# Improved Glycemic Control With No Weight Increase in Patients With Type 2 Diabetes After Once-Daily Treatment With the Long-Acting Glucagon-Like Peptide 1 Analog Liraglutide (NN2211)

## A 12-week, double-blind, randomized, controlled trial

STEN MADSBAD, MD, DMSC[1]
OLE SCHMITZ, MD, DMSC[2]
JONAS RANSTAM, PHD[3]
GRETHE JAKOBSEN, MSCPHARM[3]
DAVID R. MATTHEWS, DPHIL, FRCP[4]
ON BEHALF OF THE NN2211-1310 INTERNATIONAL STUDY GROUP

**OBJECTIVE** — Liraglutide is a long-acting glucagon-like peptide 1 analog designed for once daily injection. This study assessed the efficacy and safety of liraglutide after 12 weeks of treatment in type 2 diabetic patients.

**RESEARCH DESIGN AND METHODS** — A double-blind, randomized, parallel-group, placebo-controlled trial with an open-label comparator arm was conducted among 193 outpatients with type 2 diabetes. The mean age was 56.6 years and the mean $HbA_{1c}$ was 7.6% across the treatment groups. Patients were randomly assigned to one of five fixed-dosage groups of liraglutide (0.045, 0.225, 0.45, 0.60, or 0.75 mg), placebo, or open-label sulfonylurea (glimepiride, 1–4 mg). The primary end point was $HbA_{1c}$ after 12 weeks; secondary end points were fasting serum glucose, fasting C-peptide, fasting glucagon, fasting insulin, β-cell function, body weight, adverse events, and hypoglycemic episodes.

**RESULTS** — A total of 190 patients were included in the intention-to-treat (ITT) analysis. $HbA_{1c}$ decreased in all but the lowest liraglutide dosage group. In the 0.75-mg liraglutide group, $HbA_{1c}$ decreased by 0.75 percentage points ($P < 0.0001$) and fasting glucose decreased by 1.8 mmol/l ($P = 0.0003$) compared with placebo. Improvement in glycemic control was evident after 1 week. Body weight decreased by 1.2 kg in the 0.45-mg liraglutide group ($P = 0.0184$) compared with placebo. The proinsulin-to-insulin ratio decreased in the 0.75-mg liraglutide group (−0.18; $P = 0.0244$) compared with placebo. Patients treated with glimepiride had decreased $HbA_{1c}$ and fasting glucose, but slightly increased body weight. No safety issues were raised for liraglutide; observed adverse events were mild and transient.

**CONCLUSIONS** — A once-daily dose of liraglutide provides efficacious glycemic control and is not associated with weight gain. Adverse events with the drug are mild and transient, and the risk of hypoglycemia is negligible.

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Type 2 diabetes is characterized by insulin resistance and defective β-cell function and is associated with hyperglucagonemia, increased hepatic glucose production, and obesity (1). In addition, patients with type 2 diabetes experience a subnormal secretion of the incretin hormone glucagon-like peptide 1 (GLP-1) during meals (2,3). Sulfonylureas, although efficient in stimulating insulin secretion and lowering blood glucose, pose the disadvantages of weight gain and risk of hypoglycemia (4). Studies have demonstrated that GLP-1 stimulates insulin secretion, inhibits glucagon secretion in a glucose-dependent manner, and delays gastric emptying (2,5–7). In addition, several studies have shown GLP-1 to have an appetite-reducing effect (8–10), and one study has demonstrated weight loss after treatment with GLP-1 (11). These mechanisms make this hormone an attractive candidate for the treatment of type 2 diabetes. However, native GLP-1 has a very short half-life (1 min) (12), being rapidly metabolized by the enzyme dipeptidyl peptidase IV (13). It has been shown that GLP-1 must be present continuously in the blood stream to exert its actions (14).

Liraglutide is a long-acting, acylated GLP-1 analog, acting as a full agonist toward the GLP-1 receptor (15). Studies in animals and humans have demonstrated promising blood glucose−lowering ef-

From the [1]Hvidovre Hospital, University of Copenhagen, Denmark; the [2]University Hospital of Aarhus, Aarhus, Denmark; [3]Novo Nordisk A/S, Bagsvaerd, Denmark; and the [4]Oxford Centre for Diabetes, Endocrinology & Metabolism, University of Oxford, Oxford, U.K.

Address correspondence and reprint requests to Dr. Sten Madsbad, Department of Endocrinology, Hvidovre Hospital, Kettegaards Allé 30, DK-2650, Hvidovre, Denmark. E-mail: sten.madsbad@hh.hosp.dk.

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**Abbreviations:** GLP-1, glucagon-like peptide 1; HOMA, homeostasis model assessment; ITT, intention to treat; OHA, oral hypoglycemic agent.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

fects as well as a favorable safety profile. The half-life of liraglutide is ~12 h in both healthy subjects and type 2 diabetic patients after single and multiple dosing (16–18). The dosing regimen is a once daily injection. This trial investigated the efficacy and safety of liraglutide after 12 weeks of treatment in type 2 diabetic patients.

## RESEARCH DESIGN AND METHODS

—This trial was a 12-week, multicenter, double-blind, randomized, parallel-group, dosage-response trial in six treatment arms. In addition, an open-label sulfonylurea (glimepiride) arm was included as a reference group. Patients were instructed to maintain their diet, exercise program, and daily routines during the course of the trial. After a 4-week wash-out period during which current oral hypoglycemic agent (OHA) treatment was discontinued, patients were equally randomized to double-blind treatment of one of six arms (one of five dosages of liraglutide or placebo) or to the open-label reference group (glimepiride). The trial was conducted between December 2000 and October 2001 in Scandinavia and the U.K. The trial was conducted in accordance with the Helsinki Declaration (19), and the protocol was approved by each institution's independent ethics committee. The trial was explained to all patients, and their written informed consent was obtained before any trial-related procedures were initiated.

Eligible patients were men and women age ≥30 years who had a type 2 diabetes diagnosis (according to American Diabetes Association criteria) (20), had BMI ≤40 kg/m$^2$, were being treated with diet or an OHA, and had an $HbA_{1c}$ ≤ 9.5% (OHA) or 7.5–10.0% (diet). For patient safety, an upper limit for $HbA_{1c}$ was defined as a 4-week wash-out period and a placebo arm was included in the trial. Patients were excluded if any of the following were present: liver or renal disease, heart failure (New York Heart Association class III and IV) (21), unstable angina pectoris, myocardial infarction within the previous 12 months, concomitant treatment with thiazolidinediones or other investigational drugs, or other significant conditions likely to affect a patient's diabetes and/or ability to complete the trial. Women who were pregnant, breast-feeding, or not using an adequate method of contraception were also excluded. At randomization, fasting blood glucose had to be 6–13 mmol/l. Patients were withdrawn from the trial if fasting plasma glucose was >15 mmol/l.

In total, 311 patients were screened and 193 patients were randomized to a treatment group (Table 1). The reasons for failing screening were not meeting any inclusion criteria or meeting any exclusion criteria ($n$ = 86), not meeting randomization criteria ($n$ = 7), withdrawn consent ($n$ = 6), and other ($n$ = 19). The majority of patients ($n$ = 158) were being treated with OHA(s) and the remaining 35 patients were being treated with diet only. Most patients were on monotherapy with either metformin (65 patients) or sulfonylureas (55 patients); 22 patients received a combination of metformin and sulfonylureas, 14 patients received repaglinide, and 2 patients received acarbose treatment. In all, 190 patients were exposed to the experimental protocol; 3 patients withdrew consent before receiving randomized treatment.

Patients were recruited from the participating investigators' outpatient clinics or by local advertisements. Each patient was seen on seven occasions: screening; baseline; after 1, 4, 8, and 12 weeks of treatment; and follow-up. Current treatment with oral antidiabetic medication was discontinued at screening. Patients were supplied with a blood glucose meter (One Touch Profile Glucometer) and instructed in its use. Fasting blood glucose was measured every morning. $HbA_{1c}$, fasting serum glucose, insulin, C-peptide, and glucagon were measured every 4 weeks. Fasting serum glucose was also measured after the first week of treatment. Proinsulin was assessed in a subset of patients ($n$ = 74, equally distributed among the groups). Fasting samples were obtained before administration of the trial drug. Safety parameters (adverse events, hypoglycemic episodes, weight, standard hematology and biochemistry profile, vital signs, and electrocardiogram) were assessed at each visit. Liraglutide antibodies were measured before and after treatment.

The trial was double blind for the five dosage levels of liraglutide and placebo, and open label for glimepiride. The blinding was kept until database release.

Liraglutide and placebo (Novo Nordisk A/S, Bagsvaerd, Denmark) were administered as a once-daily injection (subcutaneously) in the morning before breakfast. The five dosages of liraglutide administered were 0.045, 0.225, 0.45, 0.60, and 0.75 mg. These dosages were chosen based on observations from previous trials (16–18). In one of those trials, a single dose of 10 μg/kg (corresponding to ~0.80 mg) showed significant effects on glycemia, but 2 of 11 patients reported nausea (18). Further, once-daily dosing for 7 days showed a 40% increase in $C_{max}$ in the steady state (17). Therefore, to avoid causing unacceptable side effects, the highest dosage included in this trial was 0.75 mg, corresponding to 7.5 μg/kg (equivalent to 10.5 μg/kg in steady state) for a person weighing 100 kg. The lowest dosage of 0.045 mg was considered too low to have any significant effect on glycemic control. Glimepiride (Amaryl; Aventis Pharma, Frankfurt, Germany) was supplied as 1- and 2-mg tablets for oral use, with the dosage adjusted according to glycemic control during the first 4 weeks, with the aim to achieve a fasting plasma glucose level <7 mmol/l. The mean glimepiride dosage during the trial was 2.7 mg. Compliance was assessed by drug accountability and plasma concentration measurements.

### Analytic methods

$HbA_{1c}$ was analyzed with a Unimate $HbA_{1c}$ assay (Roche Diagnostics; normal range 4.5–5.7%). Liraglutide antibodies were determined by a radioimmunoassay developed by the Department of Immunochemistry at Novo Nordisk A/S. The serum concentrations of insulin, C-peptide, and proinsulin were analyzed by enzyme-linked immunosorbent assay methods. Plasma glucagon was analyzed by MDS Pharma Services (Wangen, Switzerland) using a radioimmunoassay (Linco Research, St. Charles, MO). Standard laboratory analyses were performed by a central laboratory (Novo Medical Medi-Lab, Clinical Trials Lab, Copenhagen, Denmark, if not otherwise stated).

### Statistical analysis

Pretrial calculation showed that a two-sided test of the highest dosage versus the placebo group required 30 patients per group to detect a difference in mean $HbA_{1c}$ of at least 1% unit with 5% significance and 95% power.

The primary end point $HbA_{1c}$, as well as secondary end points (fasting serum glucose, fasting C-peptide, glucagon, insulin, homeostasis model assessment

**Table 1—*Patient disposition and characteristics***

| | Placebo | Liraglutide 0.045 mg | Liraglutide 0.225 mg | Liraglutide 0.45 mg | Liraglutide 0.60 mg | Liraglutide 0.75 mg | Glimepiride | Total |
|---|---|---|---|---|---|---|---|---|
| Patient disposition | | | | | | | | |
| Screened | — | — | — | — | — | — | — | 311 |
| Screening failures | — | — | — | — | — | — | — | 118 |
| Nonfulfillment of any inclusion/exclusion criteria | — | — | — | — | — | — | — | 86 |
| Not meeting randomization criterion | — | — | — | — | — | — | — | 7 |
| Withdrew consent | — | — | — | — | — | — | — | 6 |
| Other | — | — | — | — | — | — | — | 19 |
| Randomized | 29 | 26 | 25 | 27 | 30 | 29 | 27 | 193 |
| Exposed | 29 | 26 | 24 | 27 | 30 | 28 | 26 | 190 |
| Withdrawals | 5 | 3 | 3 | 7 | 2 | 2 | 0 | 22 |
| Adverse events | 0 | 0 | 1 | 0 | 1 | 1 | 0 | 3 |
| Ineffective therapy | 3 | 2 | 1 | 4 | 1 | 1 | 0 | 12 |
| Other | 2 | 1 | 1 | 3 | 0 | 0 | 0 | 7 |
| Completed | 24 | 23 | 21 | 20 | 28 | 26 | 26 | 168 |
| Included in ITT population | 29 | 26 | 24 | 27 | 30 | 28 | 26 | 190 |
| Baseline characteristics | | | | | | | | |
| Age (years) | 57 ± 9.4 | 53 ± 9.0 | 58 ± 7.5 | 57 ± 11.3 | 57 ± 7.7 | 58 ± 9.7 | 57 ± 9.2 | |
| Sex | | | | | | | | |
| Male | 20 | 22 | 15 | 18 | 20 | 16 | 16 | |
| Female | 9 | 4 | 9 | 9 | 10 | 12 | 10 | |
| BMI (kg/m$^2$) | 30.3 ± 4.2 | 30.2 ± 5.4 | 32.0 ± 5.3 | 30.1 ± 5.0 | 30.4 ± 4.8 | 31.9 ± 4.3 | 30.2 ± 4.6 | |
| Previous diabetes treatment | | | | | | | | |
| Diet | 4 | 2 | 11 | 2 | 4 | 4 | 7 | |
| OHA | 25 | 24 | 13 | 25 | 26 | 24 | 19 | |
| Duration of diabetes (years) | 3.4 ± 2.9 | 4.1 ± 3.7 | 4.4 ± 4.0 | 4.5 ± 4.6 | 4.6 ± 4.6 | 6.1 ± 7.9 | 3.8 ± 3.4 | |
| $HbA_{1c}$ (%) | 7.4 ± 1.2 | 7.4 ± 0.8 | 7.9 ± 0.8 | 7.7 ± 1.0 | 7.4 ± 1.2 | 7.4 ± 0.9 | 7.8 ± 0.9 | |
| Fructosamine (mmol/l) | 335 ± 72.5 | 344 ± 77.9 | 358 ± 57.7 | 374 ± 104.9 | 352 ± 74.2 | 344 ± 73.7 | 364 ± 69.5 | |
| Fasting serum glucose (mmol/l) | 9.7 ± 2.9 | 10.2 ± 2.2 | 10.9 ± 3.6 | 11.2 ± 2.8 | 10.8 ± 2.8 | 9.9 ± 2.3 | 10.6 ± 2.4 | |
| C-peptide (mmol/l) | 1.1 ± 0.4 | 1.0 ± 0.5 | 1.0 ± 0.5 | 1.1 ± 0.5 | 1.1 ± 0.6 | 1.0 ± 0.4 | 0.9 ± 0.5 | |
| Insulin (mmol/l) | 84.7 ± 43.6 | 74.1 ± 40.1 | 81.2 ± 73.0 | 73.8 ± 51.0 | 72.5 ± 55.3 | 71.5 ± 42.0 | 64.1 ± 40.4 | |
| Glucagon (mmol/l) | 110 ± 37.7 | 111 ± 47.6 | 131 ± 140.0 | 110 ± 33.0 | 99 ± 31.1 | 91 ± 23.4 | 101 ± 23.6 | |
| Proinsulin-to-insulin ratio | 0.23 ± 0.15 | 0.23 ± 0.16 | 0.26 ± 0.17 | 0.30 ± 0.20 | 0.21 ± 0.11 | 0.25 ± 0.15 | 0.28 ± 0.19 | |
| β-Cell function (%) | 44.06 ± 26.3 | 34.65 ± 23.1 | 31.83 ± 22.6 | 31.95 ± 31.7 | 34.40 ± 37.3 | 33.75 ± 21.7 | 26.78 ± 18.2 | |

Data are means ± SD. Demographics were obtained at visit 1 (screening) and diabetes characteristics at visit 2 (baseline). Of the 193 patients randomized, 3 were never exposed. Preferred terms for adverse event withdrawals include sinusitis and fever (0.225 mg), aggressive reaction (0.60 mg), and abnormal hepatic function (0.75 mg). Pro-insulin was measured only in a subset of patients ($n$ = 74).

[HOMA], proinsulin-to-insulin ratio, and weight) were analyzed in a mixed-effects model with treatment, visit, and center as fixed effects and patient as the random effect. The interaction term, baseline $HbA_{1c}$ by visit, was included in the model as a covariate. Adjusted end point levels at 12-week follow-up were calculated for each treatment group by means of this model.

The HOMA(S) (β-cell function) was determined as β-cell function (%) = 20 × insulin/(glucose − 3.5). HOMA(R) (insulin resistance) was determined as resistance = insulin/(22.5$e^{-\ln[\text{glucose}]}$) (22).

All analyses were performed for the intention-to-treat (ITT) population (i.e., all patients who received at least one dose of a trial drug). Statistical analyses were performed using SAS software (version 8; SAS Institute, Cary, NC).

## RESULTS

### Enrollment

The 193 patients randomized in this trial were evenly distributed across treatment groups (Table 1). Baseline clinical characteristics of the 190 patients exposed to the experimental protocol are given in Table 1. No apparent differences were seen among the treatment groups with regard to baseline characteristics.

### Effect on glycemic control

After 12 weeks of treatment, $HbA_{1c}$ was decreased in all groups except the lowest liraglutide dosage group (Fig. 1*A*). Treatment with the two highest dosages reduced $HbA_{1c}$ significantly more than placebo (Table 2). At these dosage levels, the effect of liraglutide was comparable with that of glimepiride with respect to effect on $HbA_{1c}$. The effect of liraglutide increased with duration of treatment. The largest decreases in $HbA_{1c}$ levels were observed at the end of the 12-week treat-

ment period for the highest dosages (Fig. 1*B*), and it seemed that $HbA_{1c}$ levels were still decreasing at the end of the treatment period at these dosages. We observed that 59% of patients completing the trial in the two highest liraglutide dosage groups achieved $HbA_{1c}$ ≤7% after 12 weeks.

As was seen with $HbA_{1c}$, fasting serum glucose levels decreased in most treatment groups during the trial, with the decreases being statistically significant for the 0.225-, 0.60-, and 0.75-mg liraglutide dosage groups compared with placebo (Table 2). In accordance with the observations for $HbA_{1c}$, the effect of the highest dosages of liraglutide was comparable with that of glimepiride with respect to fasting serum glucose (Fig. 1*C*). In the liraglutide groups, maximal effect on fasting serum glucose was evident after the first week of treatment (Fig. 1*D*).

### Effect on body weight

Treatment with liraglutide did not increase body weight (Fig. 2). Furthermore, for the 0.45-mg liraglutide dosage group (Table 2), a statistically significant decrease, compared with placebo, was observed.

### Effect on islet cell function

HOMA (22) was used to assess β-cell function and insulin resistance after 12 weeks of liraglutide treatment. Mean β-cell function (derived from fasting insulin and glucose) was significantly higher in the 0.75-mg liraglutide group after 12 weeks than in the placebo group (Table 2). The effect obtained with the highest liraglutide dosage was similar to that observed with glimepiride. For insulin resistance, no differences were seen among the three treatments (liraglutide, glimepiride, and placebo; data not shown). Further, the proinsulin-to-insulin ratio decrease was statistically significantly after treatment with 0.75 mg liraglutide compared with placebo (Table 2). No change in the proinsulin-to-insulin ratio was demonstrated after treatment with glimepiride. There were no statistically significant differences between the liraglutide groups and the placebo group for fasting insulin, C-peptide, and glucagon (Table 2).

### Safety evaluation

Of the 135 patients exposed to liraglutide, 1 (in the 0.60-mg group) experienced minor hypoglycemia (defined in the study protocol as blood glucose <2.8 mmol/l) and 7 reported symptoms of hypoglycemia only. These incidences seemed lower than in the glimepiride group ($n$ = 26), where four patients experienced minor hypoglycemia and five patients reported symptoms of hypoglycemia.

The number of patients with adverse events (based on spontaneous adverse event reporting) was comparable across the liraglutide groups and the placebo group (60% [81 of 135]) vs. 55% [16 of 29] of patients, respectively) and was lower in the open-label reference group (35% [9 of 26] of patients). For gastrointestinal events, the incidence seemed to increase with increasing doses of liraglutide; nausea was reported by 1–2 patients in each of the lowest dose groups and by 5 of 28 patients in the highest dose group (in total, reported by 10 of 135 patients exposed to liraglutide) compared

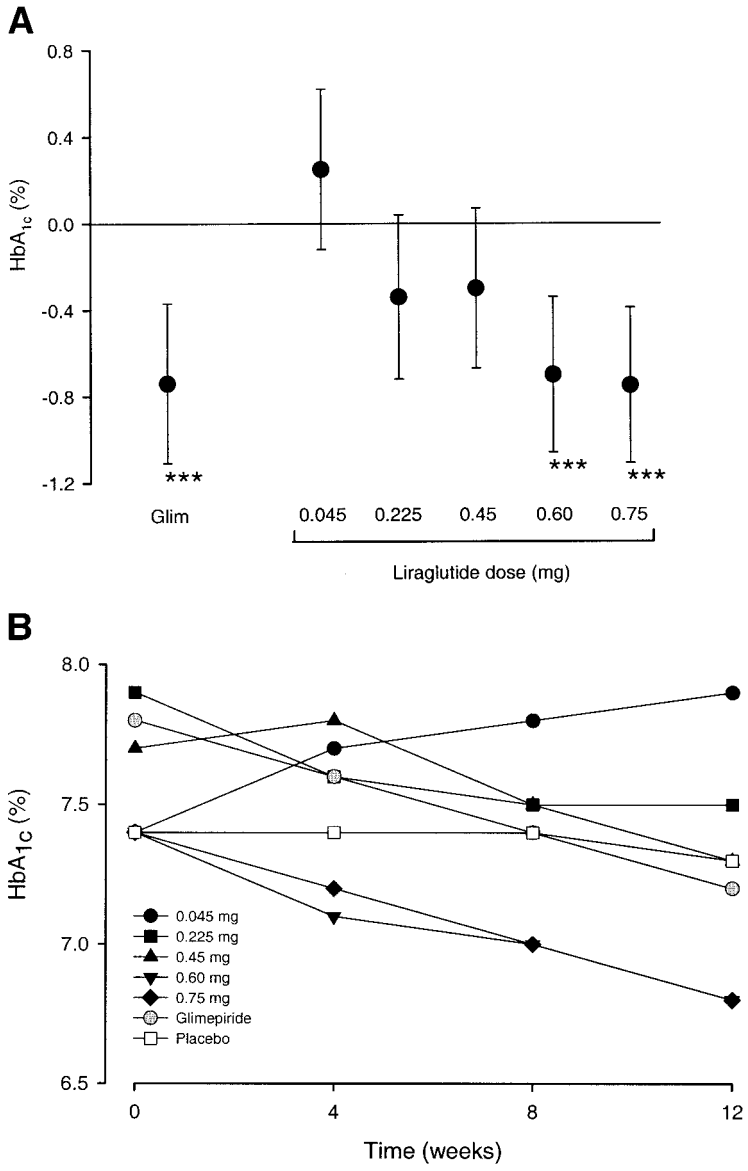
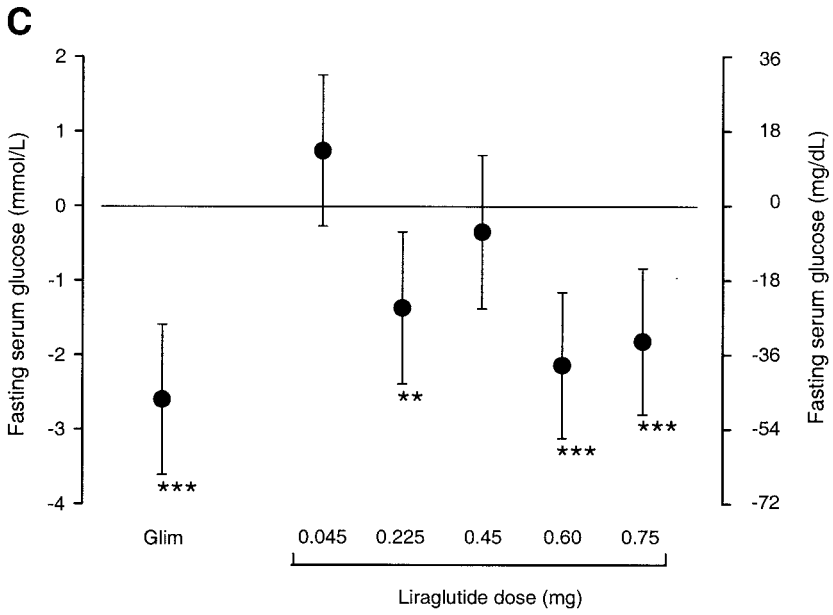



**Figure 1**—*Glycemic control. Mean difference in $HbA_{1c}$ compared with placebo (95% CI) after 12 weeks of treatment* (A)*, mean $HbA_{1c}$ (%) during the 12-week treatment period* (B)*, mean difference in fasting serum glucose compared with placebo (95% CI) after 12 weeks of treatment* (C)*, and mean fasting serum glucose (mmol/l) during the 12-week treatment period in the ITT population* (D). A *and* C: *P < *0.05*, **P < *0.01*, ***P < *0.001 vs. placebo. Glim, glimepiride.* B *and* D: ●*, 0.045 mg liraglutide;* ■*, 0.225 mg liraglutide;* ▲*, 0.45 mg liraglutide;* ▼*, 0.60 mg liraglutide;* ◆*, 0.75 mg liraglutide; [gray circles], glimepiride;* □*, placebo.*



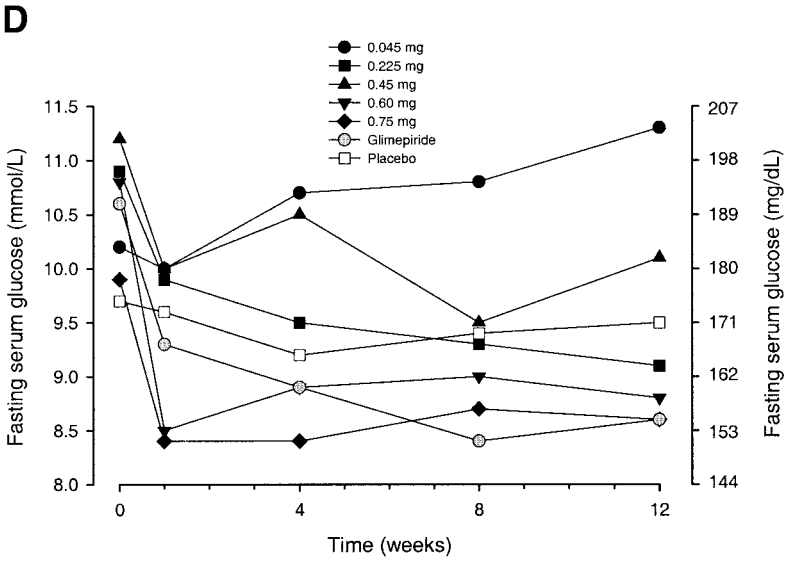




**Figure 1—*Continued***

with 1 of 29 patients in the placebo group. Other gastrointestinal events included diarrhea (5 of 135 liraglutide-treated patients), vomiting (3 of 135 patients), and constipation (3 of 135 patients). None of these events were reported in the placebo or glimepiride groups, with the exception of one patient experiencing vomiting in the glimepiride group. Approximately two-thirds of the gastrointestinal events reported during treatment with liraglutide were resolved within 1–3 days. None of the patients withdrew due to gastrointestinal events (Table 1). Overall, the most frequent adverse events were headache and nausea, which were also the events most often assessed as related to the trial product. Generally, adverse events were mild or moderate and completely resolved. Only 1 of the 135 patients exposed to liraglutide experienced two mild injection site reactions, described as an "urticarial reaction at injection place." No antibody formation against liraglutide could be detected in this trial.

No safety issues with regard to vital signs, electrocardiogram, or laboratory analysis were raised by this trial.

**CONCLUSIONS** — This trial was the first to demonstrate a sustained improvement in glycemic control after long-term treatment with the GLP-1 analog liraglutide, administered once daily. After 12 weeks of treatment with 0.60 or 0.75 mg liraglutide, both $HbA_{1c}$ and fasting serum glucose levels were significantly lower than with placebo. Glycemic control was maintained throughout the treatment period and was as effective at the highest liraglutide dosages as that provided by the open-label reference therapy glimepiride

**Table 2—*Repeated measures analysis after 12 weeks, comparison with placebo in ITT population***

| | Liraglutide (mg) | | | | | |
|---|---|---|---|---|---|---|
| | 0.045 | 0.225 | 0.45 | 0.60 | 0.75 | Glimepiride |
| *n* | 26 | 24 | 27 | 30 | 28 | 26 |
| $HbA_{1c}$ (%) | 0.25 (0.1905) | −0.34 (0.0877) | −0.30 (0.1131) | −0.70 (0.0002) | −0.75 (<0.0001) | −0.74 (0.0001) |
| Fasting serum glucose (mmol/l) | 0.74 (0.1499) | −1.37 (0.0090) | −0.35 (0.4976) | −2.14 (<0.0001) | −1.82 (0.0003) | −2.60 (<0.0001) |
| Weight (kg) | −0.03 (0.9602) | −0.74 (0.1544) | −1.20 (0.0184) | 0.27 (0.5838) | −0.39 (0.4391) | 0.94 (0.0622) |
| Proinsulin-to-insulin ratio | −0.04 (0.6468) | −0.12 (0.1314) | −0.04 (0.6502) | −0.12 (0.1775) | −0.18 (0.0244) | −0.003 (0.9635) |
| β-Cell function (%) | −6.07 (0.3546) | 7.55 (0.2514) | 8.55 (0.1978) | 7.33 (0.2409) | 23.56 (0.0002) | 24.57 (0.0002) |
| Fasting insulin (mmol/l) | −2.44 (0.8425) | −4.15 (0.7381) | −0.50 (0.9679) | −7.47 (0.5269) | 8.57 (0.4708) | 16.79 (0.1597) |
| Fasting C-peptide (mmol/l) | −0.09 (0.4033) | −0.01 (0.9449) | 0.05 (0.6374) | −0.08 (0.4308) | 0.11 (0.2921) | 0.08 (0.4636) |
| Fasting glucagon (mmol/l) | 12.74 (0.3619) | −15.84 (0.2710) | −6.77 (0.6277) | −7.68 (0.5625) | −9.33 (0.4980) | −7.21 (0.5970) |

*P* value given in parentheses.

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