 patients with type 2 diabetes having inadequate glycaemic control despite the combination of metformin and sulphonylurea therapy, exenatide therapy provided glycaemic control that was non-inferior to insulin glargine.¹⁶ In this study, HbA_{1c} reduction of -1.1% was achieved both on insulin glargine and on exenatide, starting with a baseline HbA_{1c} of 8.2% and 8.3%, respectively.¹⁶

Patients receiving 10µg exenatide twice daily experienced progressive weight loss and had a mean reduction in bodyweight of 2.3kg. In contrast, patients receiving insulin glargine gained weight during the trial and had a mean weight gain of 1.8kg. Nausea (57.1%) and vomiting (17.4%) were the most frequent adverse events in exenatide-treated patients. Patients receiving exenatide had a significantly higher incidence of gastrointestinal adverse effects – including nausea, vomiting and diarrhoea – than patients receiving insulin glargine. The two treatment groups had no difference in the overall rate of hypoglycaemia (7.3 events/patient-year in the exenatide group versus

6.3 events/patient-year in the insulin glargine group), but patients receiving exenatide had a lower incidence of nocturnal hypoglycaemia and a higher incidence of daytime hypoglycaemia than patients receiving insulin glargine.¹⁶

The safety and efficacy of exenatide versus biphasic insulin aspart was studied in a 52-week, randomised, open-label, non-inferiority trial in patients with type 2 diabetes taking metformin and a sulphonylurea who could not achieve optimal glycaemic control. An HbA_{1c} reduction of 0.89 and 1.04%, respectively, was observed in patients with the same baseline HbA_{1c} (8.6%) taking insulin aspart and exenatide.¹⁷ Similarly to other insulin comparator studies, exenatide treatment resulted in weight loss while biphasic insulin aspart resulted in weight gain. Mean bodyweight was statistically different between the two treatment groups as early as week two, and this difference was 5.4±0.2kg by the end of study. Both treatments achieved similar reductions of approximately 1.7mmol/l in fasting serum glucose. This result differs from the non-inferiority study of exenatide and insulin glargine, in which insulin glargine achieved greater reductions in fasting serum glucose. Greater reductions in post-prandial

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glucose excursions were observed in the exenatide group, consistent with the placebo-controlled studies. Mild to moderate nausea (33.2%) and vomiting (15%) were the most frequent adverse events with exenatide treatment. The incidence of gastrointestinal adverse events was higher in exenatide-treated patients than in biphasic insulin aspart-treated patients. The mean rates of overall (exenatide, 4.7±0.7 versus biphasic insulin aspart, 5.6±0.7 events/patient-year), daytime (exenatide, 4.1±0.6 versus biphasic insulin aspart, 4.4±0.7 events/patient-year) and nocturnal hypoglycaemia (exenatide, 0.6±0.2 versus biphasic insulin aspart, 1.1±0.2 events/patient-year) were similar between treatment groups. Furthermore, this trial observed that reduction in sulphonylurea dose decreased the overall hypoglycaemia rates in exenatide-treated patients.¹⁷

Weight reductions of 2.3 and 2.5kg with exenatide were observed in the

Table 3: Sitagliptin Clinical Trials

Prior Medication	Mean Diabetes Duration (years)	Baseline HbA _{1c} (%)	Trial Duration (weeks)	Wash-out Phase	Treatment	Change in HbA _{1c} (%)	Weight Effect	References
None/monotherapy/ low dose combination	4.5	8.1	18	12	Sitagliptin 100mg	-0.48	None	Raz et al. ²⁸
Metformin (≥1500mg)	6.2	8.0	24	None	Sitagliptin 100mg	-0.67	None	Charbonnel et al. ²⁷
None/monotherapy	4.4	8.0	24	12	Sitagliptin 100mg	-0.61	None	Aschner et al. ²⁶
Monotherapy Pioglitazone	6.1	8.1	24	6–21	Sitagliptin 100mg	-0.85	+1.8kg	Rosenstock et al. ²⁹
Metformin (≥1500mg)	6.5	7.7	52	None	Sitagliptin 100mg	-0.51	-1.5kg (PP)*	Nauck et al. ³⁰
	6.2	7.6			Glipizide 5–20mg	-0.56	+1.1kg (PP)*	

*PP = per protocol population.

glargine and aspart studies comparing exenatide with insulins. In contrast, insulin glargine was associated with a weight gain of 1.8kg and insulin aspart with a weight gain of 2.9kg.^{16,17}

Overall, it appears in clinical trials with exenatide that patients had a longer duration of diabetes (see *Table 1*).¹⁷

Dipeptidyl Peptidase-4 Inhibitors

DPP-4 inhibitors are compounds that prevent the degradation of endogenous GLP-1 by inhibiting the activity of the DPP-4 enzyme.¹⁹ DPP-4 inhibitors extend the half-life of endogenous GLP-1, preserving the glucoregulatory actions of GLP-1 for a longer time.¹⁹ DPP-4 inhibitors are orally administered drugs and are generally well tolerated.^{20,21}

Exenatide and dipeptidyl peptidase-4 inhibitors have a low potential to cause hypoglycaemia. The incidence of hypoglycaemia with exenatide is increased in combination with sulphonylureas due to this co-medication.

Vildagliptin

Vildagliptin (LAF237, Novartis Pharmaceuticals, Basel, Switzerland) is currently in late-stage clinical development. The mean diabetes duration in the two placebo-controlled vildagliptin (100mg p.o. once daily) studies was 2.1–5.8 years.^{22,23}

In a placebo-controlled vildagliptin study, drug-naïve patients were treated with the study drug for 24 weeks, preceded by a two- to four-week run-in period. HbA_{1c} levels decreased by 0.80% from baseline HbA_{1c} levels of 8.3%. Vildagliptin did not have an effect on bodyweight. No confirmed hypoglycaemia was reported and adverse events occurred with similar frequency in each group.²³

In another placebo-controlled trial, vildagliptin was added to pre-existing metformin therapy. Treatment duration with study drug was 24 weeks, preceded by a two- to four-week run-in period. After 24 weeks of treatment, HbA_{1c} levels decreased by 0.90% from baseline HbA_{1c} levels of 8.4%. There was no effect on body weight. Only one mild hypoglycaemia occurred in each treatment group and vildagliptin was generally well tolerated.²²

In a study comparing vildagliptin with an active comparator, rosiglitazone drug-naïve patients had a mean duration of diabetes of 2.3 (vildagliptin) and 2.7 (rosiglitazone) years and baseline HbA_{1c} of 8.7% in both treatment groups.²⁴ After 24 weeks, a 1.3 and 1.1% reduction in HbA_{1c} was observed for rosiglitazone and vildagliptin, respectively. Vildagliptin met the statistical criterion for non-inferiority. Rosiglitazone had favourable effects in reducing fasting blood glucose. Vildagliptin did not result in weight gain, while the rosiglitazone patients gained weight.

In another study, vildagliptin (100mg) with pioglitazone (30mg) and a low-dose (50mg + 15mg) and high-dose (100mg + 30mg) vildagliptin-pioglitazone combination were compared.²⁵ In this four-arm 24-week study, patients had a short duration of diabetes (1.9–2.2 years) and were drug-naïve. Baseline HbA_{1c} in all four groups was 8.6–8.8%. At treatment week 24, reductions of 1.4 and 1.1% in HbA_{1c} levels were observed for pioglitazone and vildagliptin, respectively. The reduction achieved with the vildagliptin-pioglitazone combination was -1.7% for the low dose and -1.9% for the higher dose. The combination treatments were superior to the single-agent treatments with a statistical significance. Weight gain of 1.4–2.1kg occurred in both vildagliptin-pioglitazone combinations and in the pioglitazone single-agent arm (see *Table 2*).²⁵ In the clinical trials, vildagliptin was generally well tolerated, with no increased risk of hypoglycaemia compared with placebo.

Sitagliptin

Recently, sitagliptin (MK-0431, Merck, Whitehouse Station, New Jersey) has been authorised for the treatment of type 2 diabetes in Europe. In Europe, sitagliptin is authorised as combination therapy with either metformin or a thiazolidinedione. In the four evaluated placebo-controlled sitagliptin studies (100mg p.o. once daily), the mean diabetes duration in the study population was 4.4–6.2 years.^{26–29} With respect to prior antidiabetes treatment, subjects were drug-naïve or had received single-agent therapy with metformin or pioglitazone or dual low-dose combination therapy (metformin plus sulphonylurea, though only one subgroup in one study). In addition to the two-week placebo run-in periods, these studies also included washout periods (10–21 weeks) during which the prior treatments were not taken. Baseline HbA_{1c} in these studies was established after the washout period.

With one exception (Raz et al.: 18 weeks²⁸) the duration of treatment with study drug was 24 weeks. Baseline HbA_{1c} in the sitagliptin studies was 8–8.1%. The HbA_{1c} effects achieved with sitagliptin were in the -0.48 to -0.85% range. Sitagliptin did not have an effect on bodyweight. One published study included an active sulphonylurea comparator,

glipizide. Study participants had had prior single-agent metformin therapy without satisfactory metabolic control.³⁰ Reduction in HbA_{1c} levels in the two groups (sitagliptin versus glipizide) was similar at 52 weeks, at -0.51 and -0.56% from mean baseline values of 7.7 and 7.6%, respectively. More patients in the sitagliptin group achieved target HbA_{1c} levels below 7% (63 versus 59%). Sitagliptin lowered fasting blood glucose to a greater extent than glipizide (-10 and -7.5mg/dl, respectively, for sitagliptin and glipizide). A significantly lower rate of hypoglycaemia occurred on sitagliptin than on glipizide (p<0.001). The mean weight difference at the end of the study was +2.6kg, with weight gain occurring in glipizide patients. In general, sitagliptin was not associated with weight gain (see Table 3). In the clinical trials, sitagliptin was generally well tolerated, with no increased risk of hypoglycaemia compared with placebo.

Conclusion

Study participants in the exenatide studies were mainly patients with a longer diabetes duration (4.9 to 9.9 years).^{12–14,16,17} In contrast, the DPP-4 inhibitor study patients^{22–30} had shorter diabetes duration (1.9–6.5 years). Baseline HbA_{1c} levels in all studies were similar and in general HbA_{1c} reduction was greater in patients with higher baseline HbA_{1c} levels. Significant decreases in HbA_{1c} levels observed in the vildagliptin with pioglitazone studies were seen in drug-naïve patients with high baseline HbA_{1c}. Non-inferiority studies of DPP-4 inhibitors versus insulin have not been conducted; however, two comparator studies with two different types of insulin treatments exist for exenatide.^{16,17} In these studies, exenatide was non-inferior to insulin aspart and glargine in terms of HbA_{1c} reduction and led to reduced bodyweight, while insulin therapy was associated with significant weight gain.^{16,17}

Another difference in the results of the cited exenatide and DPP-4 studies is that DPP-4 inhibitors were not associated with weight loss,^{7–9,22–30} while exenatide demonstrated the additional benefit of significant weight reduction.^{6,12–14,16–18} Exenatide and DPP-4 inhibitors have a low potential to cause hypoglycaemia. The incidence of hypoglycaemia with exenatide is increased in combination with sulphonylureas due to this co-medication. In combination regimens of this kind, reduction of the sulphonylurea dose should be considered.⁴ With respect to the side effects profile, exenatide is associated with an increase in nausea, most of which is mild to moderate (33–57% of patients reported at least one episode of nausea during the studies), and tends to resolve over time.^{5,6,12–14,16,17}

Sitagliptin and vildagliptin are generally well tolerated, with no characteristic pattern of adverse events associated with the use of these medications.^{2,4,22–30} For sitagliptin, adverse events (regardless of causal relationship) reported in at least 5% of patients and more frequently than in the control group included upper respiratory tract infections and nasopharyngitis.^{26–30} For vildagliptin, adverse events reported in at least 5% of patients included upper respiratory tract infections, nasopharyngitis, dizziness, influenza and headache.^{22–25}

DPP-4 inhibitors might be a treatment option for patients with a shorter diabetes duration. They do not cause weight gain and have low hypoglycaemic risk – important advantages over sulphonylureas or thiazolidinediones. The effect of exenatide in terms of glycaemic control has been demonstrated in insulin non-inferiority studies. It is the only antidiabetic agent with an additional weight-reduction effect, a desired goal of treatment in any stage of type 2 diabetes, especially in patients in whom weight loss may be desirable. ■

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