

# Potential of liraglutide in the treatment of patients with type 2 diabetes

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**Abstract:** Liraglutide is a long-acting analog of GLP-1, being developed by Novo Nordisk and currently undergoing regulatory review for the treatment of type 2 diabetes. Upon injection, liraglutide binds non-covalently to albumin, giving it a pharmacokinetic profile suitable for once-daily administration. In clinical trials of up to 1 year duration, liraglutide has been demonstrated to have beneficial effects on islet cell function, leading to improvements in glycemic control. Both fasting and postprandial glucose concentrations are lowered, and are associated with lasting reductions in HbA1c levels. Liraglutide is effective as monotherapy and in combination therapy with oral antidiabetic drugs, and reduces HbA1c by up to  $-1.5\%$  from baseline ( $8.2\%$ – $8.4\%$ ). Because of the glucose-dependency of its action, there is a low incidence of hypoglycemia. Liraglutide is associated with body weight loss, and reductions in systolic blood pressure have been observed throughout the clinical trials. The most common adverse events reported with liraglutide are gastrointestinal (nausea, vomiting and diarrhea). These tend to be most pronounced during the initial period of therapy and decline with time. Further clinical experience with liraglutide will reveal its long-term durability, safety and efficacy.

**Keywords:** liraglutide, GLP-1, incretin mimetic, type 2 diabetes

## Introduction

Type 2 diabetes mellitus (T2DM) is a progressive disease, characterized by both insulin resistance and declining  $\beta$ -cell function which lead to impaired glucose-induced insulin secretion. Once insulin secretion can no longer compensate for the insulin resistance, hyperglycemia ensues, and with it, the development of micro- and macrovascular diabetic complications and associated increases in morbidity and mortality. Current treatment algorithms advocate the early use of metformin, together with lifestyle interventions (dietary modification, increased physical activity, weight loss) to control the hyperglycemia.<sup>1</sup> However, for the majority of patients, this is insufficient, and most progress to require the use of several agents including insulin. Unfortunately, even with this approach, several long-term clinical trials (eg, United Kingdom Prospective Diabetes Study (UKPDS); A Diabetes Outcome Progression Trial (ADOPT)) have demonstrated that HbA1c levels continue to rise over time,<sup>2–4</sup> underscoring the need for new and more efficacious agents which not only target treatment, but also prevention of the disease, its progression and its associated complications.

One new approach is based upon the actions of the intestinal hormone glucagon-like peptide-1 (GLP-1). GLP-1, together with glucose-dependent insulinotropic polypeptide (GIP), is an incretin hormone which enhances meal-induced insulin secretion, while also having a number of other actions considered desirable in an anti-diabetic agent (Table 1).<sup>5–7</sup> Thus, GLP-1 stimulates all steps in insulin biosynthesis and secretion, and has beneficial effects on both  $\beta$ -cell function and survival. It reduces excessive hepatic glucose production by suppressing glucagon secretion, it delays gastric emptying, leading to lower postprandial glucose excursions, and it has central effects to reduce appetite

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**Table 1** Actions of GLP-1

Type 2 diabetic phenotype	Actions of GLP-1
Impaired $\beta$ -cell function	Increases insulin secretion (glucose-dependent) and biosynthesis Improves $\beta$ -cell function (glucose sensitivity, proinsulin:insulin ratio, HOMA- $\beta$ ) Upregulates other genes essential for $\beta$ -cell function (eg, GLUT 2, glucokinase)
Reduced $\beta$ -cell mass	Increases $\beta$ -cell proliferation/differentiation <sup>a</sup> Reduces $\beta$ -cell apoptosis <sup>a</sup> Increases $\beta$ -cell mass <sup>a</sup>
Glucagon hypersecretion	Reduces glucagon secretion (glucose-dependent)
Postprandial hyperglycemia	Delays gastric emptying
Overeating, obesity	Delays gastric emptying, increases satiety, reduces appetite $\rightarrow$ decreased food intake and body weight
Macrovascular complications	Beneficial cardiovascular effects
Insulin resistance	Improvements in insulin sensitivity <sup>b</sup>

**Note:** For a review, see<sup>5-7</sup>

<sup>a</sup>Effects shown only in preclinical in vitro and animal studies.

<sup>b</sup>Action which is likely to be secondary to improvements in metabolism rather than a direct effect of GLP-1.

and food intake, resulting in body weight loss, while more recent studies point to beneficial cardiovascular effects.<sup>5-7</sup> GIP has similar effects to GLP-1 on the  $\beta$ -cells, but it does not inhibit glucagon secretion, and has only minimal effects on gastric emptying. Appetite is unaffected by GIP, but GIP has been implicated in the control of lipid metabolism, and may have a role in the regulation of bone remodeling.<sup>5</sup>

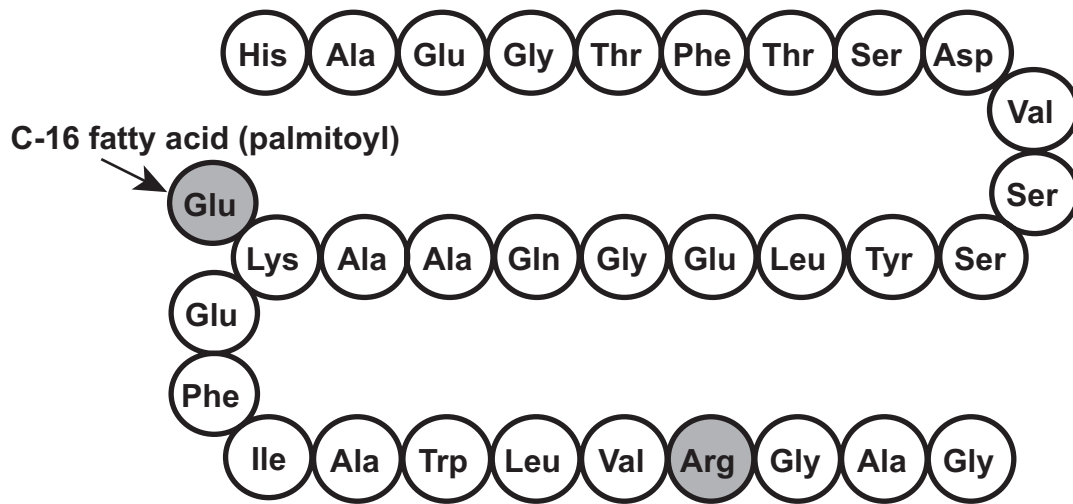
When given as an intravenous infusion, GLP-1 has been demonstrated to normalize both fasting and postprandial plasma glucose concentrations in patients with T2DM,<sup>8,9</sup> whilst continuous subcutaneous administration greatly improves metabolic control, lowering glucose profiles and HbA1c levels, improving  $\beta$ -cell function and reducing body weight over a 6-week period.<sup>10</sup> However, GLP-1 is extensively degraded in vivo,<sup>11</sup> primarily by the enzyme dipeptidyl peptidase-4 (DPP-4), with such rapidity that its apparent half-life is only in the order of 1 to 2 minutes and its metabolic clearance rate exceeds the cardiac output by 2- to 3-fold,<sup>12,13</sup> with the resultant metabolite lacking insulinotropic effects. Other enzymes, such as neutral endopeptidase 24.11 (NEP) are also able to cleave GLP-1 in vivo,<sup>14</sup> while furthermore, the peptide is efficiently cleared by the kidneys at a rate which exceeds the glomerular filtration rate.<sup>15</sup> Together, these factors mean that the native peptide cannot be used therapeutically, and there has, therefore, been much effort placed upon identifying metabolically stable analogs or derivatives of GLP-1 which are not subject to the same enzymatic degradation or renal clearance. Although a simple substitution of the penultimate N-terminal amino acid prevents degradation by DPP-4, these analogs are still rapidly cleared by the kidneys.<sup>16</sup> In the search for more stable analogs, two distinct groups of compounds

have attracted much interest: (i) compounds based upon mammalian GLP-1, which have been modified to facilitate binding to plasma proteins, such as albumin, to protract their action and (ii) compounds which are based upon the sequence of exendin-4, a naturally occurring peptide originally isolated from the saliva of the Gila monster (*Heloderma suspectum*), which shares 53% homology with GLP-1 and is a full agonist at the GLP-1 receptor.<sup>17</sup> Exendin-4 is resistant to DPP-4, and is cleared from the plasma exclusively by glomerular filtration.<sup>15</sup>

This article focuses upon liraglutide, being developed by Novo Nordisk, which is based upon mammalian GLP-1. Novo Nordisk submitted a new drug application (NDA) to the food and drug administration (FDA) in the United States and a marketing authorization application to the European Medicines Agency (EMA) in Europe in May 2008. An NDA was submitted to the Japanese regulatory authorities in July 2008.

## Liraglutide Chemistry and pharmacokinetics

Liraglutide ( $\gamma$ -L-glutamoyl(N- $\alpha$ -hexadecanoyl)-Lys,<sup>26</sup> Arg<sup>34</sup>-GLP-1(7-37)) is an acylated derivative of mammalian GLP-1, sharing 97% sequence homology with the native peptide (Figure 1). It is based upon the sequence of GLP-1 (7-37), with the addition of a glutamic acid residue at position 26, allowing attachment of a palmitoyl group, and a substitution (arginine instead of lysine) at position 34.<sup>18</sup> In vitro studies show that, despite the modifications, liraglutide retains affinity for the GLP-1 receptor.<sup>18</sup> The palmitoyl group facilitates non-covalent binding to albumin after injection,



**Figure 1** Primary structure of liraglutide (shaded residues indicate differences from mammalian GLP-1).

whereby the peptide escapes glomerular filtration. Together with self-association, this results in a pharmacokinetic profile with slow absorption ( $T_{\max}$  of ~10–14 hours) and a long half-life of around 12½ hours after subcutaneous injection,<sup>19</sup> making it suitable for once-daily administration. Although liraglutide is metabolized slowly in vitro by DPP-4 and NEP,<sup>20</sup> in vivo, the albumin binding is likely to hinder enzymatic access to the molecule, while furthermore, acting as a buffer reservoir, which contributes to the long half-life of the compound. Thus, in vivo, the majority of liraglutide (>89%) is found in the plasma as the intact molecule. No intact liraglutide and only low levels of metabolites were detected in the urine or feces, suggesting that liraglutide is probably degraded at a very slow rate into small peptides, amino acids and fatty acid fragments which are subsequently eliminated via the liver and kidney, or recycled into new endogenous proteins and lipids.<sup>20</sup> Perhaps because of this, a pharmacokinetic study indicated that dose-adjustment was unnecessary in subjects with renal impairment.<sup>21</sup> When adjusted for body weight, age or gender has no effect upon the pharmacokinetics of liraglutide (1 mg) in healthy subjects;<sup>22</sup> dose-dependent increases in exposure are seen with doses up to 12.5 µg/kg, but the  $t_{1/2}$  remains constant.<sup>19</sup> These findings were subsequently reproduced using doses up to 25 µg/kg in healthy Japanese subjects.<sup>23</sup>

### Early clinical studies

Early clinical studies with liraglutide showed that a single subcutaneous injection (10 µg/kg) reduced both fasting and postprandial blood glucose concentration in subjects with T2DM.<sup>24</sup> Subsequently, treatment with liraglutide (6 µg/kg) for 1 week improved both  $\alpha$ - and  $\beta$ -cell function,

resulting in improved 24-hour glycemic control in patients with T2DM.<sup>25</sup>

Eight weeks of treatment with liraglutide (0.6 mg) in obese subjects with T2DM (baseline HbA1c 7.5%) significantly reduced glycemia (−0.33% for liraglutide, +0.47% for placebo), but had no significant effect on body weight (−0.7 kg for liraglutide, −0.9 kg for placebo). In this study,<sup>26</sup> body composition was assessed, showing that liraglutide was associated with small (non-significant) trends towards a reduction in total fat mass and an increase in lean body mass. Overall 24-hour energy expenditure was not affected by liraglutide treatment.<sup>26</sup>

In a 12-week randomized, placebo-controlled dose-response study (baseline HbA1c 7.6%), monotherapy with liraglutide in doses of 0.045 up to 0.75 mg led to reductions in HbA1c with all but the lowest dose.<sup>27</sup> Compared with placebo, the two highest doses of liraglutide (0.60 and 0.75 mg) resulted in HbA1c changes of −0.70% and −0.75% after 12 weeks, which were similar to the reduction obtained with the active comparator (glimepiride, −0.74%). Fasting plasma glucose (FPG) levels also decreased, with the maximal effect being observed after the first week of treatment and maintained over the 12-week study period. As with the effect on HbA1c, the effect of the two highest doses of liraglutide was comparable to that of glimepiride. In this study, body weight did not increase, but there was no clear dose-response relationship; a significant reduction (−1.2 kg) was obtained with the 0.45 mg dose but not with the two highest liraglutide doses.<sup>27</sup>

In another dose-response study, patients with T2DM discontinued their usual oral anti-diabetic drug (OAD) and

entered a metformin run-in period (500 mg bid for 2 weeks, 1000 mg bid for 2 weeks) before being randomized to liraglutide monotherapy (0.045 up to 0.75 mg) or continuing metformin (1000 mg bid) for 12 weeks.<sup>28</sup> The two lowest doses of liraglutide (0.045 and 0.225 mg) were insufficient to maintain the glycemic control obtained with metformin (baseline HbA1c ~7%), but the three highest doses (0.45, 0.6 and 0.75 mg) were comparable to metformin (change in HbA1c, +0.22%, +0.16% and +0.30%, respectively vs +0.09% for metformin at week 12).<sup>28</sup> Relative to baseline, all liraglutide doses led to weight loss over the 12 weeks, which was, however, not significantly different compared with metformin, and again, no clear dose-response relationship was apparent. All treatment groups except for the lowest liraglutide dose (0.045 mg) showed a decrease in total body mass and total fat mass which was comparable to that induced by metformin alone.<sup>28</sup> Mathematical modeling of the results, however, suggested that the dose range in this trial was likely to have been sub-optimal in terms of HbA1c reduction.

Collectively, therefore, these results indicated that higher doses of liraglutide may have greater efficacy, and subsequently, Nauck et al<sup>29</sup> investigated the effect of higher doses of liraglutide (titrated weekly in 0.5 mg increments from 0.5 to 2.0 mg) in a randomized double-blinded placebo-controlled protocol in patients with poorly controlled diabetes (HbA1c ~9.4%). Subjects on metformin monotherapy (1000 mg bid) were randomized to receive continuing metformin monotherapy, metformin plus the addition of liraglutide, or liraglutide monotherapy. In addition, an open-label group received metformin plus glimepiride. FPG levels remained unchanged on metformin monotherapy, whereas they were reduced by 1.4 mmol/L in the subjects switched from metformin to liraglutide monotherapy. When compared to metformin monotherapy, the addition of liraglutide resulted in a further reduction of 3.9 mmol/L after 5 weeks of treatment, accompanied by a 0.8% reduction in HbA1c (baseline HbA1c ~9.4%). Furthermore, the combination of metformin plus liraglutide gave a greater reduction in FPG levels compared with metformin plus glimepiride (between group difference of 1.4 mmol/L in favor of liraglutide). In terms of body weight, both liraglutide as monotherapy and in combination with metformin led to body weight reductions (-2.1 and -2.2 kg from baseline, respectively) compared with metformin (-1.7 kg) and metformin plus glimepiride (+0.8 kg) after 5 weeks of treatment. Treatment effects on body weight and fasting glucose remained largely unchanged when patients experiencing nausea for more than 1 week were excluded from the analysis.<sup>29</sup>

In a 14-week study (n = 165) investigating the efficacy of liraglutide monotherapy, HbA1c was dose-dependently reduced from baseline (~8.3%) by 0.98%, 1.40% and 1.45% for liraglutide doses of 0.65, 1.25 and 1.90 mg, respectively, compared with an increase of +0.29% for placebo, with 46% of patients reaching the HbA1c goal of <7% (compared to 5% on placebo).<sup>30</sup> There were dose-related reductions in FPG (of between 2.7 and 3.4 mmol/L), and postprandial glucose was also significantly reduced by liraglutide. Body weight fell in all liraglutide groups (by up to 3.0 kg for the 1.9 mg dose).

In Japanese subjects with T2DM (n = 226, baseline HbA1c 8.3%), liraglutide (0.1–0.9 mg) dose-dependently reduced HbA1c levels by 0.79 up to 1.85% relative to placebo treatment by week 14, with 75% and 57% of subjects reaching target HbA1c levels of <7% and <6.5%, respectively, with the highest dose (vs 9 and 2%, respectively, of subjects on placebo).<sup>31</sup> Notably, in this study the HbA1c-lowering effect appeared to plateau at a dose of 0.9 mg, whereas in Caucasians, doses up to 1.9 mg are required for maximal efficacy.<sup>30</sup> This is most likely explained by the different nature of T2DM in Japanese diabetes, where  $\beta$ -cell dysfunction appears to play a greater role than insulin resistance.<sup>32</sup> There were also dose-dependent reductions in FPG (by up to 2.5 mmol/L relative to placebo) and postprandial glucose.<sup>31</sup> In this study in lean subjects (weight ~63 kg, BMI ~24 kg/m<sup>2</sup>), body weight remained relatively stable (changes ranging from +0.1 to -0.5 kg with liraglutide, vs -1.0 kg with placebo).<sup>31</sup>

## Liraglutide effect and action in diabetes (LEAD) studies

The LEAD program comprises six randomized, controlled, double-blind phase 3 studies in patients with inadequately controlled T2DM, designed to investigate the efficacy of liraglutide as monotherapy or as combination therapy with one or two OADs (Table 2). In all the trials, the liraglutide dose was initiated at 0.6 mg/day for 1 week and titrated by weekly increments of 0.6 mg to the final dose. Most of the LEAD studies included an active comparator.

LEAD-1 is a 26-week placebo-controlled study in 1041 patients with T2DM on background glimepiride (2–4 mg/day) therapy (baseline HbA1c ~8.4%), designed to compare the effects of using liraglutide (0.6, 1.2 or 1.8 mg once daily) or rosiglitazone (4 mg/day) as add-on therapy to sulfonylurea; preliminary results were presented at the annual meetings of the ADA and EASD.<sup>33,34</sup> In this study, the addition of liraglutide or rosiglitazone gave additional reductions in HbA1c compared to placebo, where HbA1c levels increased by 0.23% from baseline. Addition of rosiglitazone or the lowest

**Table 2** Summary of the Liraglutide Effects and Action in Diabetes (LEAD) program

	LEAD-1 Add-on to SU	LEAD-2 Add-on to metformin	LEAD-3 Monotherapy	LEAD-4 Add-on to metformin + TZD	LEAD-5 Add-on to metformin + SU	LEAD-6 Add-on to metformin ± SU
Patients randomized	1041	1091	746	533	581	464
Age (years)	56.1	56.8	53.0	55.1	57.5	56.7
Duration of diabetes (years)	7.9	7.4	5.4	9.2	9.4	8.2
HbA1c (%)	8.4	8.4	8.2	8.3	8.2	8.2
Comparator	Rosiglitazone, placebo	Glimepiride, placebo	Glimepiride	Placebo	Insulin glargine, placebo	Exenatide
HbA1c change from baseline (%)	Lira 1.8 mg -1.1 Rosi -0.44 Placebo +0.23	Lira 1.8 mg -1.0 Glim -1.0 Placebo +0.1	Lira 1.8 mg -1.1 Glim -0.5	Lira 1.8 mg -1.5 Placebo -0.5	Lira 1.8 mg -1.3 Insulin glar -1.1 Placebo -0.2	Lira 1.8 mg -1.1 Exenatide -0.8
Body weight change from baseline (kg)	Lira 1.8 mg -0.2 Rosi +2.1 Placebo -0.1	Lira 1.8 mg -2.8 Glim +1.0 Placebo -1.5	Lira 1.8 mg -2.5 Glim +1.1	Lira 1.8 mg -2.0 Placebo +0.6	Lira 1.8 mg -1.8 Insulin glar +1.6 Placebo -0.4	Lira 1.8 mg -3.2 Exenatide -2.9
Treatment period	26 weeks	26 weeks	52 weeks	26 weeks	26 weeks	26 weeks
Extension period	-	2 year	4 years	-	-	14 + 38 weeks
Reference	Marre et al 2008 <sup>33,34</sup>	Nauck et al 2008 <sup>35</sup>	Garber et al 2008 <sup>36</sup>	Zinman et al 2008 <sup>37</sup>	Russell-Jones et al 2008 <sup>38,39</sup>	Blonde et al 2008 <sup>40</sup>

**Abbreviations:** SU, sulfonylurea; TZD, thiazolidinedione.

liraglutide dose (0.6 mg) lowered HbA1c to a similar extent (-0.44% and -0.60%, respectively), whereas the two highest liraglutide doses were comparable and gave significantly greater reductions (-1.08% and -1.13%, respectively). At week 26, 42% of patients receiving 1.8 mg liraglutide reached the ADA recommended target of HbA1c of <7%, with 21% reaching <6.5%. FPG was reduced by both liraglutide and rosiglitazone combinations, compared to placebo, but with no significant differences between the active treatments arms (reductions of -0.7 to -1.6 mmol/L). Whereas the rosiglitazone combination resulted in a significant weight gain of 2.1 kg by week 26, in this study liraglutide had no major effect on weight compared with placebo (+0.7, +0.3 and -0.2 kg for 0.6, 1.2 and 1.8 mg liraglutide; -0.1 kg for placebo).<sup>33,34</sup>

In LEAD-2, the effect of liraglutide (0.6, 1.2 or 1.8 mg once daily) was examined in 1091 patients with T2DM (baseline HbA1c 8.4%) on background metformin (1 g twice daily) therapy in a placebo-controlled trial with glimepiride (4 mg/day) as an active comparator.<sup>35</sup> This was a 26-week study, with an on-going 2-year continuation phase. Compared to placebo treatment, the addition of liraglutide to metformin significantly reduced HbA1c (change from baseline, -0.7%, -1.0% and -1.0% for 0.6, 1.2 and 1.8 mg liraglutide, respectively vs +0.1% for placebo), with the two highest doses of liraglutide demonstrating non-inferiority to glimepiride added to metformin (-1.0%). In the 1.8 mg liraglutide group, 42% of patients reached target HbA1c of <7%, comparable to glimepiride (36%), but significantly more than in the placebo group (11%), and 24% attained an HbA1c of <6.5% (compared to 22% on glimepiride and only 4% on placebo). FPG was significantly reduced by all active treatment combinations to a similar extent (-1.1 to -1.7 mmol/L vs +0.4 mmol/L for placebo). Postprandial glucose values in all liraglutide groups were reduced compared to placebo, with the 1.2 and 1.8 mg doses (-2.3 and -2.6 mmol/L, respectively) giving similar results to glimepiride (-2.5 mmol/L). Addition of liraglutide produced dose-dependent decreases in body weight (-1.8 to -2.8 kg at week 26), which were significantly greater than in the placebo group (-1.5 kg) for the two highest doses, and which contrasted with a 1.0 kg weight gain with glimepiride.<sup>35</sup>

The LEAD-3 study is a head-to-head comparison of monotherapy with liraglutide (1.2 or 1.8 mg once daily) or glimepiride (8 mg/day) in 746 patients with T2DM (baseline HbA1c 8.2%) over 52 weeks,<sup>36</sup> with a further on-going 4-year extension period. Any previous treatment (OAD monotherapy of up to half the maximal dose) was discontinued

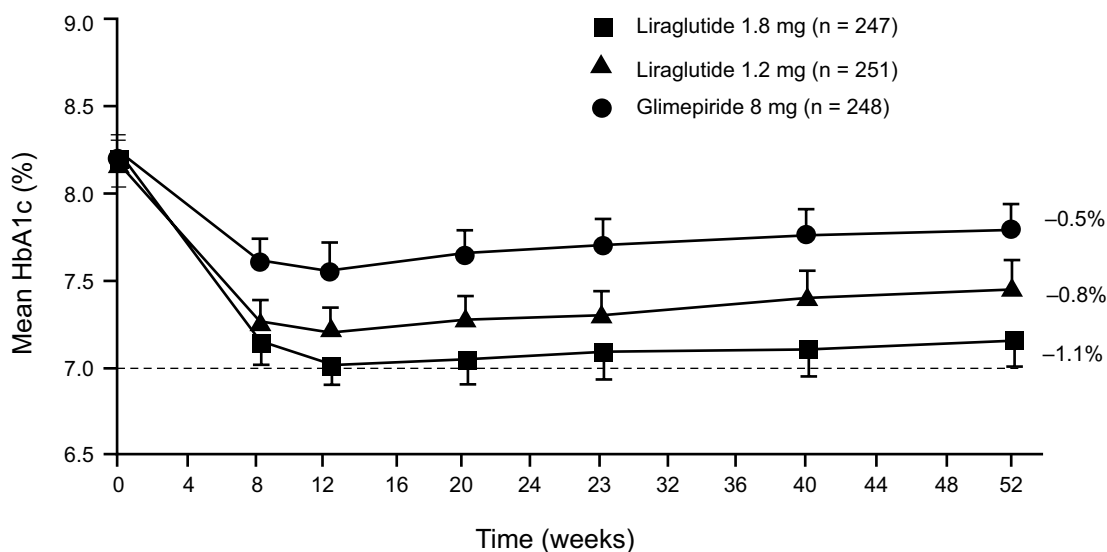
at randomization. At 1 year, HbA1c had decreased from baseline by 0.84% and 1.14% for 1.2 and 1.8 mg liraglutide compared with a reduction of 0.51% for glimepiride, with both liraglutide doses being superior to glimepiride (Figure 2). More liraglutide-treated subjects reached HbA1c targets of <7% and <6.5% (51% and 27%, respectively for liraglutide 1.8 mg) compared to glimepiride (28% and 16%, respectively). Fasting and postprandial glucose levels were dose-dependently reduced with liraglutide, with both liraglutide doses being superior to glimepiride (FPG,  $-0.8$  and  $-1.4$  mmol/L for liraglutide vs  $-0.3$  for glimepiride; postprandial glucose,  $-1.7$  and  $-2.1$  mmol/L for liraglutide vs  $-1.4$  for glimepiride). Body weight declined over the first 16 weeks and thereafter stabilized on both liraglutide doses ( $-2.1$  and  $-2.5$  kg, respectively), in contrast to a weight gain of 1.1 kg with glimepiride.<sup>36</sup>

The effect of adding liraglutide (1.2 or 1.8 mg) to therapy of patients inadequately controlled on metformin (1 g twice daily) plus rosiglitazone (8 mg/day) was evaluated in LEAD-4, in 533 patients with T2DM (baseline HbA1c 8.3%) treated for 26 weeks in a placebo-controlled trial; results were recently presented at the EASD.<sup>37</sup> Addition of liraglutide significantly reduced HbA1c to a greater extent than placebo, with both liraglutide doses being comparable (change from baseline,  $-1.48\%$  for both liraglutide doses vs  $-0.54\%$  for placebo). Of patients receiving liraglutide, 58% and 54% (1.2 and 1.8 mg dose) reached target HbA1c of <7% (vs 28% for placebo), with 35% and 37% reaching values <6.5% (14% for placebo). The addition of liraglutide resulted in additional

reductions in FPG and postprandial glucose, again with both liraglutide doses giving similar results (FPG,  $-2.2$  and  $-2.4$  mmol/L; postprandial glucose,  $-2.7$  and  $-2.6$  mmol/L for the two liraglutide groups vs  $-0.4$  and  $-0.8$  mmol/L for placebo). Whereas patients on placebo treatment experienced a small increase in body weight (+0.6 kg), those on liraglutide lost weight, with the effect being dose-dependent ( $-1.0$  and  $-2.0$  kg, respectively for 1.2 and 1.8 mg liraglutide).<sup>37</sup>

The LEAD-5 study examined the effect of adding liraglutide (1.8 mg once daily) to metformin (1 g twice daily) plus glimepiride (2–4 mg/day) in 581 patients with T2DM (baseline HbA1c 8.2%) in a placebo-controlled trial; insulin glargine was used as an active comparator (open label). Preliminary results have been presented at both ADA and EASD.<sup>38,39</sup> After 26 weeks, a greater reduction in HbA1c was obtained with liraglutide ( $-1.33\%$ ) than with either insulin glargine ( $-1.09\%$ ) or placebo ( $-0.24\%$ ) and more patients reached target HbA1c levels with liraglutide (52% reaching <7% and 36% reaching <6.5%) compared to insulin glargine (44% and 23%, respectively) or placebo (15% and 11%, respectively). Both active treatments reduced FPG to a similar extent ( $\sim -1.6$  mmol/L), in contrast to placebo-treatment which resulted in a small increase (+0.6 mmol/L). In contrast to insulin glargine treatment, where patients gained weight (+1.6 kg), liraglutide resulted in a significant weight loss of 1.8 kg from baseline (placebo,  $-0.4$  kg from baseline).<sup>38,39</sup>

Finally, the LEAD-6 trial aimed to directly compare liraglutide (1.8 mg once daily) with exenatide (10  $\mu$ g twice daily)



**Figure 2** Effects of liraglutide monotherapy in LEAD-3. Eligible patients had been treated with diet and exercise only or up to half the highest dose of OAD monotherapy, which was discontinued at randomization. Adapted from The Lancet, Garber A, Henry R, Ratner R, et al. Liraglutide versus glimepiride monotherapy for type 2 diabetes (LEAD-3 Mono): a randomised, 52-week, phase III, double-blind, parallel-treatment trial, 2008 Sep 24. [Epub ahead of print]. Copyright © 2008, with permission from Elsevier.<sup>36</sup>

in 464 patients who were inadequately treated with metformin and/or a sulfonylurea (baseline HbA1c 8.2%). Preliminary results were presented at the Canadian Diabetes Association meeting.<sup>40</sup> After 26 weeks, glycemic control was superior with liraglutide than with exenatide (HbA1c reductions of 1.12% vs 0.79%; 54% vs 43% of subjects reaching target HbA1c of <7%; 35 vs 21% of subjects reaching HbA1c <6.5%; FPG reductions of 1.6 vs 0.6 mmol/L; liraglutide vs exenatide). Body weight changes were similar for both groups (−3.2 kg for liraglutide, −2.9 kg for exenatide).<sup>40</sup> In an extension of this study, patients originally randomized to exenatide were switched to liraglutide. After 14 weeks, HbA1c in these subjects had dropped by a further 0.3%, FPG by 0.9 mmol/L and body weight by 1 kg, so that there was no longer any significant difference from those subjects who continued on liraglutide.<sup>41</sup>

### Islet cell effects

In preclinical studies, liraglutide has been demonstrated to have protective effects on the  $\beta$ -cell. Thus, in cultured primary neonatal rat islets, Bregenholt et al<sup>42</sup> showed that liraglutide inhibited both cytokine- and free fatty acid-induced apoptosis, while Friedrichsen et al<sup>43</sup> found that  $\beta$ -cell replication was increased, and similar effects in cultured human islets were recently reported.<sup>44</sup> In animal studies,  $\beta$ -cell mass was increased following treatment with liraglutide in rodent models of T2DM.<sup>45,46</sup>

While effects on  $\beta$ -cell mass have not yet been demonstrated in clinical studies (due primarily to a lack of suitable non-invasive technology), beneficial effects on islet cell function have been consistently seen. Thus, a single dose of liraglutide restores  $\beta$ -cell sensitivity to glucose,<sup>47</sup> while 1 week of treatment improves glucose-induced insulin secretion and  $\beta$ -cell function (HOMA- $\beta$ , insulin secretion during a hyperglycemic clamp, maximal insulin secretion after arginine infusion, proinsulin/insulin ratio) as well as having significant effects on  $\alpha$ -cell function (suppression of 24-hour glucagon profiles).<sup>25</sup> The beneficial effects on  $\beta$ -cell function were maintained over 12 weeks of treatment with the highest dose of liraglutide in the study of Madsbad et al.<sup>27</sup> Assessment of  $\beta$ -cell function after 14 weeks of treatment with liraglutide revealed improvements in first- and second-phase insulin secretion, together with increases in maximal (arginine-stimulated) insulin secretion during hyperglycemia.<sup>48</sup> Another study, examining the effects of liraglutide under conditions of normal living, used mathematical modeling of insulin and glucose responses to meal ingestion, and also showed that liraglutide enhanced  $\beta$ -cell

function.<sup>49</sup> Finally, in the LEAD studies, liraglutide has been associated with improved  $\beta$ -cell function, which was similar to that observed with glimepiride,<sup>35,36</sup> and superior to rosiglitazone<sup>33,34</sup> or exenatide.<sup>40</sup>

### Cardiovascular effects

Small increases in pulse rate of 2 to 3 beats per minute have been observed throughout the LEAD studies,<sup>35–37</sup> although the clinical significance (if any) of this is unknown. However, of great interest are the consistent observations that systolic blood pressure is significantly decreased. Vilsbøll et al<sup>30</sup> found reductions with all liraglutide doses, by up to 7.9 mmHg compared to placebo after 14 weeks of treatment. In LEAD-2 and LEAD-3, systolic blood pressure changes favored liraglutide over glimepiride (reductions from baseline of 2–4 mmHg with liraglutide).<sup>35,36</sup> Reductions in systolic blood pressure were also reported for the other LEAD studies, with the effects already apparent at the first assessment point (2 weeks post-randomization).<sup>50</sup> No significant changes in diastolic blood pressure were reported in any of the studies.

### Adverse events and safety

#### Gastrointestinal side effects

In common with other GLP-1 receptor agonists, such as exenatide, gastrointestinal adverse effects (nausea, vomiting and diarrhea) are the most common adverse events seen in the clinical trials with liraglutide, with the incidences appearing to be dose-related.

Thus, throughout the LEAD studies, up to 44% of subjects receiving liraglutide at the highest dose (1.8 mg) reported gastrointestinal side effects, with nausea being the most frequently reported event, occurring in up to 40% of subjects. Generally, nausea was seen predominantly in the first few weeks after initiation of treatment; in LEAD-2, less than 10% of the subjects were experiencing nausea on a weekly basis by the fourth week.<sup>35</sup> In LEAD-1 and LEAD-5, nausea was reported by less than 4% of subjects by week 2 to 4,<sup>33,34,38,39</sup> while in LEAD-4, the incidence of nausea had decreased to the same level as in the placebo group after 16 weeks.<sup>37</sup> Diarrhea was reported by 15% to 18% of subjects compared to less than 10% of subjects on comparator agents,<sup>35,36</sup> and vomiting by ~10% of subjects (vs 4% on glimepiride).<sup>35</sup> However, it is noteworthy that relatively few subjects withdrew from the studies because of gastrointestinal side effects associated with liraglutide. In LEAD-2, only 5% of all liraglutide treated subjects withdrew, with the majority of those discontinuing during the first

month of treatment,<sup>35</sup> while in LEAD-3, between 2% and 4% of subjects withdrew.<sup>36</sup> In a specifically designed sub-study, a Gastrointestinal System Rating Scale (GSRS; a validated self-reporting method) was used to quantify the duration and intensity of gastrointestinal adverse events during 14 weeks of liraglutide treatment (0.65, 1.25 and 1.9 mg).<sup>51</sup> Although liraglutide increased gastrointestinal symptoms, the average rating was low (maximum 2 on a 7-point scale), with the self-reported increase in events occurring mainly during the first two weeks of treatment, and decreasing thereafter. Only the reflux GSRS score showed a significant dose-related relationship. For indigestion and constipation, only the 1.25 mg dose was significantly greater than placebo, while there was no difference between liraglutide and placebo with respect to scores for diarrhea and abdominal pain.<sup>51</sup>

### Hypoglycemia

Overall, the risk of hypoglycemia with liraglutide is low, due to the glucose-dependency of its insulinotropic and glucagonostatic effects. Under conditions of a stepwise hypoglycemic clamp, insulin secretion is no longer enhanced by liraglutide (7.5 µg/kg) when blood glucose levels are reduced from 3.7 to 3.0 mmol/L and there is no impairment of hypoglycemia-induced glucagon secretion,<sup>52</sup> suggesting that the counter-regulatory response to hypoglycemia is unaffected by liraglutide. Thus, in the early clinical studies, minor hypoglycemia (defined as <3.1 mmol/L) was rarely observed.<sup>27–30</sup>

Throughout the LEAD program, the incidence of minor hypoglycemia with liraglutide has also been very low, ranging from 0.03 up to 1.9 events per year.<sup>33–40</sup> Overall, in the studies with active comparators, the incidence has been similar to that observed with metformin or rosiglitazone,<sup>33,34</sup> and lower than that seen with glimepiride<sup>35,36</sup> or exenatide.<sup>40</sup> Major hypoglycemia has only rarely been seen. In LEAD-1, one major hypoglycemic episode was reported, although this was considered to be related to the background sulfonylurea therapy,<sup>33,34</sup> while in LEAD-5, 2.2% of subjects experienced a major hypoglycemic event in the liraglutide arm (vs none in the other arms).<sup>38,39</sup>

### Pancreatitis

Novo Nordisk has reported a low number of incidents of acute pancreatitis in patients taking liraglutide in the clinical trials, although the incidence rate is in the normal range for T2DM; no cases of hemorrhagic or necrotizing pancreatitis have been seen.<sup>41</sup> In LEAD-3, 2 participants (out of 498 taking liraglutide) experienced pancreatitis, 1 after 197 days

(1.2 mg dose) and 1 after 333 days (1.8 mg dose); both recovered and 1 continued in the study.<sup>36</sup> In LEAD-2, 1 subject (out of 724) in the liraglutide-exposed group (1.2 mg) and 1 (out of 242) in the glimepiride group withdrew because of acute pancreatitis; after hospitalization for 7 days, both recovered.<sup>35</sup> No incidents of pancreatitis were reported in the LEAD-4 trial.<sup>37</sup>

### Antibodies

Formation of anti-liraglutide antibodies is reported to be low and not to be associated with loss of efficacy.<sup>41</sup> In LEAD-2, antibodies were detected in only 1 (out of 85) of the subjects who did not enter the open-label continuation phase of the study at week 26, and these were not immuno-neutralizing and showed no cross-reactivity with GLP-1.<sup>53</sup> Liraglutide antibodies were found in 9.3% to 12.7% of liraglutide-treated subjects in LEAD-1,<sup>33,34</sup> and in 9.8% in LEAD-5 after 26 weeks.<sup>38,39</sup>

## Discussion

Liraglutide belongs to one class of the so-called incretin-based therapies, namely the incretin mimetics (the other class being the DPP-4 inhibitors), which takes advantage of the known effects of the intestinal hormone, GLP-1. At present, clinical experience with these agents is still relatively limited, with exenatide being the only incretin mimetic so far to be approved for treatment of T2DM (launched in 2005). In clinical trials, both liraglutide and exenatide have been well tolerated, with gastrointestinal adverse events (nausea, diarrhea, vomiting) being the most common side effects (reported by ~50% of subjects). However, gradual dose escalation seems effective in reducing the incidence and severity of these gastrointestinal symptoms, such that in the majority of trials, their frequency was highest at the initiation of therapy and declined thereafter. Some concern over the safety of the incretin mimetics first arose in 2007, after the FDA issued a warning following reports of acute pancreatitis in patients taking exenatide; 30 cases were reported, although the diagnosis of acute pancreatitis (based on the presence of nausea, vomiting, abdominal pain, which notably are also known side effects of the incretin mimetics themselves) was confirmed by laboratory test in only 17 of the cases, and 27 of the cases had at least one other risk factor. Subsequently a total of 89 cases in patients on exenatide had been reported up to the end of September 2007. In August 2008, the FDA reported 6 new cases of hemorrhagic or necrotizing pancreatitis in patients using exenatide, and 6 deaths in patients who had experienced pancreatitis have been reported, although



other confounding factors were involved.<sup>54,55</sup> However, the rates of pancreatitis with exenatide<sup>56</sup> or liraglutide<sup>41</sup> are below those reported for the background T2DM population, which itself has a 2.8-fold greater incidence than the general population.<sup>57</sup> At present, a definitive causal relationship between incretin mimetics and pancreatitis has not been established, but a possible association cannot yet be fully excluded.

Consistent with the glucose dependency of its mechanism of action, the incidence of hypoglycemia has been very low with liraglutide, although occasional episodes of severe hypoglycemia have been noted when used in combination with sulfonylurea.<sup>33,34,38,39</sup> A greater incidence of hypoglycemia has also been observed when exenatide is used together with sulfonylurea,<sup>58,59</sup> and may perhaps reflect the enhanced  $\beta$ -cell function brought about by the GLP-1 agonists. Alternatively, there is some preclinical evidence that the sulfonylurea itself can uncouple the glucose-dependency of GLP-1's insulinotropic action.<sup>60</sup>

Weight loss with liraglutide in some trials has been inconsistent. In some of the earlier studies, no clear dose-response relationship was apparent,<sup>26-28</sup> but this might be explained by the doses used in these studies not being optimal. With the higher doses (up to 1.9 mg), weight reductions have generally been seen consistently, although rather surprisingly, in LEAD-1, the weight change was not different from placebo.<sup>33,34</sup> It has also been questioned whether nausea contributes to the weight loss observed with the GLP-1 analogs. In a sub-group analysis in LEAD-3, there were small trends for the magnitude of weight loss to be greater in subjects experiencing nausea for more than 7 days compared to those with none or less than 7 days' nausea (eg, for 1.8 mg liraglutide, the weight change was -3.4 kg for participants experiencing nausea for more than 7 days vs -2.3 kg for those with none or less than 7 days' nausea), although the differences were not significant for any treatment.<sup>36</sup> Liraglutide appears not to affect energy expenditure, at least in doses up to 0.6 mg,<sup>26</sup> while with higher doses (up to 1.8 mg), there was only a non-significant trend for resting energy expenditure to be higher.<sup>61</sup> It therefore appears that the major cause of weight loss is due to reduction in food intake. Thus, in sub-studies using visual analog scales, liraglutide reduced the feelings of hunger and prospective food intake, while increasing the feeling of fullness, together leading to a lower energy intake by up to 18% during an ad libitum meal.<sup>61,62</sup>

Any anti-diabetic agent that shows beneficial effects on the development of diabetic macrovascular complications will be welcome. Cardioprotective effects of GLP-1 have been observed preclinically,<sup>63</sup> and it is therefore of particular

interest that liraglutide treatment has been associated with clinically significant reductions in systolic blood pressure. This may be partly accounted for by concomitant body weight loss, although based on the profiles over time, Nauck et al<sup>35</sup> concluded that weight reductions could not fully explain the blood pressure changes. It is therefore noteworthy that reductions in blood pressure are also observed with the DPP-4 inhibitors, which are weight neutral.<sup>64,65</sup> Additionally, there is some evidence that the weight loss induced by liraglutide comes primarily from loss of fat (particularly visceral fat, which is a known cardiovascular risk factor), rather than lean tissue.<sup>66</sup> Whether these changes will be associated with reductions in macrovascular events will become apparent as clinical experience with these agents is gained and as data from longer duration trials with cardiovascular endpoints become available.

It is clear from the clinical trials that liraglutide improves glycemic control via effects on both fasting and postprandial glucose. The islet effects are likely to be of particular importance, since liraglutide has been consistently shown to improve  $\beta$ -cell function, leading to increased fasting insulin levels and improved maximal postprandial insulin levels.<sup>67</sup> Additionally, effects on the  $\alpha$ -cell are also likely to be important, given liraglutide's powerful glucagonostatic effect.<sup>25</sup> However, unlike exenatide, where delayed gastric emptying appears to play a major role in the drug's antihyperglycemic action,<sup>68</sup> delayed gastric emptying probably accounts for a smaller part of the lower postprandial glucose levels obtained with liraglutide. Thus, while a single dose of liraglutide does significantly delay gastric emptying,<sup>24</sup> liraglutide was without effect on gastric emptying when administered over several weeks, although the doses used in those early studies may not have been optimal.<sup>25,26</sup> Subsequently, studies using higher doses (up to 1.8 mg) have indicated that liraglutide is associated with a minor delay in gastric emptying, particularly over the first hour.<sup>61,67</sup> This difference in the relative effects of exenatide and liraglutide on gastric emptying may be explained by the more prolonged exposure to liraglutide leading to some tachyphylaxis of the gastric emptying effect, speculation which is supported by the observation that a long-acting formulation of exenatide, designed for once-weekly administration, has a less pronounced effect on gastric emptying (and postprandial glucose excursions) than exenatide given twice daily.<sup>69</sup> Although there is some evidence that some of the effects of endogenous GLP-1 may be mediated via interaction with autonomic nerves, at present it is unclear whether any of the effects of exogenously administered GLP-1 analogs depend on autonomic function. However, it

is noteworthy that GLP-1 is still able to normalize fasting glucose levels when given intravenously to patients with advanced diabetes, long after secondary sulfonylurea failure, in whom neuropathy is present.<sup>70</sup> Furthermore, a recent study indicates that the gastric emptying effects of exenatide are unaffected by the presence of autonomic neuropathy.<sup>68</sup>

Early studies with native GLP-1 indicated that increasing the exposure to the peptide resulted in greater efficacy with respect to lowering blood glucose levels,<sup>71,72</sup> and a similar situation seems to exist with the GLP-1 analogs. The first GLP-1 analog to be used for treatment of T2DM, exenatide, has a pharmacokinetic profile necessitating twice daily administration. In clinical use, exenatide gives sustained reductions in HbA1c levels,<sup>73</sup> but because of its relatively short plasma half-life, exposure to the drug is not optimal, even with twice-daily administration, particularly so in the overnight period. Liraglutide, with its longer plasma half-life, provides 24-hour coverage, and the preliminary results of the head-to-head comparison indicate that glycemic control is superior with liraglutide.<sup>40</sup> Similar results have also been seen with the once-weekly formulation of exenatide.<sup>69</sup> Moreover, the flatter drug profile obtained with these longer-acting analogs<sup>69,74</sup> also seems to reduce gastrointestinal symptoms. The DPP-4 inhibitors also increase intact GLP-1 levels over the full 24-hour period, but the pattern of exposure differs. Thus, whereas the GLP-1 analogs raise agonist plasma concentrations into the pharmacological range throughout the vascular system, the DPP-4 inhibitors typically increase intact GLP-1 concentrations by only 2- to 3-fold,<sup>75</sup> although with concentrations locally in the gut and portal vein being much higher than those in the periphery.<sup>76</sup> It has been argued that GLP-1 may exert many of its actions locally or in the hepato-portal bed,<sup>77</sup> and perhaps because of this, the DPP-4 inhibitors are effective, despite the low systemic GLP-1 concentrations attained. Like the GLP-1 analogs, DPP-4 inhibitors give sustained reductions in HbA1c,<sup>78</sup> and are associated with improvements in  $\beta$ -cell function.<sup>79, 80</sup> Similarly,  $\alpha$ -cell function is also improved with DPP-4 inhibitors,<sup>81</sup> but unlike the GLP-1 analogs, there are only minimal effects of gastric emptying and appetite is unaffected,<sup>82</sup> meaning that the DPP-4 inhibitors are best described as being body weight neutral. While the mechanism of action of the GLP-1 analogs relies only on GLP-1 receptor signaling, the DPP-4 inhibitors are believed to exert their effects via endogenous GLP-1 and GIP, but precisely how this difference affects the clinical profiles of the two classes of agents remains to be elucidated. The HbA1c-lowering efficacy of the two classes of incretin-based therapies has not yet been directly compared,

although a mechanistic study over 2 weeks indicated that while both agents had similar effects on FPG, exenatide had a greater effect on breakfast and dinner (but not lunch) postprandial glucose,<sup>82</sup> presumably related to the potent effect of exenatide to reduce gastric emptying.

The positioning of liraglutide in the therapeutic regimen remains to be determined. In support of an early use, the LEAD program indicates that liraglutide is effective in monotherapy, and even superior to sulfonylurea, with the additional advantage of weight loss and less hypoglycemia.<sup>36</sup> Moreover, as add-on therapy to a single OAD, it is non-inferior to sulfonylurea,<sup>35</sup> and superior to thiazolidinedione,<sup>33,34</sup> again with the favorable effect on weight. Moreover, various sub-group analyses seem to indicate that the degree of improvement is, at least partially, related to the stage of the disease. Thus, subjects previously treated with diet and exercise achieved greater HbA1c reductions than those who had previously been on OAD monotherapy in LEAD-3.<sup>36</sup> In LEAD-1, subjects previously on OAD monotherapy achieved greater HbA1c reductions than those on previous combination therapy,<sup>33,34</sup> while in LEAD-2, there was a tendency for those who were on pre-study monotherapy to achieve greater HbA1c reductions than those on previous combination therapy.<sup>35</sup> However, whether there will be patient (and physician) acceptance of using an injectable agent early in the management of the disease has yet to be determined. There is also a place for liraglutide later on in the course of the disease, with liraglutide giving significant reductions in HbA1c when used as an additional agent in patients already receiving combination therapy with 2 or 3 OADs,<sup>37-39</sup> and compared with insulin glargine, liraglutide gave better glycemic control without the weight gain.<sup>37,38</sup> Particularly the weight changes may help to encourage the use of this agent, since, with the exception of the incretin-based therapies (GLP-1 analogs and DPP-4 inhibitors) and metformin, all other agents, including insulin, are associated with weight gain. However, if lasting effects on the  $\beta$ -cell are demonstrated, then liraglutide (and other incretin-based therapies) may be able to ameliorate the progressive deterioration in glycemic control, which, at present, seems an inescapable characteristic of T2DM. It is therefore encouraging that preliminary results from a study in obese non-diabetic subjects, where around 30% of the participants had some signs of prediabetes at randomization, indicated that liraglutide was associated with a reduction in the number of prediabetic subjects after 1 year of treatment.<sup>83</sup> The success of liraglutide will ultimately depend upon not only its efficacy and durability in terms of glycemic control

and body weight, but also upon its possible impact on late diabetic complications, and compliance issues such as tolerability/safety, convenience of use and cost.

## Disclosures

Consultancy/advice: Merck & Co, Servier; Lecture fees: Merck & Co, Novartis, Novo Nordisk; Spouse: Employed by Merck & Co, holds stock/shares in Merck & Co, Novo Nordisk.

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