

## Glucagon-like peptide-1 analogs in the treatment of Type 2 diabetes: a review of the Phase II and III trials

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Glucagon-like peptide-1 (GLP-1) analogs-based therapies are a new option for Type 2 diabetes treatment that hold the promise of overcoming the major limitations of traditional treatments, including the increased risk for hypoglycemia and weight gain. GLP-1 is a naturally occurring hormone that potentiates glucose-dependent insulin secretion. The clinical utility of native GLP-1 is, however, limited by its short half-life; these observations led to the generation of GLP-1 analogs, which mimic GLP-1 action *in vivo* in humans. Here, we review the data from clinical trials that have assessed mechanism of action, efficacy and safety of GLP-1 agonists; these trials have demonstrated the efficacy of GLP-1 analogs in reducing glycosylated hemoglobin and fasting plasma glucose levels. The use of these drugs was associated with weight loss and reductions in blood pressure, with a low risk of hypoglycemia, GLP-1 agonists were generally well tolerated with the most frequent adverse effects being nausea.

**Keywords:** albiglutide • exenatide • exenatide-LAR • GLP-1 agonist • liraglutide  
• lixisenatide • taspoglutide

Type 2 diabetes is characterized by reduced insulin sensitivity, inadequate insulin secretion to compensate for increased peripheral demand and an impaired intestinal secretion of insulin (incretin) hormone response [1,2]. Despite the availability of drugs belonging to ten different antidiabetic medication classes, a substantial number of patients do not achieve or maintain glycemic targets with current treatments [3,4]. An important reason for inadequate therapy is the progressive nature of the disorder, mostly due to the unavoidable decline of pancreatic  $\beta$ -cell function. An additional limitation of current antidiabetic treatments, particularly sulfonylurea and insulin, is that they are associated with an increased risk of hypoglycemia [5]. Furthermore, several current treatments, in particular insulin, thiazolidinediones and sulfonylureas, are associated with weight gain over time [6]. Finally, cardiovascular (CV) risk management is a very important part of Type 2 diabetes care as CV risk factors, such as hypertension, are often associated with Type 2 diabetes and a reduction in systolic blood pressure of only 5.6 mmHg has been associated with a significant reduction of 18% in the relative risk of death from CVD [7].

Incretin-based therapies are a new option for Type 2 diabetes treatment that hold the promise of overcoming the major limitations of traditional treatments [8]. Glucagon-like peptide (GLP)-1 is a naturally occurring hormone that potentiates glucose-dependent insulin secretion, suppresses glucagon secretion, slows gastric emptying and decreases appetite [9,10]. Furthermore, in animal models, GLP-1 has been demonstrated to inhibit apoptosis and promote proliferation and neogenesis resulting in increased  $\beta$ -cell mass [11]. The clinical utility of native GLP-1 is limited by its short half-life (<2 min) due to its rapid degradation to inactive metabolites by the enzyme dipeptidyl peptidase (DPP)-4 [12,13]. These observations

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led to the discovery and generation of GLP-1 analogs, which mimic the actions of GLP-1 *in vivo* in humans. Herein, the data from clinical trials that have assessed mechanism of action, efficacy and safety of GLP-1 analogs are reviewed. For this review, a search using MEDLINE was performed with the following search terms: incretin, liraglutide, exenatide, exenatide long-acting release (LAR), taspoglutide, albiglutide and lixisenatide to identify relevant English language full paper publications. The NIH clinical trial registry was consulted for information on unpublished trials as full papers at the time of writing.

### Exenatide

#### ■ Phase II trials

Exenatide is a synthetic form derived from exendin-4 that was originally isolated in the saliva of the reptile, the Gila monster. It has a 53% amino acid homology to human GLP-1 and is a potent agonist of the human GLP-1 receptor. Since exenatide has a glycine residue at position 2, it is less susceptible to degradation by DPP-4 than the native hormone and thus suitable for twice-daily dosing [14].

Numerous studies have established the effectiveness of exenatide in improving glycemic control among patients with Type 2 diabetes and glycosylated hemoglobin (HbA<sub>1c</sub>). In a 28-day study carried out in 109 subjects with Type 2 diabetes treated with diet, sulfonylureas and/or metformin, patients were randomly assigned to one of three regimens of exenatide (0.08 µg/kg): twice daily (breakfast and dinner); twice daily (breakfast and bedtime); three-times daily (breakfast, dinner and bedtime); or placebo three-times daily (breakfast, dinner and bedtime) [15]. As compared with placebo, exenatide-treated patients showed 0.9% reduction from baseline of HbA<sub>1c</sub> [15]. Exenatide treatment also resulted in greater reductions ( $p < 0.004$ ) in postprandial glycemia (-72, -58 and -61 mg/dl for twice daily [b.i.d.; breakfast and dinner], b.i.d. [breakfast and bedtime] and three-times daily [t.i.d.] respectively) as compared with placebo (-11 mg/dl). The  $\beta$ -cell function, assessed by homeostasis model assessment (HOMA)- $\beta$  index, for patients treated with exenatide was 70–100% higher than baseline, contrasting with unchanged levels for placebo. The effects of exenatide in patients with Type 2 diabetes have been investigated in fasting and postprandial conditions [16]. In the postprandial study, 24 patients received placebo or exenatide 0.1 µg/kg injected subcutaneously twice daily before breakfast and dinner for 5 days. Patients ingested acetaminophen (20 mg/kg) at the time of consuming the standardized meal to assess gastric emptying. Significant reductions in mean postprandial plasma glucose levels were observed during the 300 min

following treatment with exenatide as compared with placebo ( $p < 0.05$ ). In addition, exenatide significantly delayed gastric emptying as compared with placebo as assessed by measuring appearance in plasma of acetaminophen. In the fasting study, 13 patients treated with diet alone, metformin alone, thiazolidinedione alone (rosiglitazone or pioglitazone) or a combination of metformin and one of the thiazolidinediones, were randomly assigned to receive one subcutaneous injection of placebo or exenatide 0.05, 0.1 or 0.2 µg/kg on days 1, 3, 5 and 7 followed by an overnight fast. All three doses of exenatide significantly reduced plasma glucose concentrations as compared with placebo in the fasting state during the 8-h period of observation (35% reduction,  $p < 0.0001$ ). Fasting serum insulin concentrations increased in a dose-dependent manner during the first 3 h after exenatide administration ( $p < 0.0001$ ) coincident with reaching the glucose concentration nadir. Thus, exenatide reduces fasting and postprandial glucose concentrations in patients with Type 2 diabetes. In a 52-week study performed in 69 metformin-treated patients, the effects of exenatide on  $\beta$ -cell function, glycemic control, body weight and safety was compared with those induced by insulin glargine [17]. Patients randomized to exenatide received an initial dose of 5 µg twice daily for 4 weeks followed by a dose increase to 10 µg twice daily for the remaining 48 weeks of the study. Exenatide and insulin glargine treatment resulted in similar reductions in HbA<sub>1c</sub> (-0.8 and -0.7%, respectively;  $p = 0.55$ ), with both groups achieving a mean HbA<sub>1c</sub> of 6.8% at 52 weeks. The insulin glargine group demonstrated a greater reduction in fasting plasma glucose compared with the exenatide group, whereas significantly greater reductions in postprandial glucose excursions were observed in the exenatide-treated patients. Treatment with exenatide resulted in a reduction of body weight of -3.6 kg, whereas treatment with insulin glargine was associated with an increase in body weight of +1.0 kg (between group difference, -4.6 kg;  $p < 0.0001$ ). As compared with insulin glargine, exenatide treatment significantly increased first- and second-phase glucose-stimulated C-peptide secretion ( $p < 0.0001$ ), measured by hyperglycemic clamp procedure.

#### ■ Phase III trials

##### Exenatide monotherapy

In a 24-week study performed in 232 drug-naive patients with Type 2 diabetes, twice daily exenatide monotherapy induced a significant reduction in HbA<sub>1c</sub> [18]. At the end of the study, significant changes from baseline HbA<sub>1c</sub> were observed in the exenatide 5- and 10-µg groups ( $p = 0.003$ ,  $p < 0.001$ , respectively, **Table 1**). HOMA- $\beta$  increased by 32% ( $p = 0.002$ )

Table 1. Phase III studies with exenatide twice daily: overview of key efficacy and safety data.

Study	Description/patients randomized/combination therapy	Comparators	$\Delta$ HbA <sub>1c</sub> (%)	$\Delta$ Fasting glucose (mg/dl)	$\Delta$ Body weight (kg)	$\Delta$ SBP (mmHg)	Nausea (% of patients)	Ref.
Monotherapy	24-week, double-blind, placebo-controlled, parallel-group study 232 patients on diet/exercise	Exenatide 5 $\mu$ g	-0.7	-17	-2.8	-3.7	2	[18]
		Exenatide 10 $\mu$ g	-0.9	-19	-3.1	-3.7	10	
		Placebo	-0.2	-5	-1.4	-0.3	0	
Add-on to metformin	30-week randomized, triple-blind, placebo-controlled, parallel-group study 336 patients on OADs Metformin (>1.5 g daily)	Exenatide 5 $\mu$ g	-0.40	-7	-0.3	NA	23	[19]
		Exenatide 10 $\mu$ g	-0.78	-10	-1.6	NA	36	
		Placebo	-0.08	+14	-2.8	NA	45	
Add-on to SU	30-week randomized, triple-blind, placebo-controlled, parallel-group study 377 patients on OADs SU	Exenatide 5 $\mu$ g	-0.46	-5	-0.9	NA	39	[20]
		Exenatide 10 $\mu$ g	-0.86	-11	-1.6	NA	51	
		Placebo	+0.12	+7	-0.6	NA	7	
Add-on to metformin and SU	30-week randomized, double-blind, placebo controlled parallel-group study 733 patients on OADs Metformin and SU	Exenatide 5 $\mu$ g	-0.6	-9	-1.6	NA	39	[21]
		Exenatide 10 $\mu$ g	-0.8	-11	-1.6	NA	48	
		Placebo	+0.2	+14	-0.9	NA	20	
Add-on to TZD	16-week randomized, double-blind, placebo-controlled study 233 patients on TZDs alone or in combination with metformin TZDs with or without metformin	Exenatide 10 $\mu$ g	-0.9	-28	-1.75	NA	39	[23]
		Placebo	+0.1	+1.8	-0.24	NA	15	
Comparison of exenatide with insulin glargine	26-week randomized, open-label, controlled study 551 patients on OADs Background treatment maintained	Insulin glargine	-1.11	-51	+1.8	NA	8	[24]
		Exenatide 10 $\mu$ g	-1.11	-26	-2.3	NA	57	
Comparison of exenatide with insulin glargine	16-week randomized, open-label, two period, crossover noninferiority study 138 patients on OADs Background treatment maintained	Insulin glargine	-1.36	-74	+0.6	NA	3	[25]
		Exenatide 10 $\mu$ g	-1.36	-52	-1.6	NA	42	
Comparison of exenatide with biphasic insulin aspart	52-week randomized, open-label, noninferiority study 501 patients on OADs Background treatment maintained	Biphasic insulin aspart	-0.89	-31	+2.9	+1	0.4	[26]
		Exenatide 10 $\mu$ g	-1.04	-32	-2.5	-5	33	

HbA<sub>1c</sub>: Glycosylated hemoglobin; NA: Not available; OAD: Oral antidiabetic drug; SBP: Systolic blood pressure; SU: Sulfonylurea; TZD: Thiazolidinedione.

and 28% ( $p = 0.010$ ) in the exenatide 5- and 10- $\mu$ g groups, respectively, versus 6% for placebo. The improvement in glycemic control was associated with a significant decrease in body weight in both groups treated with exenatide ( $p = 0.004$ , and  $p < 0.001$ , respectively, Table 1). Systolic blood pressure decreased

from baseline in both 5- and 10- $\mu$ g exenatide groups (both  $p = 0.037$ , Table 1) as compared with placebo. Diastolic blood pressure decreased from baseline by -0.8 mmHg in the exenatide 5- $\mu$ g group ( $p = \text{NS}$ ) and -2.3 mmHg in the exenatide 10- $\mu$ g group ( $p = 0.046$ ) as compared with -0.3 mmHg with placebo.

### Combination therapy of exenatide with oral antidiabetic agents

Three Phase III clinical trials (Access Diabetes Management for Improving Glucose Outcome [AMIGO] studies), each of 30 weeks duration, have examined the effect of exenatide on glycemic control in patients inadequately controlled with maximally effective doses of sulfonylurea monotherapy, metformin monotherapy or sulfonylurea plus metformin combination therapy [19–21]. In patients on background metformin monotherapy, there were significant reductions in HbA<sub>1c</sub> from baseline ( $p < 0.002$ ; [Table 1](#)) [19]. There was also a significant decrease in the proinsulin:insulin ratio toward more physiological proportions in the exenatide 10 µg arm ( $p < 0.001$ ), with a similar trend observed in the exenatide 5 µg arm. During the study, patients treated with exenatide exhibited a progressive weight loss regardless of baseline BMI ( $p < 0.05$  and  $p < 0.001$  for the exenatide 5 and 10-µg arms vs placebo, respectively; [Table 1](#)).

In patients on background sulfonylurea monotherapy, the reduction in HbA<sub>1c</sub> from baseline was -0.86, -0.46 and -0.12% for patients treated with exenatide 10 µg, exenatide 5 µg and placebo, respectively ( $p < 0.001$ ; [Table 1](#)) [20]. In the exenatide 10-µg arm at week 30, the mean proinsulin:insulin ratio was reduced by -0.13 compared with baseline and was significantly lower than that in the placebo group ( $p = 0.001$ ). Baseline proinsulin:insulin ratios were 0.66, 0.59 and 0.64 in the exenatide 10-, 5-µg and placebo arms, respectively. In the exenatide 10 µg arm at week 30, the mean proinsulin:insulin ratio was reduced by -0.13 compared with baseline and was significantly lower than that in the placebo group ( $p = 0.001$ ). Patients treated with exenatide 10 µg demonstrated a progressive weight reduction with a significant end-of-study loss as compared to placebo ( $p < 0.05$ ; [Table 1](#)).

In patients on background sulfonylurea plus metformin combination therapy, HbA<sub>1c</sub> showed decreases from the baseline for patients treated with exenatide ( $p < 0.001$  vs placebo; [Table 1](#)) [21]. Subjects treated with exenatide also exhibited progressive weight reduction over the entire 30-week treatment period with a significant end-of-study weight loss ( $p < 0.01$  vs placebo; [Table 1](#)).

Patients from three placebo-controlled trials and their open-label extensions were enrolled into one open-ended, open-label clinical trial [22]. Patients ( $n = 217$ ) completing 3 years of exenatide 10-µg twice daily treatment had a reduction in HbA<sub>1c</sub> of -1.0% from baseline ( $p < 0.0001$ ), and a decrease in fasting plasma glucose of -23 mg/dl ( $p < 0.0001$ ). In a subgroup of the 3-year completer subjects in whom data were collected for analyses ( $n = 92$ ), exenatide

treatment was associated with a sustained improvement in  $\beta$ -cell function (HOMA- $\beta$  index after 3 years 70.1% vs baseline 52.4%;  $p < 0.0001$ ). A progressive weight loss was observed with a net loss of 5.3 kg at the end of 3 years ( $p < 0.0001$ ). In a subgroup of 151 patients with serum lipid measurements at the time of study closure, exenatide therapy for 3.5 years also significantly improved a number of cardiovascular risk factors. Total cholesterol was reduced from baseline by -11 mg/dl ( $p = 0.0007$ ), triglyceride by -44 mg/dl ( $p = 0.0003$ ), LDL cholesterol by -11.8 mg/dl ( $p < 0.0001$ ), whereas HDL cholesterol increased from baseline by +8.5 mg/dl ( $p < 0.0001$ ). Additionally, systolic blood pressure was reduced from baseline by -3.5 mmHg ( $p = 0.0063$ ), and diastolic blood pressure by -3.3 mmHg ( $p < 0.0001$ ). The greatest improvements in CV risk factors were observed in patients who had the greatest weight reductions.

The efficacy of exenatide (10 µg b.i.d.) added to rosiglitazone alone or pioglitazone alone, or in combination with metformin, was examined in a 16-week trial [23]. The addition of exenatide to thiazolidinediones in the presence or absence of metformin resulted in a reduction of HbA<sub>1c</sub> and in significant mean body weight changes at week 16 ( $p < 0.001$ ; [Table 1](#)). Patients in the exenatide arm had reductions in body weight regardless of their experience with nausea.

### Comparison of exenatide with insulin

Exenatide therapy was also compared to insulin therapy as add-on to oral hypoglycemic agents. In a 26 week trial, 551 patients with Type 2 diabetes, who could not achieve adequate glycemic control with combination metformin and sulfonylurea therapy at maximally effective doses, were randomized to either adding exenatide 10 µg twice daily or insulin glargine once daily [24]. At the end of the study, both groups achieved similar improvements in glycemic control ([Table 1](#)). Self-monitored blood glucose profiles revealed that patients receiving insulin glargine had lower glucose levels at fasting ( $p < 0.001$ ), before meals (prelunch,  $p = 0.023$ ; predinner,  $p = 0.006$ ), and at 3:00 a.m. ( $p < 0.001$ ), but they had higher glucose levels after morning ( $p < 0.001$ ) and evening ( $p < 0.001$ ) meals than patients receiving exenatide. Patients receiving insulin glargine gained weight throughout the trial, while those receiving exenatide exhibited progressive reductions in body weight ([Table 1](#)).

Another randomized, open-label, crossover noninferiority study compared the efficacy of exenatide 10 µg twice daily and insulin glargine in 138 patients with Type 2 diabetes who could not achieve adequate glycemic control with metformin or sulfonylurea monotherapy [25]. The study included two 16-week treatment

periods. Both exenatide and insulin glargine treatments were associated with similar reductions from baseline in HbA<sub>1c</sub>. The upper limit of the 95% CI was below the *a priori* noninferiority margin of 0.4%, indicating the noninferiority of exenatide to insulin glargine. In contrast to the weight gain observed in subjects treated with insulin glargine, exenatide therapy was associated with progressive weight reduction ( $p < 0.001$  between treatments; **Table 1**). Insulin glargine treatment was associated with significantly lower premeal blood glucose concentrations compared with exenatide in the morning (mean difference, 29 mg/dl;  $p < 0.001$ ), at midday (mean difference, 16 mg/dl;  $p < 0.001$ ) and in the evening (mean difference, 11 mg/dl;  $p = 0.022$ ). In comparison, exenatide was associated with significantly lower 2-h postprandial glucose excursions (calculated as the difference between mean premeal and 2-h postprandial values) ( $p < 0.016$ ) and total daily mean glucose excursion ( $p < 0.001$ ) as compared with insulin glargine.

Exenatide was also compared to biphasic insulin aspart (30% rapid-acting insulin aspart) in addition to metformin and sulfonylurea in a 52-week trial [26]. Patients on metformin and a sulfonylurea were randomized to exenatide ( $n = 253$ ; 5  $\mu\text{g}$  b.i.d. for 4 weeks, 10  $\mu\text{g}$  thereafter) or biphasic insulin aspart ( $n = 248$ ; b.i.d. doses titrated for optimal glucose control), while continuing with metformin and sulfonylurea treatment. Patients treated with exenatide achieved similar improvement in glycemic control as those treated with biphasic insulin aspart (**Table 1**). The upper limit of the 95% CI was below the *a priori* noninferiority margin of 0.4%, indicating the noninferiority of exenatide to biphasic insulin. At week 52, the biphasic insulin group had significantly lower mean glucose values at prebreakfast ( $p = 0.037$ ), prelunch ( $p = 0.004$ ) and 3.00 a.m. ( $p = 0.002$ ). By contrast, exenatide-treated patients had lower 2-h postbreakfast ( $p < 0.001$ ) and postdinner ( $p < 0.001$ ) blood glucose concentrations. In addition, exenatide-treated patients had significantly greater reductions in postprandial glucose excursions following the morning ( $p < 0.001$ ), midday ( $p < 0.002$ ) and evening meals ( $p < 0.001$ ) than did patients treated with biphasic insulin. At the end of the study the exenatide group demonstrated a reduced body weight, while an increased weight was observed in the biphasic insulin group (**Table 1**).

The data of these trials suggest that exenatide induces a sustained reduction in HbA<sub>1c</sub>, that is significantly greater than with placebo and similar to what is achieved with insulin preparations. Furthermore, patients treated with exenatide exhibit a consistent weight loss, which becomes more evident when compared to the weight increase associated with insulin use.

#### Combination of exenatide with insulin

Currently, concomitant use of exenatide and insulin is not approved by regulatory agencies and is not recommended by the manufacturer, due to a lack of data. However, retrospective studies have evaluated the combination of exenatide and insulin. In a 26-week retrospective analysis, 52 patients were treated with exenatide 5  $\mu\text{g}$  twice daily as they were obese, had uncontrolled hyperglycemia and continued to gain weight despite being treated with a combination of oral hypoglycemic agents and insulin [27]. A total of 38 patients completed the follow-up taking exenatide regularly (group A); 14 patients discontinued exenatide owing to insurance, personal or economic reasons (group B). The HbA<sub>1c</sub> level decreased by 0.6% from 7.7 to 7.1% ( $p = 0.007$ ) in group A, while it remained unchanged at 8.4% in group B. Mean body weight decreased by 6.46 kg ( $p < 0.001$ ) in group A and increased by 2.4 kg in group B ( $p < 0.001$ ). In group A, the dosage requirements of short-acting insulins (insulin aspart, insulin lispro) and mixed insulin decreased from 50.4 to 36.6 units ( $p = 0.002$ ), and from 72.9 to 28.3 units ( $p = 0.02$ ), respectively. The mean systolic blood pressure in group A decreased from 129.9 to 120.7 mmHg ( $p = 0.02$ ). A subsequent retrospective study has evaluated the effectiveness of exenatide and insulin combination in 134 patients with a mean duration of follow-up of 14.6 months [28]. Exenatide use resulted in a significant 0.87% reduction in HbA<sub>1c</sub> ( $p < 0.001$ ) and a mean weight loss of 5.2 kg ( $p < 0.001$ ). Daily insulin dose was reduced from 63 to 58 units ( $p = \text{NS}$ ). A total of 14 patients (10%) experienced, mostly mild hypoglycemia. Lastly, a retrospective study on 188 patients has examined the effects of exenatide on glycemic control, body weight and insulin dose in patients with Type 2 diabetes treated with insulin [29]. This study included four duration intervals: 0–6, 6–12, 12–18 and 18–27 months. For the four time intervals, the mean changes in HbA<sub>1c</sub> were: -0.66% at 0–6 months ( $p < 0.001$ ); -0.55% at 6–12 months ( $p < 0.001$ ); -0.54% at 12–18 months ( $p = 0.019$ ); and -0.54% at 18–27 months ( $p = 0.020$ ). Mean weight significantly declined with increasing treatment duration ranging from -2.4 kg at 0–6 months to -5.5 kg at 18–27 months. The addition of exenatide to insulin was associated with reductions in prandial insulin requirements for treatment periods of up to 27 months, and in total insulin requirements for treatment periods of up to 12 months.

#### ■ Safety & adverse events

The most common adverse events associated with exenatide treatment are dose-dependent nausea, vomiting and diarrhea. In trials lasting 16–30 weeks, nausea was reported in 27–39% of subjects receiving exenatide

5 µg twice daily and in 28–59% of subjects receiving 10 µg twice daily [30]. Nausea was transient in nature during clinical trials, typically declining after 8 weeks, and, therefore, appeared not to have a causal relationship with reductions in weight, which were sustained for the duration of treatment. Vomiting was reported in 4–14% of subjects receiving exenatide 5 µg twice daily, and in 4–17% of subjects receiving 10 µg twice daily. Diarrhea was reported in approximately 11% of subjects receiving exenatide 5 µg twice daily, and in 3–17% of subjects receiving 10 µg twice daily [30].

Exenatide monotherapy is not associated with hypoglycemia as 5, 4 and 1% of patients in the exenatide 5- and 10-µg and placebo groups, respectively, reported hypoglycemia ( $p = \text{NS}$ ) [18]. Exenatide was associated with an increased risk for hypoglycemia when used in combination with sulfonylurea but not with metformin alone [19–21]. Exenatide stimulates insulin release and inhibits glucagon secretion in a glucose-dependent fashion so that the secretion of these two hormones is reduced when glucose levels become normal and glucagon release is not impaired during hypoglycemia. Thus, when exenatide is administered to metformin-treated patients, in which a minimal background hypoglycemia risk is expected, no increase in hypoglycemia is observed despite a lowering of HbA<sub>1c</sub>. The hypoglycemia observed when exenatide is used in combination with sulfonylurea seems most likely to be the result of an exenatide-induced improvement in glycemia superimposed upon the nonglucose-dependent actions of sulfonylurea. These findings suggest that a proactive approach to sulfonylurea dose management may limit the incidences of hypoglycemia when exenatide is added to sulfonylurea therapy.

In clinical trials lasting 16–30 weeks, 27–49% of patients treated with exenatide developed antibodies at low titer. For the majority of patients who developed antibodies, the positivity for anti-exenatide antibodies had no predictive effect on the magnitude of an individual's glycemic response or the incidence of adverse events. High-titer antibodies developed in 6% of patients, and half of those patients (3% of the study group receiving exenatide) had a decreased response to glucose-lowering effect exenatide [30].

Hemorrhagic or necrotizing pancreatitis associated with exenatide therapy have been reported to the US FDA. Between June 2005 and July 2007, the cumulative spontaneous reporting rate of acute pancreatitis was 0.20 events per 1000 patient-years of exposure [31]. Information regarding acute pancreatitis risk was added to the exenatide product label in the USA in 2007. Data regarding pancreatitis need to be evaluated in light of the fact that patients with Type 2 diabetes have a three-fold greater likelihood of developing pancreatitis

than individuals without diabetes. A recent study based on insurance records demonstrates that the risk of pancreatitis for subjects followed up to 1 year is 0.13% and that the relative risk is not significantly different from that of a control cohort treated with metformin or glibenclamide [31]. Patients at a high risk for experiencing acute pancreatitis while receiving exenatide include subjects with a history of gall stones, hypertriglyceridemia and excess alcohol intake. The FDA has advised clinicians to instruct their patients to seek immediate medical attention if these symptoms commence suddenly while receiving exenatide.

### Long-acting exenatide

#### ■ Phase II trials

A long-acting release formulation of exenatide (exenatide LAR) has been developed for use as a once-weekly injection. This sustained-release formulation consists of injectable microspheres of exenatide and poly(D,L-lactic-co-glycolic acid), a common biodegradable medical polymer with established use in absorbable sutures and extended release pharmaceuticals, that allows gradual drug delivery at a controlled rate [32].

In a Phase II study, exenatide LAR (0.8 or 2.0 mg) was administered subcutaneously for 15 weeks to 45 patients with Type 2 diabetes who were inadequately controlled with metformin and/or diet and exercise [32]. Exenatide LAR reduced HbA<sub>1c</sub> by -1.4% (0.8 mg) and -1.7% (2.0 mg), compared with +0.4% with placebo LAR ( $p < 0.0001$  for both vs placebo LAR). Exenatide LAR reduced self-monitored postprandial hyperglycemia, with the magnitude of postprandial excursions decreased by as much as fourfold with 2.0 mg exenatide LAR compared with placebo LAR. Body weight decreased in the exenatide LAR 2.0-mg group, with a reduction of -3.8 kg ( $p < 0.05$ ), whereas it was unchanged with both placebo LAR and exenatide LAR 0.8 mg.

#### ■ Phase III trials

A 30-week, randomized, comparator-controlled, noninferiority study (Diabetes Therapy Utilization: Researching Changes in A<sub>1c</sub>, Weight and Other Factors Through Intervention with Exenatide Once Weekly [DURATION-1]), has assessed the efficacy, safety and tolerability of exenatide LAR (2 mg) compared with exenatide 10 µg administered twice daily in 295 patients with Type 2 diabetes [33]. The patients were naive to drug therapy, or on treatment with metformin, a sulfonylurea, a thiazolidinedione or any combination of two of these agents. Treatment with exenatide LAR induced a significantly greater reduction in HbA<sub>1c</sub> as compared with exenatide twice daily ( $p = 0.0023$ ; Table 2). More patients treated with exenatide LAR achieved target

Table 2. Phase III studies with exenatide LAR: overview of key efficacy and safety data.

Study	Description/patients randomized/combination therapy	Comparators	$\Delta$ HbA <sub>1c</sub> (%)	$\Delta$ Fasting glucose (mg/dl)	$\Delta$ Body weight (kg)	$\Delta$ SBP (mmHg)	Nausea (% of patients)	Ref.
DURATION-1	30-week, randomized, open-label, comparator-controlled, noninferiority study 295 patients on OADs Metformin, SU, thiazolidinedione, or any combination of two of these agents	Exenatide b.i.d.	-1.5	-25	-3.6	-3.4	26.4	[33]
		Exenatide LAR	-1.9	-41	-3.7	-4.7	34.5	
DURATION-2	26-week randomized, double-blind, double-dummy, superiority study 491 patients on OADs Metformin	Pioglitazone 45 mg	-1.2	-27	+2.8	-2.0	5	[34]
		Sitagliptin 100 mg	-0.9	-16	-0.8	+0.3	10	
		Exenatide LAR	-1.5	-32	-2.3	-3.7	24	
DURATION-3	26-week, open-label, randomized, parallel study 456 patients on OADs Metformin and/or SU	Insulin glargine	-1.3	-38	+1.4	-1	1	[35]
		Exenatide LAR	-1.5	-50	-2.6	-3	13	

b.i.d.: Twice daily; HbA<sub>1c</sub>: Glycosylated hemoglobin; LAR: Long-acting release; OAD: Oral antidiabetic drug; SBP: Systolic blood pressure; SU: Sulfonylurea.

levels of HbA<sub>1c</sub> above 7% as compared to those who received exenatide twice daily (77 vs 61%, respectively;  $p = 0.0039$ ). Reductions in body weight were similar in both treatment groups ( $p = 0.89$ ; [Table 2](#)). Patients in both groups had similar, significant improvements in systolic ([Table 2](#)) and diastolic blood pressure (exenatide LAR: -1.7 mmHg; exenatide b.i.d.: -1.7 mmHg).

In the 26-week randomized, double-blind, superiority trial DURATION-2, exenatide LAR was compared to maximum approved doses of sitagliptin (100 mg) and pioglitazone (45 mg) in 491 patients with Type 2 diabetes not adequately controlled with metformin [34]. Treatment with exenatide LAR resulted in a significantly greater reduction in HbA<sub>1c</sub> than pioglitazone or sitagliptin ( $p = 0.016$  and  $p < 0.0001$ , respectively; [Table 2](#)). In all measurements of the six-point self-monitored blood glucose profile, reductions at week 26 were significantly greater with exenatide than with sitagliptin, but not with pioglitazone. Exenatide LAR treatment resulted in a significantly greater reduction in body weight than pioglitazone and sitagliptin ( $p < 0.0001$  and  $p = 0.0002$ , respectively; [Table 2](#)). Exenatide LAR treatment resulted in a significantly greater reduction in systolic blood pressure than sitagliptin, whereas no difference was observed between exenatide LAR and pioglitazone ([Table 2](#)).

In the 26-week randomized, open-label trial DURATION-3, exenatide LAR was compared with insulin glargine in subjects with Type 2 diabetes who had not adequately glycemic control despite use of maximum tolerated doses of metformin or combined metformin and sulfonylurea [35]. Treatment

with exenatide LAR resulted in a significantly greater reduction in HbA<sub>1c</sub> than insulin glargine ( $p = 0.017$ ; [Table 2](#)). Fasting plasma glucose levels were reduced in both groups; however, reduction was greater with insulin glargine ( $p = 0.001$ ). Patients receiving insulin glargine had lower glucose concentrations at 3:00 a.m. ( $p = 0.022$ ) and before breakfast ( $p < 0.0001$ ) than did those treated with exenatide LAR, whereas subjects treated with exenatide LAR had lower glucose concentrations after dinner ( $p = 0.004$ ) than those treated with insulin glargine. Exenatide LAR treatment resulted in a statistically significant reduction in body weight, whereas insulin glargine treatment was associated with a progressive increase ( $p < 0.0001$ ; [Table 2](#)).

#### ■ Safety & adverse events

Gastrointestinal complaints, including nausea, vomiting and diarrhea, were the most commonly reported adverse effects with exenatide LAR. No episodes of pancreatitis were reported [32–35]. In the DURATION-1 study, injection site pruritus was more commonly reported by subjects in the exenatide LAR group versus the twice-daily exenatide group (17.6 vs 1.4%); however, it was typically mild in intensity, and resolved with continued exenatide treatment [33]. There were no episodes of major hypoglycemia with exenatide LAR treatment, irrespective of background sulfonylurea use, and the incidence of minor hypoglycemia was low, with most cases of minor hypoglycemia limited to patients using concomitant sulfonylurea therapy (14.5% for exenatide LAR, and 15.4% mmHg for exenatide b.i.d.) [33–35]. In the DURATION-3 trial, minor hypoglycemia was

reported in 8% of patients treated with exenatide LAR as compared with 26% of patients treated with insulin glargine [35]. Anti-exenatide antibody levels were detected in 48–56% of patients on exenatide LAR, but the presence of antibodies to exenatide was not predictive of treatment response [33–35].

### Liraglutide

#### ■ Phase II trials

Liraglutide is a human acylated analog of GLP-1, with 97% amino acid sequence homology to the endogenous gut hormone that binds noncovalently to albumin. The modifications include an amino acid substitution (replacement of lysine with arginine at position 34) and an attachment of a C16 acyl chain via a glutamoyl spacer to lysine at position 26. The half-life of liraglutide has been estimated to be 13 h in patients with Type 2 diabetes, which makes it suitable for once-daily administration [36].

In an early, 1-week, randomized double-blind, placebo-controlled cross-over Phase II clinical trial carried out in 13 patients with Type 2 diabetes, it was demonstrated that liraglutide (6 µg/kg administered subcutaneously once daily) significantly reduced blood glucose during a 24-h test period ( $p = 0.01$ ) [37]. Liraglutide exposure significantly reduced daily glucagon levels ( $p = 0.04$ ), endogenous glucose release ( $p = 0.04$ ), and increased first phase insulin secretion. The fasting proinsulin:insulin ratio and the proinsulin:insulin ratio after the breakfast meal were markedly reduced during liraglutide administration ( $p < 0.01$ ). A randomized 12-week study, carried out in 190 patients, examined the effect of fixed-doses of liraglutide (0.045, 0.225, 0.45, 0.60 or 0.75 mg), compared with a sulfonylurea (glimepiride 1–4 mg) or placebo [38]. Treatment with liraglutide resulted in a dose-dependent reduction in HbA<sub>1c</sub>. Treatment with the two highest doses (0.60 or 0.75 mg) reduced HbA<sub>1c</sub> significantly more than placebo ( $p < 0.001$ ), whereas the effect of liraglutide was comparable with that of glimepiride. The proinsulin:insulin ratio decreased in the 0.75 mg liraglutide group (-0.18;  $p = 0.0244$ ) compared with placebo. No change in the proinsulin:insulin ratio was demonstrated after treatment with glimepiride. Body weight decreased by 1.2 kg with liraglutide 0.45 mg compared with placebo ( $p < 0.018$ ). An additional two studies with liraglutide (doses ranging from 0.045 to 0.75 mg/day) of 12 and 8 weeks, respectively, demonstrated improved glycemic control but indicated that higher doses of liraglutide needed to be investigated [39,40]. In a randomized double-blind trial, higher doses of liraglutide (0.65, 1.25 or 1.9 mg/day) as monotherapy were compared with placebo over 14 weeks in 163 patients with Type 2 diabetes [38]. Liraglutide treatment resulted in significant reductions from baseline

in HbA<sub>1c</sub> (-1.45, -1.40 and -0.98% for 1.90, 1.25 or 0.65 mg, respectively;  $p < 0.0001$ ) as compared with placebo (+0.29%). Body weight decreased in all treatment groups, with a maximum loss in the 1.90 mg liraglutide group (-1.21 kg vs placebo;  $p = 0.039$ ). There was a significant reduction in fasting glucagon concentrations in the liraglutide 1.90 mg group compared with placebo (-3.26 pmol/l;  $p = 0.049$ ). The median reduction from baseline in proinsulin:insulin ratio was significant for all three liraglutide groups versus placebo (1.90:-0.19 mg,  $p = 0.0111$ ; 1.25:-0.28 mg,  $p = 0.0062$ ; and 0.65:-0.15 mg,  $p = 0.0218$ ). Reductions in systolic blood pressure were also observed with the three doses of liraglutide (1.90 mg vs placebo -7.9 mmHg,  $p = 0.0023$ ; 1.25 mg vs placebo -5.2 mmHg,  $p = 0.041$ ; 0.65 mg vs placebo -7.4 mmHg,  $p = 0.0041$ ). In the same study,  $\beta$ -cell function, assessed by an insulin-modified frequently sampled intravenous glucose tolerance test, was evaluated in a subgroup of patients ( $n = 39$ ) before and after the 14-week treatment period [39]. The two highest doses of liraglutide (1.25 and 1.9 mg/day) significantly increased first-phase insulin secretion by 118 and 103%, respectively ( $p < 0.05$ ).

#### ■ Phase III trials

The Liraglutide Effect and Action in Diabetes (LEAD) Phase III trials, including more than 4000 patients, were designed to investigate liraglutide as monotherapy or in combination with various oral antidiabetic drugs, and to compare it with some other antidiabetic therapies commonly used in the treatment of Type 2 diabetes [41]. Thus, the LEAD program investigated liraglutide use across the continuum of care of Type 2 diabetes.

#### Liraglutide monotherapy

The 52-week LEAD-3 trial compared liraglutide monotherapy with glimepiride monotherapy in 746 patients suboptimally controlled with diet and exercise or oral antidiabetic drug monotherapy [42]. Liraglutide (1.2 or 1.8 mg/day) was more effective than glimepiride in reducing HbA<sub>1c</sub> level (Table 3). The proinsulin:insulin ratio and HOMA- $\beta$  demonstrated no significant difference between treatments. Moreover, a sustained weight reduction was observed with liraglutide monotherapy; conversely weight gain was observed with glimepiride ( $p = 0.0001$ ; Table 3). Systolic blood pressure was also significantly reduced in the liraglutide 1.8 mg arm as compared with the glimepiride arm ( $p < 0.01$ ; Table 3).

#### Combination therapy of liraglutide with oral antidiabetic agents

In the 26-week LEAD-2 trial, 1091 patients not adequately controlled with oral antidiabetic therapy were assigned to once-daily liraglutide (either 0.6, 1.2 or



Table 3. Phase III studies with liraglutide: overview of key efficacy and safety data.

Study	Description/patients randomized/combination therapy	Comparators	Δ HbA <sub>1c</sub> (%)	Δ Fasting glucose (mg/dl)	Δ Body weight (kg)	Δ SBP (mmHg)	Nausea (% of patients)	Ref.
LEAD-1	26-week double-blind, double-dummy, randomized, active-controlled, five-armed parallel study 1041 patients on OADs Glimepiride (2–4 mg/day)	Liraglutide 0.6 mg	-0.60	-13	+0.7	-0.9	5.1	[45]
		Liraglutide 1.2 mg	-1.08	-28	+0.3	-2.6	10.5	
		Liraglutide 1.8 mg	-1.13	-29	-0.2	-2.8	6.8	
		Rosiglitazone 4 mg	-0.44	-16	+2.1	-0.9	2.6	
		Placebo	+0.23	+18	-0.1	-2.3	1.8	
LEAD-2	26-week double-blind, double-dummy, randomized, placebo- and active-controlled, parallel-group study 1091 patients on OADs Metformin (1 g b.i.d.)	Liraglutide 0.6 mg	-0.69	-20	-1.8	-0.6	11	[43]
		Liraglutide 1.2 mg	-0.97	-29	-2.6	-2.8	16	
		Liraglutide 1.8 mg	-1.00	-30	-2.8	-2.3	19	
		Glimepiride 4 mg	-0.98	-23	+1.0	+0.4	3	
		Placebo	+0.09	+7	-1.5	-1.8	4	
LEAD-3	52-week double-blind, double-dummy, randomized, active-controlled, parallel-group study 746 patients on diet/exercise or OADs	Liraglutide 1.2 mg	-0.84	-15	-2.1	-2.1	27	[42]
		Liraglutide 1.8 mg	-1.14	-25	-2.5	-3.6	29	
		Glimepiride 8 mg	-0.51	-5	+1.1	-0.7	8	
LEAD-4	26-week double-blind, randomized, placebo-controlled, parallel-group study 533 patients on OADs Metformin (1 g b.i.d.) and rosiglitazone (4 mg b.i.d.)	Liraglutide 1.2 mg	-1.5	-40	-1.0	-6.7	29	[46]
		Liraglutide 1.8 mg	-1.5	-44	-2.0	-5.6	40	
		Placebo	-0.5	+8	+0.6	-1.1	9	
LEAD-5	26-week randomized, placebo-controlled, parallel-group study 581 patients on OADs Metformin (1 g b.i.d.) and glimepiride (4 mg/day)	Liraglutide 1.8 mg	-1.33	-1.81	-1.8	-4.0	13.9	[47]
		Insulin glargine	-1.09	+1.62	+1.6	+0.5	1.3	
		Placebo	-0.24	-0.42	-0.4	-1.4	3.5	
LEAD-6	26-week open-label, randomized, active-controlled, parallel-group study 464 patients on metformin and/or SU Background treatment maintained	Liraglutide 1.8 mg	-1.12	-29	-3.2	-2.5	25.5	[48]
		Exenatide 10 µg b.i.d.	-0.79	-11	-2.8	-2.0	28	
Liraglutide vs sitagliptin	26-week open-label, randomized, active-comparator, parallel-group study 665 patients on OADs Metformin	Liraglutide 1.2 mg	-1.24	-33	-2.8	-0–5	21	[49]
		Liraglutide 1.8 mg	-1.50	-38	-3.3	-0.7	27	
		Sitagliptin 100 mg	-0.90	-15	-0–9	-0.9	5	

b.i.d.: Twice daily; HbA<sub>1c</sub>: Glycosylated hemoglobin; OAD: Oral antidiabetic drug; SBP: Systolic blood pressure; SU: Sulfonylurea.

1.8 mg), placebo, or glimepiride (4 mg/day) [43]. All treatments were in combination therapy with metformin (1 g b.i.d.). Liraglutide (1.2 or 1.8 mg/day) was as effective as glimepiride in reducing HbA<sub>1c</sub> level (Table 3). Liraglutide treatments were associated with improvements in HOMA-β index (end-of-study values were 63, 70 and 71% for the liraglutide 0.6, 1.2 and 1.8 mg groups from baseline values of 40, 47 and 43%, respectively) as compared with placebo (baseline and end-of-study values were 45 and 43%, respectively). The glimepiride

group demonstrated a similar improvement in the mean HOMA-β value to 68% from a baseline value of 43%. Similar decrease in the proinsulin:insulin ratio from baseline was observed in the three liraglutide groups as compared with the glimepiride group. Weight reduction was observed with liraglutide therapy compared with a weight gain with glimepiride ( $p = 0.0001$  for both; Table 3). In addition, the liraglutide 1.2 and 1.8 mg groups exhibited significant reductions in systolic blood pressure ( $p = 0.04$  and  $p = 0.01$ , respectively; Table 3).

Dual-energy x-ray absorptiometry and computerized tomography substudies performed within LEAD-2 and -3 trials demonstrated that reductions in body weight with liraglutide were mainly due to a decrease in fat tissue, and that both abdominal subcutaneous and visceral adipose tissues were reduced [44].

In the 26-week LEAD-1 trial, 1041 patients not adequately controlled with oral antidiabetic therapy were assigned to once-daily liraglutide (0.6, 1.2 or 1.8 mg), placebo or rosiglitazone (4 mg/day), all receiving glimepiride (2–4 mg/day) [45]. All liraglutide doses induced significant decreases in HbA<sub>1c</sub> as compared to placebo ( $p < 0.0001$ ; **Table 3**), while only the two higher liraglutide doses were also superior to rosiglitazone ( $p < 0.0001$ ; **Table 3**). The HOMA- $\beta$  index increased with liraglutide (end-of-study values were 70, 99 and 91% for the liraglutide 0.6, 1.2 and 1.8 mg groups from baseline values of 51, 71 and 56%, respectively) compared with rosiglitazone (baseline and end-of-study values were 56 and 52%, respectively;  $p < 0.05$  vs liraglutide 1.2 or 1.8 mg). Reductions in the proinsulin:insulin ratio were greater with both liraglutide 1.2 and 1.8 mg as compared with either rosiglitazone or placebo ( $p \leq 0.02$ ). Body weight was reduced in subjects receiving liraglutide 1.8 mg ( $p < 0.0001$  vs rosiglitazone; **Table 3**), while increases occurred with either liraglutide 1.2 mg or rosiglitazone.

In the 26-week LEAD-4 trial, 533 patients not adequately controlled with oral antidiabetic therapy were assigned to treatment with once-daily liraglutide (1.2 or 1.8 mg) or placebo in combination with metformin (1 g b.i.d.) and rosiglitazone (4 mg b.i.d.) [46]. Liraglutide produced a greater reduction in HbA<sub>1c</sub> levels as compared with placebo group ( $p < 0.0001$ ; **Table 3**). Both liraglutide arms had significant improvements (increase of 27% for both arms) in HOMA- $\beta$  index compared with an improvement in the placebo group of 6% ( $p < 0.0001$  for both arms vs placebo). A significant decrease in the proinsulin:insulin ratio occurred with liraglutide as compared with placebo ( $p < 0.05$ ). Treatment with liraglutide was associated with a significant reduction in body weight as compared with placebo ( $p < 0.0001$ ; **Table 3**). The liraglutide 1.2 and 1.8 mg groups exhibited significant reductions in systolic blood pressure compared with placebo ( $p = 0.0009$ ; **Table 3**).

#### Comparison of liraglutide with insulin

In the 26-week LEAD-5 trial, the efficacy of liraglutide (1.8 mg/day) was compared to that of insulin glargine, both in combination with metformin and glimepiride, in 581 patients with Type 2 diabetes not adequately controlled with oral antidiabetic therapy [47]. Patients treated with liraglutide 1.8 mg exhibited a greater

reduction in HbA<sub>1c</sub> than those treated with insulin glargine ( $p = 0.001$ ; **Table 3**). The proinsulin:C-peptide ratio demonstrated a significant improvement in the liraglutide group compared with the insulin glargine group ( $p = 0.0019$ ). Liraglutide treatment resulted in significant weight loss compared with an increased weight in the insulin glargine group ( $p = 0.0001$ ; **Table 3**). A significant reduction in systolic blood pressure was observed with liraglutide compared with an increase with insulin glargine ( $p = 0.0001$ ; **Table 3**).

#### Comparison of liraglutide with exenatide

In the 26-week LEAD-6 trial carried out in 464 subjects with Type 2 diabetes inadequately controlled on maximally tolerated doses of metformin and/or sulfonylurea, the efficacy of liraglutide (1.8 mg/day) was assessed in a head-to-head comparison with exenatide (10  $\mu$ g b.i.d.) both in combination with metformin and/or sulfonylurea [48]. Liraglutide reduced HbA<sub>1c</sub> significantly more than exenatide ( $p < 0.0001$ ; **Table 3**). Increases of HOMA- $\beta$  index were significantly greater for the liraglutide (32.1%) than for the exenatide (2.7%;  $p < 0.0001$ ) group. The proinsulin:insulin ratio demonstrated no significant differences between treatments. Both drugs promoted similar weight losses (**Table 3**).

#### Comparison of liraglutide with the DPP-4 inhibitor sitagliptin

A 26-week trial was aimed to assess the efficacy of liraglutide (1.2 or 1.8 mg/day) versus sitagliptin (100 mg/day) as adjunct treatments in 665 subjects with Type 2 diabetes inadequately controlled with metformin monotherapy [49]. Treatments with liraglutide resulted in a significant HbA<sub>1c</sub> reductions as compared with sitagliptin ( $p < 0.0001$  for both doses of liraglutide; **Table 3**). Treatment with liraglutide was associated with significant improvements in HOMA- $\beta$  index: change from baseline +28% for liraglutide 1.8 mg; +27% for liraglutide 1.2 mg, and +4% for sitagliptin ( $p < 0.0001$  for both doses of liraglutide). Liraglutide treatment resulted in a significant improvement in the proinsulin:insulin ratio as compared with sitagliptin ( $p = 0.0004$ ). Body weight loss was significantly greater with liraglutide than with sitagliptin ( $p < 0.0001$  for both doses of liraglutide; **Table 3**).

Overall, Phase III trials demonstrate that liraglutide provides sustained HbA<sub>1c</sub> reductions in monotherapy and in combination with other antidiabetic therapies. Treatment with liraglutide is associated with weight loss, reduction in fat tissue, and both abdominal subcutaneous and visceral adipose tissues. In addition, liraglutide was found to be associated with a reduction in systolic blood pressure.

### ■ Safety & adverse events

The most common adverse events associated with liraglutide treatment were gastrointestinal disturbances, such as nausea, vomiting and diarrhea. Nausea was observed in 5–40% of patients, vomiting in 4–17% of patients, and diarrhea in 7–19% of patients [41–49]. The majority of gastrointestinal adverse events were mild and transient, and tended to decrease after 4 weeks of treatment. In the LEAD-6 trial, nausea resolved more quickly in patients treated with liraglutide than in those treated with exenatide [48]. By week 6, the proportion of participants having nausea in the liraglutide group was 8.1 versus 15.8% for exenatide, and at week 26, only 2.5% of the liraglutide group had nausea compared with 8.6% of the exenatide group. Five cases of pancreatitis have been reported in the LEAD program (one of them in a subject enrolled in the glimepiride arm of the LEAD-2 study) with an incidence rate comparable to that expected in a Type 2 diabetes population [41–51]. Liraglutide stimulates insulin secretion and inhibits glucagon secretion in a glucose-dependent manner so that its action on the regulation of the release of these two hormones diminishes as glucose levels become normal and are not present during hypoglycemia. Therefore, few minor and major hypoglycemic episodes have been reported with liraglutide across the LEAD studies. The rate of minor hypoglycemic episodes was 0.03–1.9 hypoglycemic events per patient annually [41–50]. Data from preclinical studies in rodents suggested that liraglutide was associated with an increased risk of thyroid C-cell focal hyperplasia and C-cell tumors. However, thyroid C-cell adenomas have not been reported in clinical trials. In the LEAD-3 trial, after 52 weeks, concentrations of calcitonin, a hormone secreted by thyroid C cells that is used clinically as a biomarker for the detection of medullary thyroid cancer, did not differ in participants taking liraglutide and those taking glimepiride after 52 weeks of treatment [42]. Furthermore, data from extension of LEAD-3 trial did not reveal any notable difference in mean calcitonin levels between liraglutide and control groups over 2 years follow-up [50]. In the LEAD-6 trial, small decreases in calcitonin occurred during the trial in both liraglutide and exenatide arms, without a significant difference between the groups at any time point [48].

Finally, liraglutide treatment was associated with low antibody formation, with <8.6% of patients demonstrating an increase in liraglutide antibodies across the LEAD trials. The presence of the antibodies do not appear to influence liraglutide efficacy or the incidence of adverse events [41–50].

## Albiglutide

### ■ Phase II trials

Albiglutide has been developed fusing a human GLP-1 dimer to recombinant human albumin. This structure

results in an extended half-life, while a single alanine to glycine amino acid substitution at position 8 renders the molecule resistant to DPP-4 degradation [52,53]. Preclinical studies have demonstrated circulating  $t_{1/2}$  values of 11 h in mice and of approximately 3 days in monkeys [53]; while Phase I studies in humans suggest a geometric mean half-life ranging from 6 to 8 days [54]. The long half-life of albiglutide makes it suitable for a once weekly dosing schedule.

A first Phase IIa, randomized, single-blind, placebo-controlled parallel-assignment, clinical trial assessed the effects of albiglutide 9, 16 and 32 mg injected subcutaneously at days 1 and 8 in 54 subjects with Type 2 diabetes [55]. To avoid confounding results with other antidiabetic medications, subjects on metformin only, sulfonylurea only or metformin plus sulfonylurea underwent a 2-week wash-out period before randomization. A significant dose-dependent reduction of plasma glucose levels was observed on day 2 and 9. Similarly, placebo-adjusted  $AUC_{0-24h}$  was also reduced in a dose-dependent manner in the albiglutide cohorts on day 2 and 9. In addition a modest, dose-independent reduction in glucagon concentrations was observed, while no trends were detected for insulin or C-peptide levels. Albiglutide was readily absorbed and the median  $T_{max}$  was reached 3–5 days after administration, with no clear dose-dependency. Drug accumulation analysis demonstrated that it accumulates slowly, suggesting that dose-titration strategies may not be necessary to improve tolerability. The same researchers performed a complementary injection site study in which 46 individuals with Type 2 diabetes were randomized to receive albiglutide 16 or 64 mg in the arm, leg or abdomen, and report no significant effects of injection site on the parameters examined [55]. In a subsequent Phase II, 16-week, double-blind, placebo- and active-controlled, parallel-assignment clinical trial, 356 subjects with Type 2 diabetes were randomized into one of ten treatment arms: double-blind placebo, albiglutide with weekly injection (at 4, 15 or 30 mg doses), albiglutide every 2 weeks at the same doses, albiglutide monthly at 50 or 100 mg dose; or open-label exenatide (5  $\mu$ g subcutaneously, b.i.d. for 4 weeks, followed by 10  $\mu$ g subcutaneously, b.i.d. for 12 weeks) [56]. The exenatide arm was included to provide a clinical reference; however, no formal statistical comparisons between albiglutide and exenatide were performed. Fasting plasma glucose levels were reduced in all albiglutide groups at week 2. A reduction in fasting plasma glucose was also observed in the exenatide and placebo groups. At week 16, significant reductions in fasting plasma glucose levels compared with placebo were observed in the albiglutide cohorts. Subjects in the monthly cohorts, however, did not show stable plasma glucose reduction between dose and presented higher gastrointestinal event rates.

Fasting insulin and glucagon levels were not significantly altered in any albiglutide arm, but small improvements in  $\beta$ -cell function, assessed by the HOMA- $\beta$  index, were observed in subjects receiving albiglutide, as well as in those receiving exenatide as compared to placebo. The average weight loss for patients receiving albiglutide was 1.1–1.7 kg, compared with 0.7 kg for the placebo cohort, while the exenatide treatment group demonstrated a 2.4 kg reduction. Furthermore, after 16 weeks, HbA<sub>1c</sub> levels in the albiglutide cohorts decreased in a generally dose-dependent manner, with significant changes in the 30 mg once weekly, 50 mg every 2 weeks and 100 mg monthly cohorts; a decrease was also observed in the exenatide cohort (-0.54%). The proportion of patients who achieved the American Diabetes Association target of HbA<sub>1c</sub> levels of <7% increased dose dependently within each dosing schedule. A greater proportion of patients receiving albiglutide at doses of 30 mg once weekly, 50 mg every 2 weeks and 100 mg monthly achieved the American Diabetes Association HbA<sub>1c</sub> target (52, 53 and 48%, respectively) compared with patients receiving placebo (20%) or exenatide (35%).

Finally, a randomized, single-blind, placebo-controlled Phase I/II study examined the safety, pharmacokinetics and pharmacodynamics of albiglutide in 40 Japanese subjects with Type 2 diabetes [57], treated with diet only or with a single oral antihyperglycemic drug (other than thiazolidinedione). Patients were randomized to receive albiglutide 15 mg weekly, 30 mg weekly, 50 mg every other week, 100 mg every 4 weeks or placebo. Although the treatment period ended on day 29, patients were followed for 5 additional weeks. At the end of the study (day 29) fasting plasma glucose was significantly reduced in all treatment groups from baseline, although the reduction was not significant in the 100 mg monthly group compared to placebo. Furthermore for all groups, except the 100 mg monthly, the reduction of fasting plasma glucose levels remained significant at follow-up (day 43). Greater fluctuations in glucose levels were observed in the biweekly and monthly dosing groups. HbA<sub>1c</sub> was also significantly improved from baseline compared with placebo in all treatment groups on day 29 and 2 weeks after the end of the treatment. No clinically significant changes in insulin C-peptide were observed, while there were dose-independent changes in glucagon levels, free fatty acid concentration and glycosylated albumin. A general dose-independent reduction in body weight was observed, with the largest effect seen in the 50 mg biweekly group.

#### ■ Safety & tolerability

Results from Phase II clinical trials suggest that albiglutide has a favorable safety and tolerability profile [55–57]. In a first Phase II study, the most common adverse events in albiglutide-treated subjects were headache

and nausea (14 and 12%, respectively). Two subjects on albiglutide developed skin rashes. No hypoglycemic events occurred in any subject and no clinically significant event, including ECG abnormalities, was observed during the trial period [55]. In a second larger Phase II trial on 356 subjects with Type 2 diabetes [56] the most frequent adverse events for all groups included nausea, vomiting, headache, dizziness, nasopharyngitis, back pain, influenza, upper respiratory tract infections and local skin reaction. Hypoglycemia was identified in patients in all groups, with no increase observed in the albiglutide cohorts (0–3.1%) compared with the placebo (3.9%) and exenatide (2.9%) groups. The lowest rate of gastrointestinal adverse events was observed in the cohorts receiving albiglutide  $\leq$ 30 mg; in the 30 mg once weekly cohort, 29.0% of patients experienced nausea and/or vomiting compared with 54.3% in the 50 mg every 2 weeks and 55.9% in the 100 mg monthly groups; 45.7% of patients receiving exenatide experienced gastrointestinal adverse events. Skin reactions generally small, transient and localized at the injection site were more common in the albiglutide cohorts (2.9–28.6%) compared with the placebo (5.9%) and exenatide (2.9%) groups. Anti-albiglutide antibodies were detected in eight patients, including one receiving placebo and two at baseline prior to albiglutide treatment. The appearance of antibodies was transient, with only one patient remaining antibody positive at week 27. The antibodies detected at low titers in the five patients receiving albiglutide treatment were non-neutralizing and, in four of them, demonstrated cross-reactivity with GLP-1. No obvious association between antibody detection and drug efficacy or safety was observed [56].

Overall, no cases of acute pancreatitis have been reported in clinical trials with albiglutide [51,54–57] and the incidence of gastrointestinal-related adverse events seem slightly lower than the one observed with other GLP-1 mimetics. This finding may have several explanations, including the more gradual change in plasma concentration compared to short-acting GLP-1 agonists or to the lack of a combined effect of central and peripheral stimulation of the brain centers responsible for nausea or to the fact that albiglutide plasma levels remain below the threshold for GLP-1 receptor activation for nausea.

#### ■ Phase III trials

According to the NIH trial registry, eight Phase III trials are currently ongoing [101]. A 52-week trial is investigating the long-term safety and efficacy profile of two different doses of albiglutide in patients with Type 2 diabetes. In addition, a 42-day trial examining the pharmacokinetics and safety of albiglutide in patients with varying degrees of renal function is at the recruitment

stage. The results of these two trials will begin to shed light on questions regarding the use of albiglutide long term and in special patients as those with severe renal impairment. Two additional trials that will compare the safety and efficacy of albiglutide with insulin glargine and liraglutide, respectively, are in progress. Intended outcomes of these studies include change in HbA<sub>1c</sub>, fasting plasma glucose and body weight from baseline to study end. Several additional trials examining the use of albiglutide as combination therapy are at various stages of recruitment.

### Taspoglutide

#### ■ Phase II trials

Taspoglutide is a 30-amino acid peptide derivative of native GLP-1 with aminoisobutyric substitutions at position 8 and 35. These modifications were designed to sterically hinder not only the DPP-4 cleavage site at position 8, but also cleavage sites at position 34 and 35, recognized by additional serine proteases, including plasmin and plasma kallikrein [58]. A first randomized, double-blind, parallel group, placebo-controlled multicenter Phase IIb study evaluated the efficacy of taspoglutide in 306 patients with Type 2 diabetes inadequately controlled on metformin (baseline HbA<sub>1c</sub>, 7.9%) [59]. The subjects were randomized to receive taspoglutide (5, 10 or 20 mg once weekly or 10 or 20 mg once every 2 weeks) as add-on therapy or placebo for 8 weeks. Taspoglutide reduced HbA<sub>1c</sub> and fasting plasma glucose values after 1 week from the beginning of the treatment, and at the end of the treatment a statistically significant decrease was observed in the weekly treated cohorts; while with the biweekly administration a rebound of fasting plasma glucose levels was observed. Nevertheless, the decrease reported in the 20 mg biweekly cohort was still statistically significant. In addition, mean fasting C-peptide concentrations increased in all treatment arms, although only the 10 mg biweekly change reached statistical significance ( $p = 0.009$ ). The fasting proinsulin:insulin ratio decreased in all taspoglutide cohorts, with the 10 mg weekly, 20 mg weekly and 10 mg biweekly groups demonstrating statistically significant reductions. A second Phase II trial evaluated the efficacy of 8 weeks with high-doses of taspoglutide in subjects with Type 2 diabetes ( $n = 133$ ) on stable metformin therapy [60]. The uptitration scheme consisted of an initial dose of taspoglutide 20 mg injected subcutaneously once weekly for 4 weeks, followed by 4 weeks of 20 (20/20 cohort), 30 (20/30 cohort) or 40 mg (20/40 cohort) once-weekly. Exposure to taspoglutide appeared dose-proportional and time-dependent and, at the end of the 8 weeks, plasma concentrations were 44.4, 84.2 and

109.7 pmol/l for the 20/20, 20/30 and 20/40 cohorts, respectively. HbA<sub>1c</sub> levels were significantly reduced in all taspoglutide-treated cohorts, and the percentage of subjects achieving the ADA target of HbA<sub>1c</sub> levels of below 7% was 72, 53 and 70% in the 20/20, 20/30 and 20/40 taspoglutide cohorts, respectively, as compared to 19% in the placebo-treated subjects. Fasting plasma glucose levels were also significantly decreased by all taspoglutide cohorts, and body weight decreased progressively in the taspoglutide arms during the whole treatment period, with a decrease from baseline of -2.1, -3.0 and -2.7 kg at the end of treatment for the 20/20, 20/30 and 20/40 taspoglutide arms, respectively. The study demonstrated that maximal efficacy was achieved with the 20 mg dose; in fact uptitration to 30 or 40 mg, while safe, was devoid of additional therapeutic effects [60].

#### ■ Safety & tolerability

Consistent with data on the other GLP-1 agonists, the most common adverse events reported from Phase II trials with taspoglutide were gastrointestinal effects [59,60]. In both studies the majority of these events were transient and resolved spontaneously. Other serious adverse events, including coronary artery occlusion ( $n = 1$ ), unstable angina ( $n = 1$ ), cardiac arrhythmia ( $n = 1$ ) and recurrence of prostate cancer ( $n = 1$ ) that caused discontinuation of the study, occurred both in the placebo and taspoglutide cohorts and were considered by the investigators to be unrelated to the drug. Hypoglycemia occurred infrequently and no cases of severe hypoglycemia or pancreatitis was identified in any taspoglutide-treated subject. Injection site reactions were observed in 52–69% of subjects receiving taspoglutide but were considered mild or moderate [59,60].

#### ■ Phase III trials

The T-emerge Phase III clinical trial program was designed as a multicenter, multicountry, randomized, controlled (active or placebo), double-blind and open studies to test taspoglutide efficacy [102]. However, as of September 2010, Phase III trials with taspoglutide have been halted due to a high incidence of serious hypersensitivity reactions and gastrointestinal side effects.

### Lixisenatide

#### ■ Phase II trials

Lixisenatide is a synthetic 44 amino acid exendin-4-like analog, modified C-terminally with the addition of six lysine residues and the deletion of one proline. Preclinical studies suggest that it has an high binding affinity for the human GLP-1 receptor (~fourfold higher than native GLP-1). Results from a randomized,

double-blind, placebo-controlled, parallel-group, 13-week Phase II study, evaluating the efficacy of lixisenatide as an add-on to metformin, have recently been published [61]. In this study 542 patients with Type 2 diabetes inadequately controlled with metformin were randomized to receive lixisenatide at 5, 10, 20 or 30 µg once- or twice-daily, or placebo as an add-on therapy. Lixisenatide significantly improved mean HbA<sub>1c</sub> at all doses ( $p < 0.01$  vs placebo for all). Target HbA<sub>1c</sub> below 7.0% was achieved in 68% of patients receiving lixisenatide 20 and 30 µg once daily versus 32% of subjects receiving placebo at the end of the study ( $p < 0.0001$ ). Dose-dependent improvements were observed for fasting, postprandial and average self-monitored blood glucose levels. Weight changes at the end of the 13 weeks ranged from  $-2.0 \pm 0.4$  kg with the 5 µg once-daily dose to  $-3.89 \pm 0.41$  kg with lixisenatide 30 µg twice-daily. According to the NIH trial registry [103] a second Phase II study comparing lixisenatide to liraglutide has recently been completed.

#### ■ Safety & tolerability

The most frequent adverse events in subjects receiving lixisenatide were gastrointestinal, primarily dose-dependent nausea. No cases of pancreatitis was observed during the 13 weeks of treatment. Symptomatic hypoglycemic episodes ranged from 1 to 3 events (0.9–5.7%) per group, with no evidence of a dose relationship; the episodes were mostly mild in intensity and none of the patients experienced severe hypoglycemia. Serious adverse events that caused the discontinuation of the study included: one patient in the lixisenatide 30 µg once-daily group experienced a few seconds of loss of consciousness, and one subject in the lixisenatide 10 µg once-daily group had an allergic reaction. In addition two nonserious cases of urticaria were reported with lixisenatide and three with placebo. No clinically significant changes were detected by laboratory safety assessments and on 12-lead ECG. The percentages of antilixisenatide antibody-positive subjects at end of the 13-weeks of treatment ranged from 43.1% in the 10 µg once-daily group to 71.2% in the 20 µg twice-daily group; however, no differences were observed in terms of safety and efficacy between the antibody-positive and -negative subjects at any dose [61].

#### ■ Phase III

Currently, 13 Phase III trials are at different stages of recruitment, according to the NIH trial website [103]. These trials are assessing lixisenatide efficacy as monotherapy or in association with standard Type 2 diabetes therapy (metformin, insulin, pioglitazone and sulfonylurea). Interestingly, one ongoing

trial has been specifically designed to evaluate CV outcomes with lixisenatide compared to placebo in Type 2 diabetic patients who had experienced an acute coronary syndrome.

#### Semaglutide

Semaglutide is a once weekly human GLP-1 analog that is being developed for the treatment of Type 2 diabetes. Semaglutide lowers blood glucose through stimulating the release of insulin, and additionally lowers body weight. The Phase II program, including more than 400 people, was completed in 2009, but no data have been published yet.

#### Conclusion & future perspective

GLP-1 analogs, such as liraglutide and exenatide, have recently been added to the current algorithm for the management of Type 2 diabetes by several national and international guidelines [3,104]. These guidelines reflect the growing use of incretin-based therapies in clinical practice as monotherapy or in combination with other antidiabetic drugs, and may signal a paradigm shift in the management of patients with Type 2 diabetes. Phase III trials of GLP-1 analogs have demonstrated the efficacy and safety across the spectrum of treatments for Type 2 diabetes, from monotherapy to combination with one or two commonly used antidiabetic drugs [18–26,30–32,41–46]. Throughout the trials, treatment with GLP-1 analogs was associated with an improvement in  $\beta$ -cell function, weight loss and reductions in blood pressure. GLP-1 analogs therapy was associated with a low risk of hypoglycemia and was generally well tolerated with the most frequent adverse effects being nausea. GLP-1 analogs may be particularly effective in patients who need to lose weight due to concomitant obesity, and in individuals in whom hypoglycemia prevention is an important issue. Significant improvements in biomarkers of CV risk have been observed during GLP-1 analogs treatment in clinical trials. Interestingly, a clinical study has demonstrated that a 72-h infusion of GLP-1 improved left ventricular function in subjects with acute myocardial infarction and left ventricular dysfunction after successful reperfusion [62]. More recently, the same group studied the effects of a 5-week infusion of GLP-1 added to standard therapy in 12 subjects with New York Heart Association class III/IV heart failure [63]. Chronic infusion of GLP-1 significantly improves left ventricular function, myocardial oxygen uptake, 6-min walking distance and quality of life in patients with severe heart failure. In addition, acute infusion of GLP-1 has also been shown to improve endothelial function measured by flow-mediated vasodilation in patients with Type 2

diabetes and established coronary artery disease [64]. Whether treatment with GLP-1 analogs may provide CV benefit remains to be investigated in trials of sufficient size and duration. Longer-acting GLP-1 receptor agonists administered weekly or biweekly, such as exenatide LAR and albiglutide, are currently undergoing Phase III trials testing, and may have more robust effects on glucose control and body weight reduction.

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#### Executive summary

- Glucagon-like peptide (GLP-1) is a naturally occurring hormone responsible for the 'incretin effect'; a phenomenon where more insulin is secreted in response to glucose ingested during a meal than in response to the glucose given intravenously under isoglycemic conditions.
- The incretin effect is impaired in patients with Type 2 diabetes.
- Exogenous administration of GLP-1 stimulates insulin secretion, inhibits glucagon secretion, slows gastric emptying, decreases appetite and decreases body weight in diabetic subjects.
- Native GLP-1, however, is rapidly inactivated by dipeptidyl peptidase-4; therefore, a continuous infusion would be required to achieve a clinical effect.
- To overcome this difficulty, several GLP-1 agonists, that mimic GLP-1 effects *in vivo*, have been developed.
- Results from large Phase III trials with liraglutide and exenatide have demonstrated their efficacy and safety across the spectrum of treatments for Type 2 diabetes.
- Liraglutide and exenatide have been released to the market and were recently been added to the current algorithms for the management of Type 2 diabetes.
- Long-acting analogs, including exenatide-LAR and albiglutide, have been designed that will allow for a once weekly dosage.
- Phase III trials have demonstrated that once weekly administration of exenatide-LAR controls glucose levels, even more effectively than the shorter-acting drug, and reduces body weight.
- Results from Phase III trials with albiglutide will be available in the next few months.

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