Liraglutide, the first once-daily human GLP-1 receptor analogue

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Abstract
Liraglutide is the first human GLP-1 receptor analogue, based on the structure of native GLP-1 with pharmacokinetic properties suitable for once daily dosing. In the phase 2 studies and the phase 3 LEAD™ programme, liraglutide has been shown to lower HbA1c to the same degree or more than other oral antidiabetic drugs. Liraglutide also induces weight loss, and improves beta-cell function, blood pressure and some cardiovascular risk markers. Liraglutide is well tolerated. The adverse effect most frequently reported being transient nausea. This article reviews the phase 3 LEAD™ programme. In July 2008 the European Commission granted marketing authorisation for liraglutide for treatment of type 2 diabetes.

Keywords: Liraglutide, GLP-1 receptor analogue, GLP-1 mimetic, type 2 diabetes, glycaemic control, weight loss, beta-cell function.

Introduction
The GLP-1 receptor agonist exenatide (Byetta®, Eli Lilly, Indianapolis, USA) was approved by FDA in April 2005 and released in Europe in May 2007 for the treatment of people with type 2 diabetes mellitus (T2DM). Liraglutide (Victoza®, Bagsværd, Novo Nordisk, Denmark) is a once-daily human GLP-1 analogue with 24-hour duration of action. In July 2008 the European Commission granted marketing authorisation for liraglutide for treatment of T2DM.

The incretin effect in normal subjects and people with type 2 diabetes
Beta-cell dysfunction is a central defect characterizing people with T2DM. One factor contributing to failing beta-cell function in T2DM is loss of the incretin effect. The incretin effect is the augmentation of glucose-stimulated insulin secretion by intestinal insulinotropic peptides (reviewed in 3), among which, glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1), secreted from endocrine K- and L-cells in response to nutrient ingestion, seem to be the most important.3 Together, they are responsible for up to 60-70% of the insulin response following a meal.3 Both hormones stimulate insulin secretion glucose-dependently, meaning that they cannot cause hypoglycaemia.3 Several studies have indicated that the poor incretin effect in patients with T2DM results from a severe defect in beta-cell sensitivity to GIP, while the insulinotropic effect of GLP-1 is relatively more preserved.3 In fact, infusion of slightly supraphysiological amounts of GLP-1 can increase glucose-induced insulin secretion to normal levels.3 An additional contributory factor to the impaired incretin effect may be that meal-induced GLP-1 secretion is often attenuated in people with T2DM, while GIP responses are less affected.3

GLP-1, also glucose dependently suppresses inappropriately elevated glucagon secretion, slows gastric emptying, and decreases appetite, energy intake and body weight.3 Furthermore, animal studies have shown that GLP-1 inhibits beta-cell apoptosis and promotes neogenesis and proliferation and increases beta-cell mass.3,5

Native GLP-1 is rapidly degraded by the enzyme dipeptidyl peptidase-4 (DPP-4), resulting in a half-life of only 1-2 min, while supraphysiological amounts of GLP-1 can increase glucose-induced insulin secretion to normal levels.3 Together, they are responsible for up to 60-70% of the insulin response following a meal.3 Both hormones stimulate insulin secretion glucose-dependently, meaning that they cannot cause hypoglycaemia.3 Several studies have indicated that the poor incretin effect in patients with T2DM results from a severe defect in beta-cell sensitivity to GIP, while the insulinotropic effect of GLP-1 is relatively more preserved.3 In fact, infusion of slightly supraphysiological amounts of GLP-1 can increase glucose-induced insulin secretion to normal levels.3 An additional contributory factor to the impaired incretin effect may be that meal-induced GLP-1 secretion is often attenuated in people with T2DM, while GIP responses are less affected.3

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Native GLP-1 is rapidly degraded by the enzyme dipeptidyl peptidase-4 (DPP-4), resulting in a half-life of only 1-2 min, which limits its therapeutic usefulness.3,5 This has led to development of stable, DPP-4 resistant GLP-1 analogues with a longer half-life.

Therapies for treatment of hyperglycaemia
Currently available therapies act by either increasing insulin secretion (sulfonylureas or glinides), decreasing insulin resistance (glitazones or metformin) or delaying the absorption of glucose from the intestine (acarbose).6,7 None of the drugs address the elevated glucagon secretion. The newer incretin-based therapies include the DPP-4 inhibitors sitagliptin (Januvia®, Merck, New Jersey, USA) and vildagliptin (Galvus®, Novartis, Basel, Switzerland), which reduces HbA1c with about 0.7 to 1.0% point and are weight neutral.8-10 Exenatide, a DPP-4 resistant GLP-1 receptor agonist, reduces HbA1c with approximately 0.7 to 1.0% point and also induces weight loss.8,9 The “old” OADs are associated with side effects as weight gain (sulfonylureas, glinides and glitazones), hypoglycaemia (sulphonylureas and glinides), lactate acidosis and intestinal side effects (metformin), and peripheral oedema and fractures (glitazones).6,7 The side effects with exenatide are primarily gastrointestinal, while the DPP-4 inhibitors have been associated with slightly more upper respiratory infections.6,9 Insulin can decrease any level of elevated HbA1c to, or close to, the therapeutic goal, but is often associated with risk of weight gain and hypoglycaemia.7

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Abbreviations:
Liraglutide

Liraglutide is a once daily human GLP-1 analogue, based on the structure of native GLP-1 with an amino acid substitution (lysine with arginine at position 34) and attachment of a C16 acyl chain via a glutamoyl spacer to lysine at position 26, and is formulated as an isotonic solution for subcutaneous injection by a 31G pen device. The maximal concentration is observed after 10-14 hours and the half-life is 11-13 hours providing 24-h duration of action. Liraglutide is relatively resistant to DPP-4 degradation. No effect of gender, age or injection site has been seen on the pharmacokinetics of liraglutide. After initiation of treatment steady-state concentrations are obtained after 3-4 days.

The glucoregulatory action of liraglutide includes an increase in insulin secretion and suppression of glucagon secretion together with a slowing of gastric emptying. Liraglutide also decreases appetite and body weight.

Clinical efficacy

The liraglutide phase 3 development programme “Liraglutide Effect and Action in Diabetes” (LEAD) was completed in 2007. The programme includes around 6,500 people in 41 countries worldwide of which approximately 4,445 patients received liraglutide. The LEAD programme has compared the efficacy and safety of liraglutide as monotherapy and in combination with sulfonylurea, glitazone, insulin glargine and exenatide and includes 6 studies. In addition to assessment of glycaemic control, these studies include important endpoints such as assessments of body-weight, beta cell function, and safety and tolerability.

Liraglutide in monotherapy

The LEAD 3 trial

A 52-week randomised trial comparing two doses of liraglutide (1.2 mg and 1.8 mg QD) to glimepiride (8 mg QD). 746 subjects previously treated with diet and exercise (36%) or oral antidiabetic drugs in monotherapy were randomised to the three groups of treatment (table 1). Liraglutide 1.2 mg and 1.8 mg reduced HbA₁c more than glimepiride (table 1, figure 3), and more of the subjects in the liraglutide groups reached HbA1c ≤ 6.5% and <7.0% (table 1). In addition, the decrease in HbA1c with liraglutide 1.8 mg was significantly greater than with liraglutide 1.2 mg (table 1, figure 3). The decrease in HbA₁c was most pronounced in the group previously treated with only lifestyle changes (liraglutide 1.2 mg: −1.2%, liraglutide 1.8 mg: −1.6% and glimepiride: −0.9%). At the end of the study there was a significant weight decrease in the liraglutide groups, as compared to weight gain in the glimepiride group (table 1), resulting in a weight difference of 3.2 to 3.6 kg between the liraglutide groups and glimepiride treated patients. Nausea occurred in 29% of the participants in the 1.8 mg liraglutide group, but was transient, compared with 9% in the glimepiride group. The rates of minor hypoglycaemic episodes (blood glucose <56 mg/dl [3.0 mmol/l]) were significantly lower for the liraglutide 1.2 and 1.8 mg groups versus glimepiride (table 1). No subjects reported major hypoglycaemic events. About 320 pa-

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**Figure 1.** The glucoregulatory action of liraglutide includes an increase in insulin secretion and suppression of glucagon secretion together with a slowing of gastric emptying. Liraglutide also decreases appetite and body weight.

**Figure 2.** The LEAD programme compared the efficacy and safety of liraglutide as monotherapy and in combination with sulfonylurea, glitazone, insulin glargine and exenatide and includes 6 studies. In addition to assessment of glycaemic control, these studies include important endpoints such as assessments of body-weight, beta cell function, and safety and tolerability.
tients out of the 440 patients completed the LEAD 3 study entered into an open-label extension. Two-year data showed, that liraglutide lowered HbA1c by 1.1% compared with 0.6% point for glimepiride (p <0.05). 60% of the patients treated with 1.8 mg liraglutide reach the ADA target of 7.0%. The difference in weight between patients treated with liraglutide and glimepiride, respectively, was of more than 3 kg in favor of liraglutide (press release, Novo Nordisk, 29 January 2009). Therefore, liraglutide monotherapy lowered HbA1c more than glimepiride and, at the same time, resulted in weight loss and lower rates of hypoglycaemia.

Liraglutide in combination therapy

The LEAD 1 trial

This randomized 26-week five arms trial investigated the effect on glycaemic control of three doses of liraglutide (0.6, 1.2 or 1.8 mg) added to glimepiride 4 mg QD compared with glimepiride 4 mg plus placebo or glimepiride 4 mg plus rosiglitazone 8 mg QD.\textsuperscript{16} The trial included 1041 subjects with T2DM previously treated with an oral antidiabetic drug in monotherapy (30%), or combination therapy (table 2).\textsuperscript{16} All doses of liraglutide reduce HbA1c more than glimepiride plus placebo (table 2, figure 3). The reduction in HbA1c was greater in patients previously treated with monotherapy –0.8%, –1.4%, and –1.5% for 0.6 mg, 1.2 mg and 1.8 mg of liraglutide, respectively, compared with –0.4% in the placebo-treated group and a reduction of –0.8% in the rosiglitazone treated patients (table 2). The reduction in HbA1c for the two highest doses of liraglutide was significant greater than for rosiglitazone (figure 3).\textsuperscript{16} Weight remained stable or increased slightly for all doses of liraglutide in combination with glimepiride compared with rosiglitazone and glimepiride on which pa-

\begin{figure}
\centering
\includegraphics[width=\textwidth]{figure3.png}
\caption{Summarises the reduction in HbA1c from baseline in LEAD study 1 to 5. The reduction in HbA1c is given for the groups treated with liraglutide, placebo or comparator, which in LEAD 1 was rosiglitazone, in LEAD 2 glimepiride, in LEAD 3 glimepiride, in LEAD 4 placebo, and in LEAD 5 insulin glargine.}
\end{figure}
Patients gained weight (table 2). The main adverse event with liraglutide was nausea (all <11%), and this was mostly mild and transient. Minor hypoglycaemia occurred in <10% of all patients treated with liraglutide plus glimepiride. Antibodies to liraglutide were detected in 9–13% of patients. Therefore, liraglutide added to glimepiride provided superior control compared with rosiglitazone with a favourable weight regulation and good overall safety.

The LEAD 2 trial
This randomized 26-week five arm trial investigated the effect on glycaemic control of three doses of liraglutide (0.6, 1.2 or 1.8 mg) added to metformin 1 g BD compared with metformin monotherapy plus placebo or metformin plus glimepiride 4 mg QD (table 3). The trial included 1091 subjects with T2D previously treated with oral antidiabetic drugs in monotherapy (35%), or combination therapy (table 3). All doses of liraglutide reduce HbA1c more than metformin plus placebo (table 3, figure 3). The reduction in HbA1c did not differ between metformin plus glimepiride and the two highest doses of liraglutide (table 3, figure 3). The reduction in weight was greater in the two group treated with the highest doses of liraglutide compared with metformin plus placebo (table 3). In the group treated with glimepiride weight increased with 1.0 kg. Minor hypoglycaemic events were reported in 0.8 to 3.7% of the patients treated with metformin and liraglutide compared with 17% in the glimepiride group. Nausea occurred initially in 6–12% of subjects in the liraglutide groups, declining to 2% after 8–16 weeks of treatment.

Liraglutide in triple therapy
The LEAD 4 study
Participants with T2DM were during a 11 week run-in period titrated until stable on rosiglitazone 4 mg BD and metformin 1 g BD. Before screening 20% of patients were on monotherapy, while 80% were treated with combination therapy of oral antidiabetic drugs. Patients were randomised to treatment with liraglutide 1.2 mg per day (n= 178), 1.8 mg per day (n= 178) or placebo (n= 177) for 26 weeks. Baseline HbA1c (8.3%) was reduced by −1.5% in both liraglutide treated groups compared with a −0.5% reduction in the placebo group (figure 3). A HbA1c <7.0 was obtained in 58%, 54%, and 28% of participants treated with 1.2 mg, 1.8 mg and placebo, respectively. 80% of the participants treated with monotherapy when entering the study obtained a HbA1c <7.0%. The reduction in fasting plasma glucose and the weight changes were in favour of liraglutide.

Table 2. Main results from LEAD 1 study

<table>
<thead>
<tr>
<th>LEAD 1</th>
<th>Glimepiride + liraglutide (0.6 mg/day)</th>
<th>Glimepiride + liraglutide (1.2 mg/day)</th>
<th>Glimepiride + liraglutide (1.8 mg/day)</th>
<th>Glimepiride + rosiglitazone</th>
<th>Glimepiride + placebo</th>
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</thead>
<tbody>
<tr>
<td>Participants</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Subjects randomized</td>
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<td>228</td>
<td>233</td>
<td>232</td>
<td>114</td>
</tr>
<tr>
<td>Completers (%)</td>
<td>213 (91%)</td>
<td>196 (86%)</td>
<td>208 (89%)</td>
<td>194 (84%)</td>
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<td></td>
</tr>
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<td>Age (years)</td>
<td>55.6</td>
<td>57.7</td>
<td>55.7</td>
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<td>54.7</td>
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<td>30.0</td>
<td>29.4</td>
<td>30.3</td>
</tr>
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<td>Duration (years)</td>
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<td>8.1</td>
<td>7.7</td>
<td>8.0</td>
<td>7.8</td>
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<tr>
<td>Glycemia</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline HbA1c (%)</td>
<td>8.5</td>
<td>8.5</td>
<td>8.4</td>
<td>8.4</td>
<td>8.4</td>
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<tr>
<td>Final HbA1c (%)</td>
<td>7.9</td>
<td>7.5</td>
<td>7.5</td>
<td>8.0</td>
<td>8.7</td>
</tr>
<tr>
<td>Change in HbA1c (%)</td>
<td>−0.6*</td>
<td>−1.1**</td>
<td>−1.1**</td>
<td>−0.4</td>
<td>+0.2</td>
</tr>
<tr>
<td>% HbA1c &lt;7.0%</td>
<td>23*</td>
<td>34**</td>
<td>40**</td>
<td>21</td>
<td>7</td>
</tr>
<tr>
<td>% HbA1c ≤6.5%</td>
<td>12</td>
<td>21***</td>
<td>21***</td>
<td>10</td>
<td>4</td>
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<tr>
<td>Baseline FPG (mmol/l)</td>
<td>9.7</td>
<td>9.8</td>
<td>10.0</td>
<td>9.5</td>
<td>9.9</td>
</tr>
<tr>
<td>Final FPG (mmol/l)</td>
<td>9.2</td>
<td>8.4</td>
<td>8.3</td>
<td>9.1</td>
<td>10.7</td>
</tr>
<tr>
<td>Change in FPG (mmol/l)</td>
<td>−0.7**</td>
<td>−1.6*</td>
<td>−1.6**</td>
<td>−0.9</td>
<td>+1.0</td>
</tr>
<tr>
<td>Minor hypoglycemic events/subjects/year</td>
<td>0.17</td>
<td>0.51</td>
<td>0.47</td>
<td>0.12</td>
<td>0.17</td>
</tr>
<tr>
<td>Weight change (kg)</td>
<td>+0.7**</td>
<td>+0.3**</td>
<td>−0.2**</td>
<td>+2.1</td>
<td>−0.1</td>
</tr>
</tbody>
</table>

*p <0.05 vs glimepiride + placebo; **p <0.05 vs glimepiride + rosiglitazone. FPG: fasting plasma glucose.
Nausea was observed in approximately 30% of the liraglutide treated subjects.\textsuperscript{18}

The LEAD 5 study
Liraglutide (1.8 mg) in combination with metformin (1 g twice daily) plus glimepiride (2-4 mg once daily) was compared with placebo or treatment with insulin glargine over 26 weeks (table 4).\textsuperscript{19} Insulin glargine was titrated according to the published AT.\textsuperscript{20} Mean reduction in HbA\(_1c\) was significantly greater with liraglutide than in the placebo or insulin glargine treated groups (table 4, figure 3). More than half of the patients treated with liraglutide reached the ADA target of HbA\(_1c\) <7.0%, and 37% reached the goal of HbA\(_1c\) ≤6.5%, which was significant more than in the insulin glargine group (table 4, figure 3). Fasting plasma glucose was similarly reduced in the liraglutide and glargine groups. Reduction in body weight was superior with liraglutide resulting in a weight difference of 3.5 kg compared to the insulin glargine treated group (table 4). Nausea was reported in 14% of the liraglutide treated patients, but decreased during the trial to 2-4% after the first 12 weeks. Five patients (2.2%) experienced major hypoglycaemic episodes in the 1.8 mg liraglutide treated group. There were no major episodes in the other treatment groups. Incidence of minor hypoglycaemic events did not differ between the groups (table 4). 10% of the liraglutide treated patients developed liraglutide antibodies.\textsuperscript{19}

### Efficacy of liraglutide once daily compared with exenatide twice daily

The LEAD 6 Study
Patients treated with metformin or sulfonylurea or a combination of metformin and sulfonylurea were directly randomised to once daily liraglutide 1.8 mg or twice daily exenatide 10 \(\mu g\) for 26 weeks study (table 5).\textsuperscript{21} Patients treated with liraglutide achieved a reduction in HbA\(_1c\) of more than –1.1%, compared to a reduction in HbA\(_1c\) of less than –0.8% in the exenatide treated group, a difference which was statistically significant (figure 4).\textsuperscript{21} 54% in the liraglutide group reached HbA\(_1c\) <7%, compared to 43% in the exenatide group, which was significant different. For a HbA\(_1c\) ≤6.5% the numbers reaching target were 35% and 21%, respectively.\textsuperscript{21} Both groups lost around 3 kg in weight, with a trend towards more weight loss in the liraglutide group.

The most frequently reported adverse events for both liraglutide and exenatide were nausea at a level of around 25% (percent of all study participants reporting nausea at least once) (figure 4).\textsuperscript{21} After week 8-10 the percentage of patients reporting nausea with liraglutide was below 10%, while in the exenatide group the level remained at about 10%. At week 26 only 2.5% of the liraglutide group had nausea compared with 8.6% in the exenatide group (figure 4). The rate of minor hypoglycaemia primarily seen in combination with sulfonylureas was statistically significantly lower in the liraglutide group, but the overall rate was low.

### Table 3. Main results from LEAD 2 study

<table>
<thead>
<tr>
<th>LEAD 2</th>
<th>Metformin + Liraglutide (0.6 mg/day)</th>
<th>Metformin + Liraglutide (1.2 mg/day)</th>
<th>Metformin + Liraglutide (1.8 mg/day)</th>
<th>Metformin + Glimepiride</th>
<th>Metformin + Placebo</th>
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<tr>
<td>Participants</td>
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<td>Subjects randomized</td>
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<td>241</td>
<td>242</td>
<td>244</td>
<td>122</td>
</tr>
<tr>
<td>Completers (%)</td>
<td>208 (86%)</td>
<td>197 (82%)</td>
<td>191 (79%)</td>
<td>210 (86%)</td>
<td>74 (61%)</td>
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<td>Demographics</td>
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<tr>
<td>Age (years)</td>
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<td>BMI (kg/m(^2))</td>
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<td>Duration (years)</td>
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<td>Glycemia</td>
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<td></td>
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<td>Baseline HbA(_1c) (%)</td>
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<td>8.3</td>
<td>8.4</td>
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<tr>
<td>Final HbA(_1c) (%)</td>
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<td>7.5</td>
<td>7.5</td>
<td>7.5</td>
<td>8.6</td>
</tr>
<tr>
<td>Change in HbA(_1c) (%)</td>
<td>–0.7*</td>
<td>–1.0*</td>
<td>–1.0*</td>
<td>–1.0</td>
<td>+ 0.1</td>
</tr>
<tr>
<td>% HbA(_1c) &lt;7.0%</td>
<td>28***</td>
<td>35*</td>
<td>42*</td>
<td>36</td>
<td>11</td>
</tr>
<tr>
<td>% HbA(_1c) ≤6.5%</td>
<td>11***</td>
<td>20*</td>
<td>25*</td>
<td>22</td>
<td>4.2</td>
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<td>Change in FPG (mmol/l)</td>
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<td>–1.6*</td>
<td>–1.7*</td>
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<td>% reporting minor hypoglycemic events</td>
<td>3.3**</td>
<td>0.8**</td>
<td>2.5**</td>
<td>16.9</td>
<td>2.5**</td>
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<tr>
<td>Weight change (kg)</td>
<td>–1.8***</td>
<td>–2.6***</td>
<td>–2.8***</td>
<td>+ 1.0</td>
<td>–1.5</td>
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</table>

*p <0.05 vs metformin + placebo; **p <0.05 vs metformin + glimepiride. FPG: fasting plasma glucose.
for both groups. HOMA-B and triglycerides improved significantly more with liraglutide. Overall treatment satisfaction was significantly better in the liraglutide group than in the exenatide group.

Meta-analysis of LEAD 1, 2 and 5 trials
Participants from LEAD 1, 2 and 5 were stratified by baseline HbA1c quartiles. Treatment with liraglutide resulted in a reduction of HbA1c of about 0.4 - 0.9% in quartile 1 (mean HbA1c about 7.3%) to a reduction of 1.3 to 2.3% in quartile 4 (mean HbA1c of about 9.7%). The greatest decrease in body weight occurred in subjects with BMI >35 kg/m². The weight reduction in subjects with BMI <25 kg/m² was from 0 to 2 kg increasing to 1 to 4.5 kg in subjects with a BMI ≥ 35 kg/m². The lowest weight loss was observed in LEAD 1, where metformin was removed and sulfonylurea added to the treatment. The greatest weight loss was observed with the combination liraglutide and metformin. The highest dose of liraglutide (1.8 mg/day) reduced systolic blood pressure by 1.9 to 4.5 mm Hg versus comparator treatment. The reduction in blood pressure was already observed after 2 weeks treatment, before any significant weight loss. Finally, significantly improved beta-cell function evaluated from HOMA beta-cell function and the proinsulin/insulin ratio.

Safety and tolerability of liraglutide
Liraglutide has been well tolerated with a low risk of hypoglycaemia, even in participants also treated with sulfonylurea. The incidence of nausea has been acceptable and primarily observed during the first weeks of treatment. The low incidence of nausea is probably explained by the rather flat profile of action for liraglutide, and that a three week titration scheme was introduced in all the studies. In less than 15% of patients, antibodies to liraglutide were detected, but without influence on glycaemic control. Five cases of pancreatitis have been registered in the liraglutide treated patients. Whether this is more than expected in individuals with type 2 diabetes needs further investigations.

In relation to adverse events of the GLP-1 receptor agonists some focus has been on thyroid C-cell neoplastic changes in rodents and mice with liraglutide, have not been observed in humans. Increased blood calcitonin and goitre have been reported in clinical trials in particular in patients with pre-existing thyroid disease.

Regulatory affairs
In July 2009 the European Commission granted marketing authorisation for liraglutide for treatment of T2DM in combination with metformin or a sulphonylurea in patients with insufficient glycaemic control despite maximal tolerated dose of monotherapy with metformin or sulphonylurea, and combination treatment with metformin and a sulphonylurea or metformin and a thiazolidinedione in patients with insufficient glycaemic control.

Conclusions

The LEAD phase 3 programme has shown the superiority of liraglutide compared with other antidiabetic drugs including insulin glargine and exenatide BD. The programme also illustrated that liraglutide lowers both HbA\textsubscript{1c} and weight. Liraglutide was well tolerated with a low incidence of nausea. Liraglutide reduced HbA\textsubscript{1c} more than glimepiride (HbA\textsubscript{1c} reduction of 1.2-1.6%), with 50% of the participants reaching HbA\textsubscript{1c} levels <7.0% (baseline HbA\textsubscript{1c}, 8.3%) in the liraglutide group.\textsuperscript{15} Furthermore, significantly fewer hypoglycaemia events and lower blood pressure were observed with liraglutide compared with glimepiride.\textsuperscript{15} The weight reduction was 3-4 kg in the liraglutide group compared with the glimepiride group.\textsuperscript{15} In combination therapy with metformin (LEAD 2) liraglutide reduces HbA\textsubscript{1c} similar to metformin plus glimepiride (app. –1.0%) with minimal risk of hypoglycaemia.\textsuperscript{17} In LEAD 1 the combination of liraglutide and glimepiride lowered HbA\textsubscript{1c} significant more than glimepiride plus rosiglitazone.\textsuperscript{16} The reduction in the liraglutide treated group was for the highest dose –1.5% after 26 weeks.\textsuperscript{16} The weight reduction was more pronounced when liraglutide was added to metformin than when combined with glimepiride. In triple therapy, the combination of liraglutide, metformin and rosiglitazone reduces HbA\textsubscript{1c} by –1.5% compared with a reduction of –0.5% in the placebo treated patients, but with a weight reduction of 2.6 kg in favour of liraglutide (LEAD 4).\textsuperscript{27} In LEAD 5 significantly lower HbA\textsubscript{1c} was observed with liraglutide compared with insulin glargine treatment.\textsuperscript{18} Weight difference to insulin glargine treated subjects was 3.0 to 3.5 kg.\textsuperscript{19} A significant reduction in blood pressure was observed with liraglutide versus insulin glargine.\textsuperscript{19} The LEAD 6 study indicates that liraglutide once daily is more effective than exenatide twice daily in reducing HbA\textsubscript{1c}.\textsuperscript{21} Weight loss did not differ between subjects treated with either liraglutide or exenatide.\textsuperscript{21} The LEAD studies also indicate that liraglutide has a beneficial effects on blood pressure and beta-cell function.

Commentary

During treatment with liraglutide the regulation of both insulin and glucagon secretion is glucose dependent, which reduces the risk of hypoglycaemia. Especially, when liraglutide is combined with metformin or a glitazone the risk of hypoglycaemia is minimal. Liraglutide also induces weight loss, which is important since most people with T2DM are obese, while sulfonylureas, glitazones and insulin therapy are usually associated with weight gain, while the DPP-4 inhibitors are weight neutral. Liraglutide is very convenient in relation to flexibility over timing of injection and need not to be injected in relation to meals. The need of self-monitoring of blood glucose is minimal, especially when compared with insulin treatment.

More data on durability of glycaemic control is of interest, especially in comparison with other oral antidiabetic drugs. Long-term studies on the effect of liraglutide on beta-cell function in humans will also be of interest. Whether liraglutide can prevent the progression of the disease by preventing beta-cell failure is yet unknown. The observation that GLP-1 receptor agonists improve myocardial function in human patients after myocardial infarction, improve endothelial function, and reduce blood pressure highlights the need for studies with cardiovascular endpoints (reviewed in\textsuperscript{21,28}). Liraglutide may be attractive to use in subjects with T2DM and heart failure since GLP-1 promotes renal sodium and water excretion and lower blood pressure.\textsuperscript{23,29,30} Liraglutide induces transient nausea in up to 20% of subjects treated with 1.2 to 1.8 mg per day. The nausea in most patients is transient, and dose escalating over weeks minimized this side effect.

The most recent guidelines recommend that metformin therapy is initiated in association with a lifestyle-intervention program at time of diagnosis.\textsuperscript{7} Subsequent therapy involved the use of additional sulfonylurea or basal insulin treatment. Liraglutide may be considered as an attractive second drug to add to metformin, especially when hypoglycaemia is particularly undesirable and when weight loss is a consideration, or in patients who do not wish to start insulin treatment due to the risk of weight gain and fear of hypoglycaemia. The final position of liraglutide in the T2DM treatment algorithm will first be clarified when we have long-term trials with cardiovascular endpoints, and data illustrating the effects on the progression of T2DM.
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Practical considerations

- Liraglutide is the first human GLP-1 receptor analogue suitable for once daily dosing.
- Liraglutide has been shown to lower HbA1c to the same degree or more than other oral antidiabetic drugs, inducing weight loss and improving beta-cell function, blood pressure and some cardiovascular risk markers.
- Liraglutide induces transient nausea in up to 20% of subjects with higher doses, but this adverse effect is transient and can be minimized by dose escalating over weeks.

References