

# Liraglutide: A Review of the First Once-Daily GLP-1 Receptor Agonist

Bruce Bode, MD, FACE

**L**iraglutide is an analog with 97% homology to human glucagon-like peptide-1 (GLP-1). It acts as a GLP-1 receptor agonist when injected subcutaneously.<sup>1-3</sup> On January 25, 2010, the Food and Drug Administration (FDA) approved liraglutide as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus (T2DM).<sup>1</sup>

## The LEAD Trials and Comparison With Sitagliptin

Liraglutide efficacy and safety were evaluated in the Liraglutide Effect and Action in Diabetes (LEAD) studies, which were large, randomized multicenter phase 3 trials in adults with T2DM (Table 1).<sup>4-9</sup> Liraglutide was also evaluated in a head-to-head comparison with sitagliptin.<sup>3</sup>

All trials except LEAD-3 were 26 weeks in duration; LEAD-3 was 52 weeks in duration. LEAD-2 and LEAD-3 had extensions. Active treatment and/or placebo were used as comparators, and the primary end point in all studies was the change from baseline in glycosylated hemoglobin (A1C) at 26 weeks (or 52 weeks for LEAD-3).<sup>4-9</sup>

In this section, the design and key results from each of the LEAD studies will be discussed. The design and key results of the head-to-head comparison with sitagliptin will also be discussed. The trials are presented in the following order:

- Monotherapy: LEAD-3<sup>4</sup>
- Add-on to metformin: LEAD-2<sup>5</sup>
- Add-on to glimepiride: LEAD-1<sup>6</sup>
- Add-on to metformin + rosiglitazone: LEAD-4<sup>7</sup>
- Add-on to metformin + glimepiride: LEAD-5<sup>8</sup>
- Comparison with exenatide: LEAD-6<sup>9</sup>
- Comparison with sitagliptin<sup>3</sup>

This progression mirrors the way therapies are usually administered in clinical practice: treatment is usually initiated with monotherapy, then intensified by increasing the dose and/or number of antidiabetic agents as needed to achieve glycemic control.<sup>10,11</sup>

### Monotherapy (LEAD-3)

LEAD-3 compared liraglutide 1.2 or 1.8 mg/day with glimepiride 8 mg/day for 52 weeks; study arms included oral and injected

## Abstract

Liraglutide is an analog with 97% homology to human glucagon-like peptide (GLP-1) and acts as a GLP-1 receptor agonist. Several large, randomized, multicenter phase 3 trials evaluated the efficacy and safety of liraglutide by comparing monotherapy and combination therapy with other antidiabetic medications in adult patients with type 2 diabetes. The Liraglutide Effect and Action in Diabetes (LEAD) program demonstrated that liraglutide, when used alone or in combination with other antidiabetic medications, effectively controls hyperglycemia (glycosylated hemoglobin [A1C] reductions up to 1.6%) and assists patients in meeting established glycemic targets. Compared with certain other classes of antidiabetic agents, liraglutide is associated with a lower risk of hypoglycemia. Liraglutide has also been associated with weight loss (1.8 to 3.4 kg) and improved patient satisfaction and health-related quality of life. Several studies have demonstrated that GLP-1 receptor agonists may improve pancreatic beta cell function, which may delay disease progression if maintained over the long term. As with any drug, liraglutide is not without risk, and a patient's complete clinical status and benefit-to-risk profile should be considered before prescribing treatment. For patients with type 2 diabetes who have failed to achieve glycemic control through diet and exercise, liraglutide may be an important treatment option. The current consensus statement of the American Association of Clinical Endocrinologists (AACE) and the American College of Endocrinology (ACE) cites efficacy and low risk of hypoglycemia in preferring GLP-1 agonists and dipeptidyl peptidase-4 (DPP-4) inhibitors over sulfonylureas and glinides, after initial treatment with metformin. The guidelines prefer GLP-1 agonists over DPP-4 inhibitors because of their actions that promote weight loss and their somewhat greater effectiveness in reducing postprandial glucose excursions.

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For author information and disclosures, see end of text.

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■ **Table 1.** The Liraglutide Clinical Development Program

Trial	Design, Sample Size	Study Arms	Primary End Point	Secondary End Points
<b>LEAD-3:</b> Monotherapy, 52 weeks <sup>4</sup>	Double-blind, double-dummy, randomized, active control, parallel group  N = 746 (randomized)	Liraglutide 1.2 mg/day + glimepiride placebo Liraglutide 1.8 mg/day + glimepiride placebo Liraglutide placebo + glimepiride 8 mg/day	Change from baseline A1C after 52 weeks  Avg Baseline A1C = 8.3	Changes in weight, FPG, 8-point plasma glucose profiles, blood pressure, fasting glucagon, proinsulin:insulin ratio, HOMA-B, HOMA-IR, and patient assessment of QOL
<b>LEAD-2:</b> Add-on to metformin, 26 weeks <sup>5</sup>	Double-blind, double-dummy, randomized, active control, parallel group  N = 1091 (randomized)	Liraglutide 0.6 mg/day + metformin 1 g twice daily + glimepiride placebo Liraglutide 1.2 mg/day + metformin 1 g twice daily + glimepiride placebo Liraglutide 1.8 mg/day + metformin 1 g twice daily + glimepiride placebo Liraglutide placebo + metformin 1 g twice daily + glimepiride placebo Liraglutide placebo + metformin 1 g twice daily + glimepiride 4 mg/day	Change from baseline A1C after 26 weeks  Avg Baseline A1C = 8.4	Changes in weight, FPG, 7-point plasma glucose profiles, fasting insulin, fasting C-peptide, fasting proinsulin:insulin ratio, and HOMA-B
<b>LEAD-1:</b> Add-on to glimepiride, 26 weeks <sup>6</sup>	Double-blind, double-dummy, randomized, active control, parallel group  N = 1041 (randomized)	Liraglutide 0.6 mg/day + glimepiride 2-4 mg/day + rosiglitazone placebo Liraglutide 1.2 mg/day + glimepiride 2-4 mg/day + rosiglitazone placebo Liraglutide 1.8 mg/day + glimepiride 2-4 mg/day + rosiglitazone placebo Liraglutide placebo + glimepiride 2-4 mg/day + rosiglitazone placebo Liraglutide placebo + glimepiride 2-4 mg/day + rosiglitazone 4 mg/day	Change from baseline A1C after 26 weeks  Avg Baseline A1C = 8.4	Proportions of patients reaching targets of A1C <7% and A1C ≤6.5%, FPG 5.0-7.2 mmol/L, and PPG 10.0 mmol/L; changes in body weight, FPG, PPG, proinsulin:insulin ratio, HOMA-B, HOMA-IR, and blood pressure
<b>LEAD-4:</b> Add-on to metformin + rosiglitazone, 26 weeks <sup>7</sup>	Double-blind, randomized, placebo control, parallel group  N = 533 (randomized)	Liraglutide 1.2 mg/day + metformin 1 g twice daily + rosiglitazone 4 mg twice daily Liraglutide 1.8 mg/day + metformin 1 g twice daily + rosiglitazone 4 mg twice daily Liraglutide placebo + metformin 1 g twice daily + rosiglitazone 4 mg twice daily	Change from baseline A1C after 26 weeks  Avg Baseline A1C = 8.5	Changes in weight, FPG, 7-point plasma glucose profiles, fasting insulin, fasting C-peptide, fasting proinsulin:insulin ratio, HOMA-B, HOMA-IR, and lipids
<b>LEAD-5:</b> Add-on to metformin + glimepiride, 26 weeks <sup>8</sup>	Randomized, parallel group, placebo-controlled (injected liraglutide placebo; open-label insulin glargine)  N = 581 (randomized)	Liraglutide 1.8 mg/day + metformin 1 g twice daily + glimepiride 2-4 mg/day Liraglutide placebo + metformin 1 g twice daily + glimepiride 2-4 mg/day Insulin glargine (individually titrated) + metformin 1 g twice daily + glimepiride 2-4 mg/day	Change from baseline A1C after 26 weeks  Avg Baseline A1C = 8.3	Changes in weight, waist circumference, FPG, 8-point plasma glucose profiles, proinsulin to C-peptide ratio, and blood pressure
<b>LEAD-6:</b> Comparison with exenatide (head-to-head), 26 weeks <sup>9</sup>	Randomized, parallel group, open-label, active-comparator  N = 464 (randomized)	Liraglutide 1.8 mg/day + maximally tolerated OADs (metformin, sulfonylurea, or both) Exenatide 10 µg twice daily + maximally tolerated OADs (metformin, sulfonylurea, or both)	Change from baseline A1C after 26 weeks  Avg Baseline A1C = 8.2	Proportions of patients reaching <7% and ≤6.5% A1C and changes in FPG, 7-point plasma glucose profiles, weight, beta cell function, glucagon, blood pressure, and lipids
<b>Liraglutide compared with sitagliptin,</b> 26 weeks <sup>3</sup>	Randomized, parallel group, open-label, active-comparator  N = 665 (randomized)	Liraglutide 1.2 or 1.8 mg/day + metformin ≥1500 mg/day Sitagliptin 100 mg/day + metformin ≥1500 mg/day	Change from baseline A1C after 26 weeks  Avg Baseline A1C = 8.5	Proportions of patients reaching <7% and ≤6.5% A1C, changes in FPG and PPG levels, weight, beta cell function, fasting lipid levels, several cardiovascular risk markers, blood pressure, heart rate, waist circumference, waist-to-hip ratio, treatment satisfaction, and a composite of proportions of patients with A1C level less than 7%, no hypoglycemia, and a weight increase of 0 kg or less

A1C indicates glycosylated hemoglobin; FPG, fasting plasma glucose; HOMA-B, homeostasis model assessment of beta cell function; HOMA-IR, homeostasis model assessment of insulin resistance; LEAD, Liraglutide Effect and Action in Diabetes; OADs, oral antidiabetic drugs; PPG, postprandial plasma glucose; QOL, quality of life.

placebos.<sup>4</sup> Note that in the United States, the maximum PI-recommended dose of glimepiride is 8 mg/day.<sup>12</sup>

Analyses were based on the intent-to-treat (ITT) population exposed to at least 1 dose of treatment.<sup>4</sup> Of the 746 patients randomized, 259 (34.8%) did not complete the study.<sup>4</sup> Withdrawal among patients treated with glimepiride was 38.7% (6.0% from adverse events [AEs]), with liraglutide 1.2 mg was 35.5% (10.0% from AEs), and with liraglutide 1.8 mg was 30.1% (7.3% from AEs).<sup>4</sup>

A1C decreased by 0.84% from baseline with liraglutide 1.2 mg versus 0.51% with glimepiride ( $P = .0014$ ), and 1.14% with liraglutide 1.8 mg versus 0.51% with glimepiride ( $P < .0001$ ).<sup>4</sup> Mean A1C values over the course of the 52-week study are shown in **Figure 1**.<sup>4</sup> A1C decreased by 1.6% from baseline with liraglutide 1.8 mg in patients who were previously treated only with lifestyle modifications (drug-naïve).<sup>4</sup> Also, compared with 28% of patients in the glimepiride group, 51% of patients treated with 1.8 mg liraglutide ( $P < .0001$ ) and 43% treated with 1.2 mg ( $P = .0007$ ) reached target A1C levels of less than 7%.<sup>4</sup> Fasting plasma glucose (FPG) level decreases were greater with liraglutide than glimepiride (-1.42 mmol/L with liraglutide 1.8 mg vs -0.29 mmol/L with glimepiride,  $P = .0001$ ; -0.84 mmol/L with liraglutide 1.2 mg,  $P = .027$  vs glimepiride).<sup>4</sup> FPG values over the course of the 52-week study are shown in **Figure 2**.<sup>4</sup> Systolic blood pressure measurements decreased by 0.7 mm Hg with glimepiride, 2.1 mm Hg with liraglutide 1.2 mg, and 3.6 mm Hg with liraglutide 1.8 mg (significant difference with liraglutide 1.8 mg versus glimepiride,  $P < .0118$ ).<sup>4</sup>

Body weight significantly decreased with both doses of liraglutide and increased with glimepiride ( $P = .0001$  for both).<sup>4</sup> Weight loss with liraglutide from the first 16 weeks was sustained for the 52 weeks of the study.<sup>4</sup> Patients who had nausea for more than 7 days had mean weight changes of -3.24 kg (1.2 mg), -3.39 kg (1.8 mg), and -1.43 kg (glimepiride). Those who had nausea for 7 days or less had mean changes of -1.85 kg (1.2 mg), -2.26 kg (1.8 mg), and +1.22 kg (glimepiride). Weight loss differences between those with nausea lasting greater than 7 days and those with nausea lasting 7 days or less were not significant.<sup>4</sup>

Liraglutide was associated with less minor hypoglycemia than glimepiride (0.30 events/year and 0.25 events/year with liraglutide 1.2 mg and 1.8 mg, respectively, versus 1.96 events/year with glimepiride,  $P < .0001$ ).<sup>4</sup> Pancreatitis occurred in 2 patients receiving liraglutide (1 at each dose), both recovered, and 1 withdrew from the study.<sup>4</sup> Gastrointestinal (GI) disorders were reported by 122 patients (49%) receiving liraglutide 1.2 mg, 126 patients (51%) receiving liraglutide 1.8 mg, and 64 patients (26%) receiving glimepiride.<sup>4</sup> Of

patients receiving liraglutide 1.2 mg and 1.8 mg, 4% and 2%, respectively, withdrew because of GI events, versus none of the patients receiving glimepiride.<sup>4</sup>

Extension data have recently been published, and show that liraglutide monotherapy for 2 years provides significant and sustained improvements in glycemic control and body weight compared with glimepiride monotherapy, at a lower risk of hypoglycemia. In the ITT population, A1C reductions were -0.3% with glimepiride, -0.6% with liraglutide 1.2 mg ( $P = .0076$  vs glimepiride), and -0.9% with liraglutide 1.8 mg ( $P < .0001$  vs glimepiride).<sup>13</sup>

#### Add-on to Metformin (LEAD-2)

LEAD-2 randomized patients receiving metformin 1 g twice daily to additional therapy of liraglutide (1.8 mg, 1.2 mg, or 0.6 mg/day), glimepiride 4 mg/day, or placebo for 26 weeks.<sup>5</sup> The double-dummy design included both oral and injected placebos.<sup>5</sup> Note that in the United States but not in all other countries participating in the trial, the maximum PI-recommended dose of metformin is 2550 mg/day, and the maximum PI-recommended dose of glimepiride is 8 mg/day.<sup>12,14</sup>

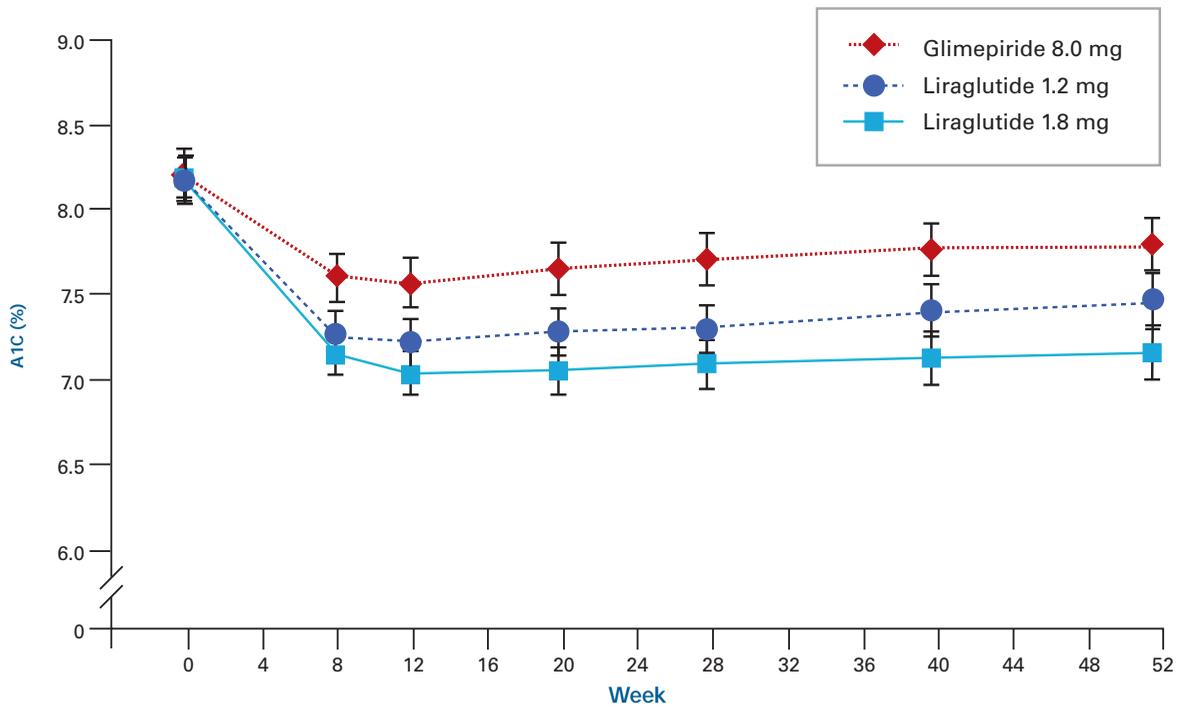
The safety population comprised those exposed to at least 1 dose of trial drug; the ITT population for efficacy analyses also had 1 post-baseline measurement of the parameter.<sup>5</sup> Of the 1091 patients randomized,<sup>5</sup> 211 (19.3%) did not complete the study.<sup>5</sup> Withdrawal rates among patients were 39% with placebo (2% from AEs), 14% with glimepiride (3% from AEs), 14% from liraglutide 0.6 mg (5% from AEs), 18% from liraglutide 1.2 mg (10% from AEs), and 21% from liraglutide 1.8 mg (12% from AEs).<sup>5</sup>

In the ITT population, A1C levels decreased 1.0% with liraglutide 1.2 mg, liraglutide 1.8 mg, and glimepiride, decreased 0.7% with liraglutide 0.6 mg, and increased 0.1% with placebo.<sup>5</sup> Efficacy in reaching target A1C level was comparable with active treatments: A1C less than 7% was reached by 42.4% of patients treated with liraglutide 1.8 mg, 35.3% with liraglutide 1.2 mg, 28.0% with liraglutide 0.6 mg, and 36.3% with glimepiride.<sup>5</sup> However, only 10.8% of placebo patients reached the target (all doses of liraglutide vs placebo,  $P < .02$ ).<sup>5</sup> Decreases in FPG levels with all doses of liraglutide were comparable to those with glimepiride and greater than the decrease with placebo ( $P < .0001$ ).<sup>5</sup> Decreases in postprandial plasma glucose (PPG) levels with 1.2 mg and 1.8 mg liraglutide were comparable to those with glimepiride and greater than that with placebo ( $P < .001$ ).<sup>5</sup>

All 3 liraglutide groups lost weight (dose dependent, 1.8-2.8 kg) and the glimepiride group gained weight (1.0

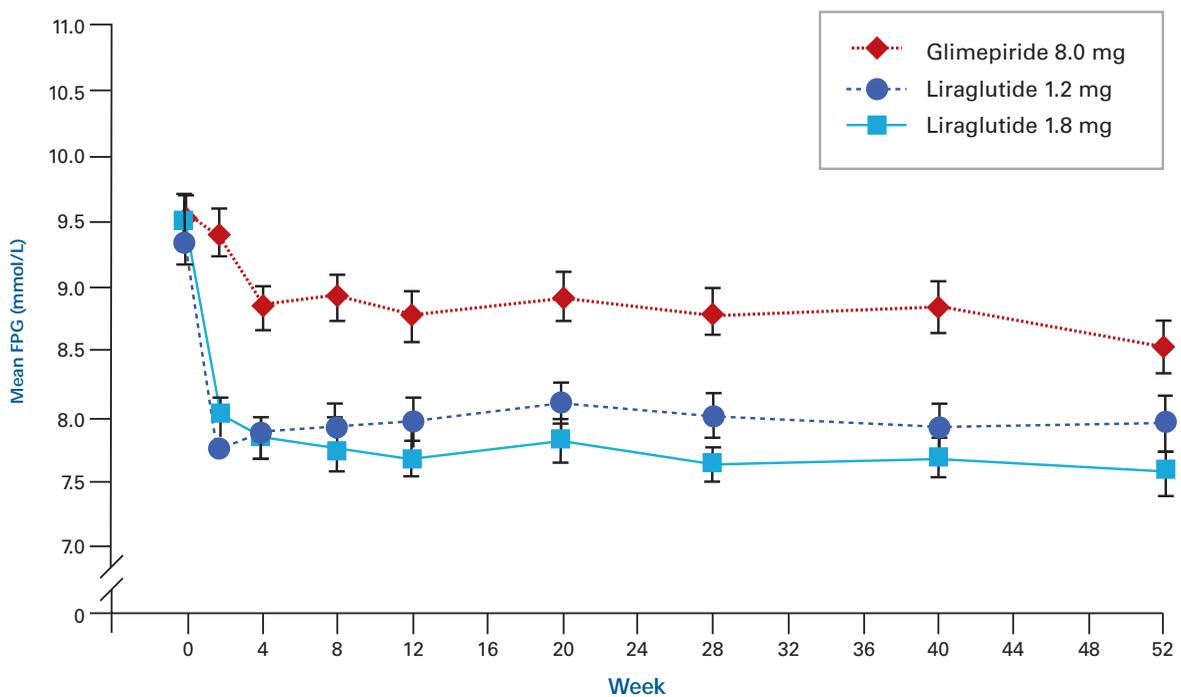
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■ **Figure 1. Changes in A1C Over Time for Study Population in LEAD-3 (Monotherapy)<sup>4</sup>**



A1C indicates glycosylated hemoglobin; LEAD, Liraglutide Effect and Action in Diabetes. Reprinted with permission from Garber A, et al. *Lancet*. 2009;373(9662):473-481.

■ **Figure 2. Changes in FPG Over Time for Study Population in LEAD-3 (Monotherapy)<sup>4</sup>**



FPG indicates fasting plasma glucose; LEAD, Liraglutide Effect and Action in Diabetes. Reprinted with permission from Garber A, et al. *Lancet*. 2009;373(9662):473-481.

kg) ( $P < .0001$  for all).<sup>5</sup> Weight loss with 1.2 mg and 1.8 mg liraglutide was also significantly greater than the 1.5-kg loss associated with placebo added to metformin background therapy ( $P \leq .01$ ).<sup>5</sup>

Liraglutide was associated with substantially less minor hypoglycemia than glimepiride (0.03-0.14 events/year vs 1.23 events/year,  $P < .001$ ).<sup>5</sup> Acute pancreatitis occurred in 1 patient receiving 1.2 mg liraglutide and 1 receiving glimepiride; both withdrew, were hospitalized, and subsequently recovered.<sup>5</sup> GI symptoms (nausea, vomiting, and/or diarrhea) occurred in 35% of liraglutide 0.6 mg patients, 40% of 1.2 mg patients, 44% of 1.8 mg patients, and 17% of glimepiride and placebo patients.<sup>5</sup>

#### **Add-on to Glimepiride (LEAD-1)**

LEAD-1 randomized patients receiving glimepiride 2 to 4 mg/day to add-on treatment with liraglutide (1.8, 1.2, or 0.6 mg/day), rosiglitazone 4 mg/day, or placebo for 26 weeks; study arms included both oral and injected placebo controls.<sup>4</sup> Note that in the United States, the maximum PI-recommended doses of glimepiride and rosiglitazone are 8 mg/day.<sup>12,15</sup> All efficacy and safety analyses were based on ITT criteria (exposure to  $\geq 1$  dose of trial drug).<sup>4</sup> Of 1041 patients randomized, 147 (14.1%) did not complete the study.<sup>4</sup> Withdrawal rates among patients were 27% with placebo, 16% with rosiglitazone, 11% with liraglutide 0.6 mg, 14% with liraglutide 1.2 mg, and 9% with liraglutide 1.8 mg.<sup>4</sup> AEs were associated with 3.7% of withdrawals.<sup>4</sup>

In the ITT population, liraglutide 1.8 mg and 1.2 mg/day were associated with greater reductions in A1C levels (-1.1%) compared with rosiglitazone (-0.4%) or placebo (+0.2%); 0.6 mg liraglutide showed greater reductions than placebo ( $P < .0001$  for all comparisons) but not significantly greater than rosiglitazone.<sup>4</sup> The percentages of patients who reached an A1C level less than 7% or 6.5% or less were greater with liraglutide 1.8 mg and 1.2 mg than rosiglitazone ( $P \leq .0003$ ) or placebo ( $P < .0001$ ).<sup>4</sup> Similarly, the 2 highest doses of liraglutide were associated with greater reductions in FPG levels than rosiglitazone ( $P < .01$ ) or placebo ( $P < .0001$ ).<sup>4</sup> The 2 highest doses of liraglutide were associated with greater reductions in PPG than rosiglitazone (1.2 mg  $P = .043$ , 1.8 mg  $P = .0022$ ) or placebo ( $P < .0001$ ).<sup>4</sup> Percentages reaching A1C targets, reductions in FPG levels, and reductions in PPG levels were not significantly greater with liraglutide 0.6 mg than with rosiglitazone.<sup>4</sup> Patients lost weight with liraglutide 1.8 mg (-0.2 kg) and placebo (-0.1 kg) and gained weight with liraglutide 1.2 mg (+0.3 kg), liraglutide 0.6 mg (+0.7 kg), and rosiglitazone (+2.1 kg).<sup>4</sup> The differences in weight change between liraglutide

(all doses) and rosiglitazone were significant ( $P < .0001$ ), but not the differences versus placebo.<sup>4</sup>

Minor hypoglycemia occurred in less than 10% of each treatment group and was greater with liraglutide 1.8 mg ( $P = .0065$ ) and 1.2 mg ( $P = .0024$ ) versus rosiglitazone and with liraglutide 1.2 mg versus placebo ( $P = .048$ ).<sup>4</sup> There was 1 case of major hypoglycemia, which occurred after 9 days of therapy with liraglutide 1.8 mg in combination with glimepiride.<sup>4</sup> One subject receiving 0.6 mg liraglutide developed chronic pancreatitis but completed the trial.<sup>4</sup> Nausea occurred more commonly with liraglutide than with rosiglitazone or placebo.<sup>4</sup> For other AEs in this and other LEAD trials, see [Table 2](#).

#### **Add-on to Metformin + Rosiglitazone (LEAD-4)**

LEAD-4 included 3 treatment arms: patients receiving metformin 1 g twice daily plus rosiglitazone 4 mg twice daily were randomized to additional therapy of liraglutide 1.2 or 1.8 mg/day or injected placebo for 26 weeks.<sup>7</sup> Note that in the United States, the maximum PI-recommended dose of metformin is 2550 mg/day, and the maximum PI-recommended dose of rosiglitazone is 8 mg/day.<sup>14,15</sup>

Efficacy analyses were based on the ITT population exposed to at least 1 dose of treatment and with 1 postbaseline measurement of the parameter.<sup>7</sup> Of the 533 patients randomized,<sup>7</sup> 126 (23.6%) did not complete the study.<sup>7</sup> Withdrawal rates among patients were 25% with liraglutide 1.8 mg (15% from AEs), 14% with liraglutide 1.2 mg (6% from AEs), and 32% with placebo (3% from AEs).<sup>7</sup>

Compared with placebo, both doses of liraglutide were associated with significant reductions in A1C levels ( $P < .0001$ ), FPG levels ( $P < .0001$ ), and PPG levels ( $P < .001$ ).<sup>7</sup> At the end of the study, 57.5% and 53.7% of participants in the 1.2 mg and 1.8 mg liraglutide groups, respectively, had an A1C level less than 7%, compared with 28.1% in the placebo group, with 37.3% and 36.2%, respectively, reaching an A1C level of 6.5% or less compared with 14.4% with placebo ( $P < .0001$ ).<sup>7</sup> In patients receiving 1.8 mg liraglutide, 1.2 mg liraglutide, and placebo, systolic blood pressure measurements decreased by 5.6, 6.7, and 1.1 mm Hg, respectively (liraglutide vs placebo,  $P < .05$ ).<sup>7</sup> In patients receiving 1.8 mg liraglutide, 1.2 mg liraglutide, and placebo, mean body weight change was -2.0 kg, -1.0 kg, and +0.6 kg, respectively (liraglutide vs placebo,  $P < .0001$ ).<sup>7</sup>

Minor hypoglycemia occurred at rates of 0.4 events/year, 0.6 events/year, and 0.2 events/year with liraglutide 1.2 mg, 1.8 mg, and placebo, respectively; the rate was significantly higher with the 1.8 mg dose than placebo ( $P = .004$ ).<sup>7</sup> GI

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■ **Table 2.** Adverse Events That Occurred in at Least 5% of Patients Given Liraglutide in the LEAD Trials<sup>1,9</sup>

### A. Monotherapy (LEAD-3)

	Liraglutide (both doses) N = 497	Glimepiride N = 248
Adverse Event Term	(%)	(%)
Nausea	28.4	8.5
Diarrhea	17.1	8.9
Vomiting	10.9	3.6
Constipation	9.9	4.8
Upper respiratory tract infection	9.5	5.6
Headache	9.1	9.3
Influenza	7.4	3.6
Urinary tract infection	6.0	4.0
Dizziness	5.8	5.2
Sinusitis	5.6	6.0
Nasopharyngitis	5.2	5.2
Back Pain	5.0	4.4

### B. Add-on to Metformin (LEAD-2)

	Liraglutide (all doses) + Metformin N = 724	Placebo + Metformin N = 121	Glimepiride + Metformin N = 242
Adverse Event Term	(%)	(%)	(%)
Nausea	15.2	4.1	3.3
Diarrhea	10.9	4.1	3.7
Headache	9.0	6.6	9.5
Vomiting	6.5	0.8	0.4

### C. Add-on to Glimepiride (LEAD-1)

	Liraglutide (all doses) + Glimepiride N = 695	Placebo + Glimepiride N = 114	Rosiglitazone + Glimepiride N = 231
Adverse Event Term	(%)	(%)	(%)
Nausea	7.5	1.8	2.6
Diarrhea	7.2	1.8	2.2
Constipation	5.3	0.9	1.7
Dyspepsia	5.2	0.9	2.6

### D. Add-on to Metformin + Rosiglitazone (LEAD-4)

	Liraglutide (both doses) + Metformin + Rosiglitazone N = 355	Placebo + Metformin + Rosiglitazone N = 175
Adverse Event Term	(%)	(%)
Nausea	34.6	8.6
Diarrhea	14.1	6.3
Vomiting	12.4	2.9
Decreased appetite	9.3	1.1
Anorexia	9.0	0.0
Headache	8.2	4.6
Constipation	5.1	1.1
Fatigue	5.1	1.7

(Continued)

■ **Table 2.** Adverse Events That Occurred in at Least 5% of Patients Given Liraglutide in the LEAD Trials<sup>1,9</sup>  
(Continued)

**E. Add-on to Metformin + Glimepiride (LEAD-5)**

	Liraglutide 1.8 mg + Metformin + Glimepiride N = 230	Placebo + Metformin + Glimepiride N = 114	Glargine + Metformin + Glimepiride N = 232
Adverse Event Term	(%)	(%)	(%)
Nausea	13.9	3.5	1.3
Diarrhea	10.0	5.3	1.3
Headache	9.6	7.9	5.6
Dyspepsia	6.5	0.9	1.7
Vomiting	6.5	3.5	0.4

**F. Comparison with Exenatide (LEAD-6)**

	Liraglutide 1.8 mg/day + maximally tolerated OADs (metformin, sulfonyleurea, or both) N = 235	Exenatide 10 µg twice daily + maximally tolerated OADs (metformin, sulfonyleurea, or both) N = 232
Adverse Event Term	(%)	(%)
Nausea	25.5	28.0
Nasopharyngitis	11.5	13.4
Diarrhea	12.3	12.1
Headache	8.9	10.3
Vomiting	6.0	9.9
Dyspepsia	8.9	4.7
Upper respiratory infection	6.4	6.0
Constipation	5.1	2.6
Bronchitis	5.1	6.9
Back pain	6.0	3.4

LEAD indicates Liraglutide Effect and Action in Diabetes; OADs, oral antidiabetic drugs.

AEs including nausea, vomiting, and diarrhea were reported by 45%, 56%, and 19% of liraglutide 1.2 mg, 1.8 mg, and placebo patients, respectively.<sup>7</sup> Most nausea occurred in the first 4 weeks of treatment.<sup>7</sup>

**Add-on to Metformin + Glimepiride (LEAD-5)**

LEAD-5 had 3 treatment arms: patients receiving metformin 1 g twice daily plus open-label glimepiride 2 to 4 mg/day were randomized to additional treatment of liraglutide 1.8 mg/day, insulin glargine, or injected placebo for 26 weeks; because of necessary individualized titration, the insulin glargine was open label.<sup>8</sup> Note that in the United States, the maximum PI-recommended dose of metformin is 2550 mg/day, and the maximum PI-recommended dose of glimepiride is 8 mg/day.<sup>12,14</sup>

Analyses were based on the ITT population exposed to at least 1 dose of treatment.<sup>8</sup> For the primary end point, change in A1C levels, a statistical analysis was also performed

without last observation carried forward on the per-protocol population (those who completed the study without significant protocol violations).<sup>8</sup> Of the 581 patients randomized, 59 (10.2%) did not complete the study.<sup>8</sup> Of patients treated with liraglutide 1.8 mg, 10% withdrew (5% from AEs); with insulin glargine, 6% withdrew (2% from AEs); and with placebo, 16% withdrew (1% from AEs).<sup>8</sup>

In the ITT population (n = 576),<sup>8</sup> liraglutide was associated with significant reductions in A1C values versus glargine and placebo (-0.24% vs glargine,  $P = .0015$ ; -1.09% vs placebo,  $P < .0001$ ).<sup>8</sup> The difference between glargine and placebo was also significant (-0.85%,  $P < .0001$ ).<sup>8</sup> The per-protocol analysis produced similar results.<sup>8</sup> Significantly more patients reached A1C levels less than 7% and 6.5% or less with liraglutide than with glargine or placebo.<sup>8</sup> Differences between liraglutide and insulin glargine groups in FPG and PPG level reductions were not significant; differences between liraglutide and placebo groups in FPG and PPG

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level reductions were significant.<sup>8</sup> The difference in systolic blood pressure measurements between liraglutide and insulin glargine was significant; the difference in systolic blood pressure measurements between liraglutide and placebo was not significant.<sup>8</sup>

Weight change was -1.8 kg with liraglutide, -0.4 kg with placebo, and +1.6 kg with insulin glargine (liraglutide vs placebo difference -1.4 kg,  $P = .0001$ ; liraglutide vs glargine difference -3.4 kg,  $P < .0001$ ).<sup>8</sup> Reduction in waist circumference was greater with liraglutide (-1.50 cm) compared with insulin glargine (+0.89 cm;  $P < .0001$ ), but not with placebo (-0.62 cm;  $P = .0608$ ).<sup>8</sup>

Minor hypoglycemia occurred at rates of 1.2 events/year, 1.3 events/year, and 1.0 events/year with liraglutide, glargine, and placebo, respectively.<sup>8</sup> Five patients reported major hyperglycemia episodes in the liraglutide group (2.2%), and no events were reported in the glargine or placebo groups.<sup>8</sup> GI symptoms occurred significantly more frequently with liraglutide than glargine or placebo (nausea  $P < .0001$  in both comparisons, diarrhea  $P < .0001$ , dyspepsia  $P = .0042$ , vomiting  $P = .0005$ ) (Table 2).<sup>8</sup>

### Comparison With Exenatide (LEAD-6)

LEAD-6 added liraglutide 1.8 mg/day or exenatide 10  $\mu$ g twice daily to maximally tolerated doses of metformin, a sulfonylurea, or both for 26 weeks; the trial was open label.<sup>9</sup> Note that in the United States, the maximum PI-recommended dose of exenatide is 10  $\mu$ g twice daily.<sup>16</sup>

Efficacy analyses were based on the ITT population.<sup>9</sup> Three subjects were not randomized but received treatment; they were included in the safety but not the ITT population.<sup>9</sup> Of the 464 patients in the ITT population,<sup>9</sup> 78 (16.8%) did not complete the study.<sup>9</sup> Of patients treated with liraglutide, 14.2% withdrew (9.9% from AEs) and of those treated with exenatide, 19.5% withdrew (13.4% from AEs).<sup>9</sup>

Significantly greater reductions in A1C levels occurred with liraglutide (-1.12%) than exenatide (-0.79%,  $P < .0001$ ).<sup>9</sup> Per-protocol analysis showed similar A1C results (-0.29,  $P < .0001$ ).<sup>9</sup> The percentage of patients who reached A1C levels less than 7% and 6.5% or less was higher with liraglutide than exenatide (target <7%: 54% vs 43%,  $P = .0015$ ; target  $\leq 6.5\%$ : 35% vs 21%,  $P < .0001$ ).<sup>9</sup> Greater reductions in FPG levels occurred with liraglutide than exenatide (-1.01 mmol/L,  $P < .0001$ ).<sup>9</sup> PPG increment levels (self-measured with 7-point plasma glucose profiles) after breakfast and dinner decreased more with exenatide than liraglutide (breakfast: estimated treatment difference, 1.33 mmol/L;  $P < .0001$ ; dinner: estimated treatment difference, 1.01 mmol/L;  $P = .0005$ ).<sup>9</sup>

Similar weight losses occurred with liraglutide (-3.24 kg) and exenatide (-2.87 kg).<sup>9</sup> Patients expressed greater treatment satisfaction with liraglutide than exenatide ( $P = .0004$ ), as assessed by the Diabetes Treatment Satisfaction Questionnaire (DTSQ), which was administered to a subgroup of patients.<sup>9</sup>

Two patients receiving exenatide combined with a sulfonylurea experienced major hypoglycemic episodes; 1 patient given liraglutide had pancreatitis reported as chronic.<sup>9</sup> Minor hypoglycemia was less frequent with liraglutide than exenatide (1.932 events/year vs 2.600 events/year,  $P = .0131$ ).<sup>9</sup> The liraglutide group had fewer overall reported AEs (74.9% vs 78.9%) but more AEs defined as serious and severe (serious 5.1% vs 2.6%, severe 7.2% vs 4.7%).<sup>9</sup>

In a 14-week extension of LEAD-6, 386 patients who completed the 26 weeks entered the extension ITT population.<sup>17</sup> Of these, 202 who began the trial with liraglutide continued and 187 who began with exenatide switched to liraglutide.<sup>17</sup> Of the patients continuing on liraglutide, 1.5% withdrew (none because of AEs), and of the switching patients, 5.3% withdrew (3.2% from AEs).<sup>17</sup>

In patients who continued liraglutide therapy, further decreases in weight (-0.4 kg,  $P = .0089$ ) and systolic blood pressure measurements (-2.2 mm Hg,  $P = .0128$ ) occurred.<sup>17</sup> Those who switched from exenatide to liraglutide had further reductions in A1C levels (-0.32%,  $P < .0001$ ), FPG levels (-0.9 mmol/L,  $P < .0001$ ), body weight (-0.9 kg,  $P < .0001$ ), and systolic blood pressure measurements (-3.8 mm Hg,  $P < .0001$ ).<sup>17</sup> PPG levels after lunch decreased in the switching group (-0.64 mmol/L,  $P = .0032$ ).<sup>17</sup> Changes in other parameters in the 14-week extension did not reach statistical significance.<sup>17</sup>

### Liraglutide Compared With Sitagliptin

Although not part of the LEAD program, the most recently completed phase 3b study was an open-label trial that randomized patients receiving at least 1500 mg/day metformin to additional therapy of liraglutide 1.2 mg or 1.8 mg/day, or sitagliptin 100 mg/day for 26 weeks.<sup>3</sup> The average baseline A1C value in the study population was 8.5%.<sup>3</sup> The primary end point was change in A1C level from baseline to 26 weeks.<sup>3</sup> Secondary end points included proportions of subjects achieving A1C level less than 7% or of 6.5% or less, changes in FPG and PPG levels, weight, beta cell function, fasting lipid levels, several cardiovascular risk markers, blood pressure measurements, heart rate measurements, waist circumference, waist-to-hip ratio, treatment satisfaction, and a composite of proportions of subjects with A1C level less than 7%, no hypoglycemia, and a weight increase of 0 kg or less.<sup>3</sup>

Efficacy analyses except for treatment satisfaction were based on the full analysis set of participants exposed to at least 1 dose of trial drug and with at least 1 measurement of A1C level taken postbaseline.<sup>3</sup> Of the full analysis set of 658 participants,<sup>3</sup> 104 patients (15.8%) did not complete the study.<sup>3</sup> Withdrawal among patients was 23.5% with liraglutide 1.2 mg (6.3% from AEs), 12.4% with liraglutide 1.8 mg (6.9% from AEs), and 11.4% with sitagliptin (1.8% from AEs).<sup>3</sup>

A1C levels decreased with all treatments.<sup>3</sup> Liraglutide 1.8 mg and 1.2 mg were associated with greater reductions in A1C levels than sitagliptin (-0.6% and -0.34%, respectively,  $P < .0001$ ).<sup>3</sup> Significantly more patients receiving liraglutide 1.8 mg and 1.2 mg than sitagliptin reached A1C targets of less than 7% ( $P < .0001$ ) and 6.5% or less ( $P < .0001$  for 1.8 mg,  $P = .0059$  for 1.2 mg).<sup>3</sup> For A1C of less than 7.0%, odds ratios versus sitagliptin were 4.50 (95% CI 2.90-6.97) for 1.8 mg liraglutide, and 2.75 (1.78-4.25) for 1.2 mg liraglutide; for A1C of 6.5% or lower, odds ratios versus sitagliptin were 4.25 (2.55-7.08) for 1.8 mg liraglutide, and 2.11 (1.24-3.59) for 1.2 mg liraglutide.<sup>3</sup> Liraglutide 1.8 mg and 1.2 mg were associated with greater reductions in FPG levels than sitagliptin ( $P < .0001$ ).<sup>3</sup>

Weight loss occurred in all 3 groups. Mean weight change was -3.38 kg with liraglutide 1.8 mg ( $P < .0001$ ) and -2.86 kg with liraglutide 1.2 mg ( $P < .0001$ ) versus -0.96 kg with sitagliptin.<sup>3</sup> Significantly greater decreases in waist circumference occurred with liraglutide than sitagliptin (-2.63 cm with 1.8 mg liraglutide vs -1.12 cm with sitagliptin,  $P = .0017$ ; -2.69 cm with 1.2 mg liraglutide vs -1.12 cm with sitagliptin,  $P = .0010$ ), but waist-to-hip ratio did not change significantly with any treatment.<sup>3</sup> Significantly more patients achieved the composite secondary end point (composite of A1C level less than 7%, no hypoglycemia, and a weight increase of 0 kg or less) with liraglutide than sitagliptin: 46% (99/214) of those on 1.8 mg liraglutide, 37% (77/210) of those on 1.2 mg liraglutide, and 14% (30/210) of those on sitagliptin achieved the composite secondary end point ( $P < .0001$  for both doses of liraglutide vs sitagliptin).<sup>3</sup> The increase in patient treatment satisfaction on the DTSQ was significantly greater with 1.8 mg liraglutide than sitagliptin ( $P = .03$ ), but the difference between 1.2 mg liraglutide and sitagliptin was not.<sup>3</sup> No difference in perceived convenience of oral versus injected treatment was recorded.<sup>3</sup>

Sitagliptin, liraglutide 1.2 mg, and liraglutide 1.8 mg were associated with low percentages of patients with serious AEs (2%, 3%, and 3%, respectively) and severe AEs (4%, 3%, and 3%).<sup>3</sup> Compared with sitagliptin, liraglutide 1.2 mg and 1.8 mg were associated with higher percentages of overall

AEs of any severity (58%, 66%, and 73%, respectively).<sup>3</sup> GI disorders were common with sitagliptin, but more common with liraglutide 1.2 mg and 1.8 mg (21%, 33%, and 40%, respectively); these included nausea (5%, 21%, and 27%), vomiting (4%, 8%, and 10%), and diarrhea (5%, 7%, and 11%).<sup>3</sup> Nervous system disorders and infections occurred with similar frequency in the sitagliptin and liraglutide 1.2 mg and 1.8 mg groups.<sup>3</sup> Other categories of frequent AEs included musculoskeletal and connective tissue disorders, general and administration-site disorders, and metabolism and nutrition disorders; the latter 2 categories occurred in less than 10% of sitagliptin patients but at least 10% of liraglutide patients.<sup>3</sup>

*52 Week Results:* After 1 year, both liraglutide 1.2 mg and 1.8 mg produced greater reductions in A1C (change from baseline: -1.5 for liraglutide 1.8 mg, -1.3 for liraglutide 1.2 mg, -0.9 for sitagliptin;  $P < .0001$  for both doses of liraglutide vs sitagliptin), FPG (change from baseline: -2.0 mmol/L for liraglutide 1.8 mg, -1.7 mmol/L for liraglutide 1.2 mg, -0.6 mmol/L for sitagliptin;  $P < .0001$  for both doses of liraglutide vs sitagliptin), and weight (change from baseline: -3.7 kg for liraglutide 1.8 mg, -2.8 kg for liraglutide 1.2 mg, -1.2 kg for sitagliptin;  $P < .0001$  for both doses of liraglutide vs sitagliptin) compared with sitagliptin. Overall scores on the DTSQ were better for liraglutide 1.8 mg than sitagliptin (+1.35 points;  $P < .05$ ). The proportions of patients reporting serious AEs and AEs (including hypoglycemia) were generally comparable among all 3 groups.<sup>18</sup>

## Safety and Tolerability of Liraglutide as Evidenced in LEAD

### Immunogenicity

*LEAD 1-5:* Approximately 50% to 70% of patients given liraglutide were tested for the presence of anti-liraglutide antibodies; low titers of anti-liraglutide antibodies were detected in 8.6%.<sup>1</sup> Because sampling was not performed uniformly across all patients in the 5 trials, the percentage who developed antibodies may have been underestimated.<sup>1</sup> Among liraglutide-treated patients who developed anti-liraglutide antibodies, the most common AEs were infections (40% of these patients vs 36%, 34%, and 35% of liraglutide-treated antibody-negative, placebo-treated, and comparator-treated patients, respectively), and these were primarily nonserious upper respiratory tract infections (11% of antibody-positive patients).<sup>1</sup> Antibody formation did not appear to be associated with reduced efficacy in lowering A1C levels when comparing mean A1C of all antibody-positive and all antibody-negative patients.<sup>1</sup> However, the 3 patients with the highest titers of anti-liraglutide antibodies had no

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reduction in A1C with liraglutide treatment.<sup>1</sup> Events from a composite of AEs potentially related to immunogenicity (eg, urticaria, angioedema) occurred in 0.8% of liraglutide-treated patients and 0.4% of comparator-treated patients.<sup>1</sup>

**LEAD 6:** The investigators found that treatment with liraglutide resulted in a lower incidence of antibody formation than exenatide, even when switching from exenatide to liraglutide.<sup>19</sup> Of patients who started and continued on liraglutide, 2.6% (4/154) had anti-liraglutide antibodies at 78 weeks.<sup>19</sup> After 26 weeks of treatment with exenatide, 61.1% of patients (113/185) had anti-exenatide antibodies.<sup>19</sup> Patients with high anti-exenatide antibody titers had smaller A1C reductions (-0.5%) than those with low titers (-1.0%). Patients with the highest anti-exenatide antibody titers had a -0.1% A1C reduction.<sup>19</sup> Of patients who started on exenatide and switched to liraglutide at week 26, 3.0% (4/134) had anti-liraglutide antibodies at week 78.<sup>19</sup>

### Thyroid C-cell AEs

The prescribing information for liraglutide includes a black box warning regarding the risk of thyroid C-cell tumors.<sup>1</sup>

Liraglutide has been found to cause thyroid C-cell tumors in rats and mice. It is unknown whether liraglutide will cause thyroid C-cell tumors, including medullary thyroid carcinoma (MTC), in humans.<sup>1</sup>

Calcitonin is a biological marker of MTC. Patients with MTC usually have calcitonin values greater than 50 ng/L. In liraglutide clinical trials, among patients with pre-treatment serum calcitonin less than 50 ng/L, 1 liraglutide-treated patient and no comparator-treated patients developed serum calcitonin greater than 50 ng/L. The liraglutide-treated patient who developed serum calcitonin greater than 50 ng/L had an elevated pre-treatment serum calcitonin. The clinical significance of these findings is unknown.<sup>1</sup>

It is unknown whether monitoring with serum calcitonin or thyroid ultrasound will mitigate the potential risk of MTC, and such monitoring may increase the risk of unnecessary procedures. Routine monitoring of serum calcitonin is of uncertain value in patients treated with liraglutide.<sup>1</sup> In an alert issued in 2010, the former president of the American Association of Clinical Endocrinologists (AACE), Dr Jeffery Garber, stated that the AACE in agreement with the FDA does not recommend special surveillance in liraglutide-treated individuals.<sup>20</sup>

In the 5 trials, 4 cases of thyroid C-cell hyperplasia were reported in liraglutide-treated patients and 1 case in a comparator-treated patient.<sup>1</sup> Subsequently, 1 additional case of thyroid C-cell hyperplasia in a liraglutide-treated patient and 1 case of medullary thyroid carcinoma in a comparator-treated patient were reported.<sup>1</sup> All cases were

diagnosed after thyroidectomy prompted by abnormal results on protocol-specified measurements of serum calcitonin; 4 of the 5 liraglutide-treated patients had elevated calcitonin at baseline and throughout the trial.<sup>1</sup>

Liraglutide is contraindicated in patients with personal or family history of medullary thyroid carcinoma or in patients with multiple endocrine neoplasia syndrome type 2.<sup>1</sup> Whether liraglutide causes thyroid C-cell tumors, including medullary thyroid carcinoma, in humans is unknown and could not be ruled out by the current clinical or nonclinical studies.<sup>1</sup> However, the FDA concluded that the incidence of carcinomas among rodents translated into low risk for humans.<sup>21</sup> Further, the FDA has required further surveillance studies, which are ongoing.

### Pancreatitis

In the 5 clinical trials, 7 liraglutide-treated patients and 1 comparator-treated patient developed pancreatitis (2.2 vs 0.6 cases per 1000 patient-years).<sup>1</sup> Five pancreatitis cases with liraglutide were reported as acute and 2 as chronic; 1 led to death, but clinical causality could not be established.<sup>1</sup> One subsequent case was reported in a liraglutide-treated patient.<sup>1</sup> No conclusive data establish a risk of pancreatitis with liraglutide, but it should be used with caution in patients with a history of pancreatitis.<sup>1</sup> Patients treated with liraglutide should be observed for symptoms of pancreatitis, including persistent severe abdominal pain, sometimes radiating to the back, with or without vomiting.<sup>1</sup>

To address these safety concerns the FDA required a Risk Evaluation and Mitigation Strategy, including a patient Medication Guide and a communication plan, as part of its approval of liraglutide.<sup>22</sup> The FDA also required additional studies for better understanding of the risks associated with this medication.<sup>22</sup>

### Liraglutide: Incidence of Hypoglycemia and Use With Other Medications

Patients treated with liraglutide in combination with an insulin secretagogue may have increased risk of hypoglycemia.<sup>1</sup> A reduction in the secretagogue dose may lower this risk.<sup>1</sup>

### Cardiovascular Safety of Liraglutide

The liraglutide clinical development program was completed before December 2008, when the FDA published industry guidelines for assessing cardiovascular risk of new antidiabetic drugs pre- and postapproval.<sup>21,22</sup> The FDA found no evidence of increased cardiovascular risk with liraglutide, but required a large postapproval study of cardiovascular safety.<sup>21,22</sup>

A long term evaluation trial (Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular disease outcome Results [LEADER]) is currently in progress, and aims to determine the long term effect of liraglutide on cardiovascular events in subjects with T2DM. Subjects will be randomized to receive liraglutide or placebo, in addition to the subject's standard treatment. The primary outcome is time from randomization to first occurrence of cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke (a composite cardiovascular outcome) from randomization up to 60 months.<sup>23</sup>

### Liraglutide: Indication and Place in Current Guidelines

Liraglutide is indicated as an adjunct to diet and exercise to improve glycemic control in adults with T2DM, though liraglutide is not recommended as first-line therapy.<sup>1</sup>

The current consensus statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) and the subsequent Standards of Medical Care in Diabetes of the ADA predate the FDA approval of liraglutide.<sup>10</sup> These guidelines place top priority on effective treatment of hyperglycemia,<sup>10</sup> but do not prefer specific classes of antidiabetic drugs over others.<sup>10,11</sup> The guidelines also recommend minimizing the risk of hypoglycemia, encouraging weight loss (or at least avoidance of weight gain), and achieving control of lipids and blood pressure.<sup>10,11</sup> The guidelines are based on achieving and maintaining an A1C level less than 7% and recommend intensifying treatment as necessary for that goal.<sup>10,11</sup> Pre- and postapproval studies have amply demonstrated the efficacy of liraglutide, including achieving A1C levels less than 7% in many patients.<sup>6,9</sup>

The current consensus statement of the AACE and the American College of Endocrinology (ACE) panel on T2DM also predates the FDA approval of liraglutide.<sup>24</sup> The statement does recommend specific treatment strategies and drug classes, including "GLP-1 agonist" (singular because exenatide, but not liraglutide, had FDA approval at the time of publication).<sup>24</sup> The algorithm shows GLP-1 agonists as options in all treatment strategies except concomitant use with insulin.<sup>24</sup>

### Conclusions

Clinical trials have demonstrated that liraglutide, used alone or in combination with other antidiabetic agents, effectively controls hyperglycemia by reducing A1C, FPG, and PPG levels, and can help patients meet established

glycemic targets with weight loss and minimal risk of hypoglycemia.<sup>5-9</sup> Because of its glucose-dependent actions, liraglutide carries a low risk of hypoglycemia compared with certain other classes of antidiabetic medications, but lowering the dose of a sulfonylurea should be considered when initiating liraglutide in patients already on a sulfonylurea.<sup>1</sup> Unlike some other treatments, and similar to exenatide, liraglutide has the added benefit of significant weight loss (1.8 kg to 3.7 kg).<sup>8,18</sup> The prospect of weight loss instead of weight gain may inspire good adherence. Studies have shown that liraglutide treatment and its associated weight loss can improve patient satisfaction and health-related quality of life.<sup>3,4,26</sup>

Controlled studies have found that liraglutide can be more effective at glycemic control than some non-incretin-based therapies.<sup>4,6</sup> Based upon results from open-label trials, liraglutide may be associated with greater efficacy and weight loss than sitagliptin, a member of the DPP-4 inhibitor class, and may be more effective than exenatide for achieving overall glycemic control.<sup>3,9</sup> However, additional studies are needed to further validate these findings.

In several studies, liraglutide was associated with improved pancreatic beta cell function,<sup>4,5,7-9</sup> results that suggest the possibility of delayed disease progression if maintained over the long term. It is possible that liraglutide may help alleviate the deterioration of glycemic control that is an important feature of T2DM development and progression.<sup>2</sup>

Liraglutide has been studied versus active comparators,<sup>4,6,8,9</sup> providing a body of evidence for liraglutide in terms of comparative effectiveness research (CER), as discussed in the first article in this supplement.<sup>25</sup>

As with any drug, liraglutide is not without risk and should be prescribed only with careful consideration of the manufacturer's prescribing information and all aspects of the clinical status of the patient. Liraglutide is contraindicated in patients with multiple endocrine neoplasia syndrome type 2 or personal or family history of medullary thyroid carcinoma and should be used with caution in patients with a history of pancreatitis.

Liraglutide is an important treatment option for many patients with T2DM who have not achieved glycemic control with diet and exercise. The current AACE/ACE consensus statement cites efficacy and low risk of hypoglycemia in preferring GLP-1 agonists and DPP-4 inhibitors over sulfonylureas and glinides, after initial treatment with metformin. The guidelines prefer GLP-1 agonists over dipeptidyl peptidase-4 inhibitors because of their actions that promote weight loss and their somewhat greater effectiveness in reducing PPG excursions.

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**Author Affiliation:** Department of Medicine, Emory University School of Medicine and Diabetes Resource Center, Atlanta Diabetes Associates, Atlanta, GA.

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**Address correspondence to:** Bruce Bode, MD, FACE, Atlanta Diabetes Associates, 77 Collier Rd, Ste 2080, Atlanta, GA 30309. E-mail: bbode001@aol.com.

## REFERENCES

1. Victoza [prescribing information]. Princeton, NJ: Novo Nordisk, Inc; 2010.
2. Deacon CF. Potential of liraglutide in the treatment of patients with type 2 diabetes. *Vasc Health Risk Manag*. 2009;5:199-211.
3. Pratley RE, Nauck M, Bailey T, et al; 1860-LIRA-DPP-4 Study Group. Liraglutide versus sitagliptin for patients with type 2 diabetes who did not have adequate glycaemic control with metformin: a 26-week, randomized, parallel-group, open-label trial. *Lancet*. 2010;375(9724):1447-1456.
4. Garber A, Henry R, Ratner R, et al; LEAD-3 (Mono) Study Group. Liraglutide versus glimepiride monotherapy for type 2 diabetes (LEAD-3 Mono): a randomized, 52-week, phase III, double-blind, parallel-treatment trial. *Lancet*. 2009;373(9662):473-481.
5. Nauck M, Frid A, Hermansen K, et al, for the LEAD-2 Study Group. Efficacy and safety comparison of liraglutide, glimepiride, and placebo, all in combination with metformin, in type 2 diabetes. *Diabetes Care*. 2009;32(1):84-90.
6. Marre M, Shaw J, Brandle M, et al, on behalf of the LEAD-1 SU study group. Liraglutide, a once-daily human GLP-1 analogue, added to a sulphonylurea over 26 weeks produces greater improvements in glycaemic and weight control compared with adding rosiglitazone or placebo in subjects with Type 2 diabetes (LEAD-1 SU). *Diabetic Med*. 2009;26:268-278.
7. Zinman B, Gerich J, Buse JB, et al; the LEAD-4 Study Investigators. Efficacy and safety of the human glucagon-like peptide-1 analog liraglutide in combination with metformin and thiazolidinedione in patients with type 2 diabetes (LEAD-4 Met+TZD). *Diabetes Care*. 2009;32(7):1224-1230.
8. Russell-Jones D, Vaag A, Schmitz O, et al; Liraglutide Effect and Action in Diabetes 5 (LEAD-5) met+SU Study Group. Liraglutide vs insulin glargine and placebo in combination with metformin and sulphonylurea therapy in type 2 diabetes mellitus (LEAD-5 met+SU): a randomised controlled trial. *Diabetologia*. 2009;52(1):2046-2055.
9. Buse JB, Rosenstock J, Sesti G, et al; LEAD-6 Study Group. Liraglutide once a day versus exenatide twice a day for type 2 diabetes: a 26-week randomized, parallel-group, multinational, open-label trial (LEAD-6). *Lancet*. 2009;374(9683):39-47.
10. Nathan DM, Buse JB, Davidson MB, et al; American Diabetes Association; European Association for Study of Diabetes. Medical management of hyperglycemia in type 2 diabetes: a consensus algorithm for the initiation and adjustment of therapy: a consensus statement of the American Diabetes Association and the European Association for the Study of Diabetes. *Diabetes Care*. 2009;32(1):193-203.
11. American Diabetes Association. Standards of medical care in diabetes—2011. *Diabetes Care*. 2011;34(suppl 1):S11-S61.
12. Amaryl [prescribing information]. Bridgewater, NJ: sanofi-aventis US LLC; 2009.
13. Garber A, Henry RR, Ratner R, Hale P, Chang CT, Bode B; LEAD-3 Study Group. Liraglutide, a once-daily human glucagon-like peptide 1 analogue, provides sustained improvements in glycaemic control and weight for 2 years as monotherapy compared with glimepiride in patients with type 2 diabetes. *Diabetes Obes Metab*. 2011;13(4):348-356.
14. Glucophage/Glucophage XR [prescribing information]. Princeton, NJ: Bristol-Myers Squibb Company; 2009.
15. Avandia [prescribing information]. Research Triangle Park, NC: GlaxoSmithKline; 2011.
16. Byetta [prescribing information]. San Diego, CA: Amylin Pharmaceuticals, Inc; 2010.
17. Buse JB, Sesti G, Schmidt WE, et al; Liraglutide Effect Action in Diabetes-6 Study Group. Switching to once-daily liraglutide from twice-daily exenatide further improves glycemic control in patients with type 2 diabetes using oral agents. *Diabetes Care*. 2010;33(6):1300-1303.
18. Pratley R, Nauck M, Bailey T, et al. Liraglutide treatment for 1 year offers sustained and more effective glycemic control and weight reduction compared with sitagliptin, both in combination with metformin, in patients with type 2 diabetes [abstract]. *Diabetes*. 2010;59(suppl 1). [http://professional.diabetes.org/Abstracts\\_Display.aspx?TYP=1&CID=78847](http://professional.diabetes.org/Abstracts_Display.aspx?TYP=1&CID=78847). Accessed January 18, 2011.
19. Buse J, Montanya E, Sesti G, et al. Frequency and magnitude of antibody formation are lower with liraglutide than exenatide: LEAD-6 Results [abstract]. *Diabetes*. 2010;59(suppl 1). [http://professional.diabetes.org/Abstracts\\_Display.aspx?TYP=1&CID=79621](http://professional.diabetes.org/Abstracts_Display.aspx?TYP=1&CID=79621). Accessed January 18, 2011.
20. Garber JR. 2010. American Association of Clinical Endocrinologists Web site. [www.aace.com/alert/liraglutide03152010.php](http://www.aace.com/alert/liraglutide03152010.php). Accessed March 1, 2011.
21. Parks M, Rosebraugh C. Weighing risks and benefits of liraglutide – the FDA’s review of a new antidiabetic therapy. *N Engl J Med*. 2010;362(9):774-777.
22. U.S. Food and Drug Administration. Postmarket Drug Safety Information for Patients and Providers. Questions and Answers – Safety Requirements for Victoza (liraglutide). Available at: <http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm198543.htm>. Accessed December 10, 2010.
23. Novo Nordisk. Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results - A Long Term Evaluation (LEADER). <http://novonordisk-trials.com/website/search/trial-registry-details.aspx?id=15076>. Updated February 8, 2011. Accessed February 23, 2011.
24. Rodbard HW, Jellinger PS, Davidson JA, et al. Statement by an American Association of Clinical Endocrinologists/American College of Endocrinology consensus panel on type 2 diabetes mellitus: an algorithm for glycemic control. *Endocr Pract*. 2009;15(6):540-559.
25. Ahmann A. Application of comparative effectiveness research in evaluation of treatments for type 2 diabetes mellitus. *Am J Manag Care*. 2011;17:17:S41-S51.
26. Campbell RK, Cobble ME, Reid TS, Shomal ME. Safety, tolerability, and nonglycemic effects of incretin-based therapies. *J Fam Pract*. 2010;59(9 suppl 1):S20-S27. Available at: <http://www.jfponline.com/Pages.aspx?AID=8945>. Accessed September 29, 2010.