

Efficacy and Safety Comparison of Liraglutide, Glimepiride, and Placebo, All in Combination With Metformin, in Type 2 Diabetes

The LEAD (Liraglutide Effect and Action in Diabetes)-2 study

MICHAEL NAUCK, MD, PHD¹
ANDERS FRID, MD²
KJELD HERMANSEN, MD³
NALINI S. SHAH, MD⁴
TSVETALINA TANKOVA, MD⁵

ISMAIL H. MITHA, MD⁶
MILAN ZDRAVKOVIC, MD, PHD⁷
MARIA DÜRING, PHD⁷
DAVID R. MATTHEWS, MD⁸
FOR THE LEAD-2 STUDY GROUP*

OBJECTIVE — The efficacy and safety of adding liraglutide (a glucagon-like peptide-1 receptor agonist) to metformin were compared with addition of placebo or glimepiride to metformin in subjects previously treated with oral antidiabetes (OAD) therapy.

RESEARCH DESIGN AND METHODS — In this 26-week, double-blind, double-dummy, placebo- and active-controlled, parallel-group trial, 1,091 subjects were randomly assigned (2:2:2:1:2) to once-daily liraglutide (either 0.6, 1.2, or 1.8 mg/day injected subcutaneously), to placebo, or to glimepiride (4 mg once daily). All treatments were in combination therapy with metformin (1g twice daily). Enrolled subjects (aged 25–79 years) had type 2 diabetes, A1C of 7–11% (previous OAD monotherapy for ≥ 3 months) or 7–10% (previous OAD combination therapy for ≥ 3 months), and BMI ≤ 40 kg/m².

RESULTS — A1C values were significantly reduced in all liraglutide groups versus the placebo group ($P < 0.0001$) with mean decreases of 1.0% for 1.8 mg liraglutide, 1.2 mg liraglutide, and glimepiride and 0.7% for 0.6 mg liraglutide and an increase of 0.1% for placebo. Body weight decreased in all liraglutide groups (1.8–2.8 kg) compared with an increase in the glimepiride group (1.0 kg; $P < 0.0001$). The incidence of minor hypoglycemia with liraglutide (~3%) was comparable to that with placebo but less than that with glimepiride (17%; $P < 0.001$). Nausea was reported by 11–19% of the liraglutide-treated subjects versus 3–4% in the placebo and glimepiride groups. The incidence of nausea declined over time.

CONCLUSIONS — In subjects with type 2 diabetes, once-daily liraglutide induced similar glycemic control, reduced body weight, and lowered the occurrence of hypoglycemia compared with glimepiride, when both had background therapy of metformin.

Diabetes Care 32:84–90, 2009

Type 2 diabetes is a progressive disease characterized by declining β -cell function that, in concert with insulin resistance, leads to loss of glycemic control and eventual diabetes compli-

cations (1). An oral antidiabetes drug (OAD) such as metformin is commonly used in first-line pharmacotherapy for type 2 diabetes. Sulfonylureas and thiazolidinediones are alternative OAD thera-

pies, but both can elicit weight gain, whereas sulfonylureas can elicit hypoglycemia. Glucagon-like peptide-1 (GLP-1) has received attention as a therapeutic agent to provide glycemic control while avoiding hypoglycemia and weight gain.

GLP-1 is an incretin hormone produced in the gut that stimulates glucose-dependent endogenous insulin secretion, decreases glucagon secretion, slows gastric motility and emptying, and reduces appetite and food intake (2,3). Furthermore, native GLP-1 stimulates β -cell proliferation in animal models and inhibits apoptosis in vitro, which may increase β -cell mass and function (2). However, native GLP-1 is not a viable therapeutic agent because it has a short half-life of < 2 min resulting from rapid degradation by the enzyme dipeptidyl peptidase 4 (DPP-4) and rapid renal elimination (4).

Liraglutide is a human GLP-1 analog with 97% homology to native GLP-1 (5). The addition of a fatty acid (palmitate) side chain and a single amino acid substitution produces self-association of the molecule that prolongs absorption from the subcutaneous depot. The fatty acid side chain also promotes albumin binding that renders the molecule resistant to degradation by DPP-4. The resultant plasma half-life of liraglutide is substantially prolonged to 13 h compared with the very short half-life of native human GLP-1 (6,7). The pharmacokinetic profile makes liraglutide suitable for once-daily administration while achieving 24-h glycemic control, in contrast to exenatide which needs to be injected twice daily because it has a half-life of ~ 2.4 h (5,8,9). Depending upon dose and duration of treatment, type 2 diabetic subjects receiving liraglutide had mean reductions in A1C of 0.8–1.5%, reductions in fasting blood glucose of 1.4–3.4 mmol/l, and reductions in body weight of 1.2–3.0 kg (10–13). In a recent 52-week monotherapy study, 51% of subjects treated with 1.8 mg liraglutide reached the American Diabetes Association (ADA) target of A1C $< 7.0\%$ and had weight loss in the first 16

From the ¹Diabeteszentrum Bad Lauterberg, Harz, Germany; the ²Öresund Diabetes Team AB, Lund, Sweden; ³Aarhus University Hospital, Aarhus, Denmark; ⁴Seth G.S. Medical College and KEM Hospital, Mumbai, India; the ⁵Clinic of Diabetology, Sophia, Bulgaria; ⁶Benmed Hospital, Benoni, Republic of South Africa; ⁷Novo Nordisk, Bagsvaerd, Denmark; and the ⁸Oxford Centre for Diabetes Endocrinology and Metabolism, Oxford, U.K.

Corresponding author: Michael A. Nauck, nauck@diabeteszentrum.de.

Received 22 July 2008 and accepted 28 September 2008.

Published ahead of print at <http://care.diabetesjournals.org> on 17 October 2008. DOI: 10.2337/dc08-1355.

Clinical trial reg. no. NCT00318461, clinicaltrials.gov.

*A complete list of the LEAD-2 study investigators can be found in an online appendix available at <http://dx.doi.org/10.2337/dc08-1355>.

© 2009 by the American Diabetes Association. Readers may use this article as long as the work is properly cited, the use is educational and not for profit, and the work is not altered. See <http://creativecommons.org/licenses/by-nc-nd/3.0/> for details.

The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked "advertisement" in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

weeks (2.4 kg) that was sustained throughout the remainder of the study (13).

This current trial is part of a phase 3 clinical development program for liraglutide. The trial investigates whether glycemic control (measured by A1C) achieved by type 2 diabetic subjects using combination therapy of liraglutide and metformin is significantly better than that achieved with metformin monotherapy or at least as good as that achieved with combination therapy of metformin and glimepiride.

RESEARCH DESIGN AND METHODS

Adult subjects with type 2 diabetes were screened and enrolled if they were 18–80 years of age, had A1C between 7 and 11% (prestudy OAD monotherapy for ≥ 3 months) or between 7 and 10% (prestudy combination OAD therapy for ≥ 3 months), and had BMI ≤ 40 kg/m². Subjects were excluded if they had used insulin during the previous 3 months (except short-term treatment). The protocol was approved by local institutional review boards, and all subjects provided written informed consent before initiation of any trial-related activities. The study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines (14).

In this 26-week, double-blind, double-dummy, active-control, parallel-group, multicenter (170 sites), multinational (21 countries) trial, subjects were randomly assigned (2:2:2:1:2) to receive one of three once-daily doses of liraglutide (0.6, 1.2, or 1.8 mg/day; Novo Nordisk, Bagsvaerd, Denmark) injected subcutaneously in combination with metformin, to receive liraglutide placebo with metformin monotherapy (placebo group), or to receive combination therapy with glimepiride and metformin (4 mg glimepiride once daily with the first meal of the day). The most relevant position for initiating treatment with GLP-1 may be after metformin failure, but to facilitate recruitment into the trial other monotherapy or combination treatments were allowed. Accordingly, the objective of this study was to compare the efficacy and safety of liraglutide with both placebo and another commonly used therapeutic option (glimepiride) after metformin failure. The double-dummy design required that subjects in the liraglutide and placebo groups received a glimepiride placebo, whereas subjects in the glimepiride and placebo

groups received an injection of liraglutide placebo.

Randomization was performed using a telephone-based or web-based randomization system. Subjects were randomly assigned to the lowest available randomization number and stratified with respect to their previous use of OAD monotherapy or combination therapy. Subjects completing the study could enroll in an 18-month open-label extension period.

Randomization to treatment occurred after a 3-week forced metformin titration period (dose increased up to 2,000 mg/day: 1,000 mg in the morning and 1,000 mg in the evening) followed by a 3-week metformin maintenance period. Subjects taking metformin at enrollment could go through a modified titration period or advance directly to the metformin maintenance period. After randomization, subjects underwent a 2- and 3-week titration period for liraglutide (up to 0.6, 1.2, or 1.8 mg, as per randomization, at 0.6-mg increases per week) and glimepiride (up to 4 mg, with 1-, 2-, and 4-mg doses at weeks 1, 2, and 3). Glimepiride (active and placebo) was taken orally once daily in the morning. Liraglutide (active or placebo) was injected subcutaneously once daily at any time of the day in the upper arm, abdomen, or thigh using a pen injector device. Subjects were encouraged to inject liraglutide at the same time each day.

The titration period was followed by a 23- or 24-week maintenance period during which the doses of study drugs were to be maintained. However, metformin could be decreased to a minimum of 1,500 mg/day in the case of unacceptable hypoglycemia or other adverse events but had to be maintained between 1,500 and 2000 mg/day during the maintenance period.

The primary outcome measure was change in A1C at the end of the study. Secondary end points included changes in body weight, fasting plasma glucose (FPG), 7-point plasma glucose profiles (before each meal, 90 min after breakfast, lunch, and dinner, and at bedtime), and β -cell function based on fasting insulin, fasting C-peptide, fasting proinsulin-to-insulin ratio, and the homeostasis model assessment index of β -cell function (HOMA-B) (15). Laboratory analyses were performed by a central laboratory (MDS Pharma Services in Canada, France, Germany, Singapore, and Switzerland and Laboratories Hildago in Argentina). A1C was assayed by a method certified by the National Glycohemoglo-

bin Standardization Program. Subjects were provided with MediSense Precision Xtra/MediSense Optium glucose meters (Abbott, Maidenhead, U.K.) calibrated to plasma glucose to determine self-measured plasma glucose and recorded values in their diaries. Serum insulin and C-peptide values were determined using a chemiluminescence immunoassay, and proinsulin was measured in serum using an enzyme-linked immunosorbent assay.

Safety variables included adverse events, vital signs, electrocardiogram, biochemical and hematology measures, and subject-reported hypoglycemic episodes (based on symptoms and plasma glucose < 3.1 mmol/l). Minor hypoglycemic episodes were self-treated; major episodes required third-party assistance.

Statistical analysis

The analyses of efficacy end points were based on the intent-to-treat population defined as subjects who were exposed to at least one dose of trial product and had one postbaseline measurement of the parameter. Each end point was analyzed using an ANCOVA model with treatment, country, and previous antidiabetic treatment as fixed effects and baseline as the covariate. Missing data were imputed as the last observation carried forward. Sample size calculations were based on showing A1C and body weight differences of 0.5 and 3%, respectively, after 6 months of treatment. The assumed standard deviation for A1C and the coefficient of variance for weight were 1.2 and 3%, respectively. The combined power (calculated as the product of the marginal powers for A1C and weight) was at least 85%.

Superiority or noninferiority of glycemic control with liraglutide versus comparators was concluded if the upper limit of the two-sided 95% CI for the treatment difference was $< 0\%$; noninferiority was concluded if it was $< 0.4\%$. The proportion of subjects achieving A1C targets (ADA target $< 7\%$; American Association of Clinical Endocrinologists [AACE] target $\leq 6.5\%$) was compared between treatments using a logistic regression model with treatment and baseline A1C as covariates. CIs for secondary end points were corrected using Dunnett's test. Hypoglycemic episodes were analyzed using a general linear model including treatment as a fixed effect. Values are expressed as means \pm SD unless otherwise noted. The significance level was set at $P < 0.05$.

Table 1—Characteristics of enrolled population and subject disposition

	Once-daily liraglutide			Once-daily 4 mg glimepiride	Placebo
	0.6 mg	1.2 mg	1.8 mg		
Sex: male/female (%)	62/38	54/46	59/41	57/43	60/40
Age (years)	56 ± 11	57 ± 9	57 ± 9	57 ± 9	56 ± 9
Race: C/B/A/O (%)	84/2/13/2	88/4/8/1	88/2/7/2	89/2/9/1	88/3/7/3
BMI (kg/m ²)	30.5 ± 4.8	31.1 ± 4.8	30.9 ± 4.6	31.2 ± 4.6	31.6 ± 4.4
Duration of diabetes (years)	7 ± 5	7 ± 5	8 ± 5	8 ± 5	8 ± 6
Prestudy OAD treatment					
Monotherapy	81 (34)	91 (38)	83 (34)	89 (37)	41 (34)
Metformin	70 (86)	78 (86)	72 (87)	82 (92)	38 (93)
Sulfonylurea	9 (11)	12 (13)	11 (13)	7 (8)	3 (7)
Repaglinide	2 (3)	1 (1)	0	0	0
Combination therapy	161 (67)	150 (62)	159 (66)	155 (63)	81 (66)
A1C (%)	8.4 ± 0.9	8.3 ± 1.0	8.4 ± 1.0	8.4 ± 1.0	8.4 ± 1.1
FPG (mmol/l)	10.2 ± 2.4	9.9 ± 2.3	10.1 ± 2.3	10.0 ± 2.6	10.0 ± 2.3
SBP (mmHg)	131 ± 14	132 ± 14	131 ± 14	132 ± 16	135 ± 16
DBP (mmHg)	80 ± 8	80 ± 10	79 ± 8	80 ± 8	81 ± 9
Randomized	242	241	242	244	122
Exposed (ITT and safety populations)	242	240	242	242	121
Completers	208 (86)	197 (82)	191 (79)	210 (86)	74 (61)
Withdrawals	34 (14)	44 (18)	51 (21)	34 (14)	48 (39)
Adverse events	11 (5)	23 (10)	29 (12)	8 (3)	2 (2)
Nausea/vomiting/diarrhea	3 (1)	13 (5)	20 (8)	0	0
Ineffective therapy	19 (8)	8 (3)	13 (5)	9 (4)	29 (24)
Noncompliance	2 (1)	4 (2)	4 (2)	5 (2)	4 (3)
Other	2 (1)	9 (4)	5 (2)	12 (5)	13 (11)

Data are means ± SD or n (%) unless otherwise noted. *Race: C, Caucasian; B, Black; A, Asian/Pacific Islander; O, other. DBP, diastolic blood pressure; ITT, intention to treat.

RESULTS— A total of 1,662 subjects were screened for the study; 571 subjects failed the screening criteria or withdrew consent, and the remaining 1,091 subjects were randomly assigned to treatment after the metformin run-in period. Four subjects were randomly assigned but were withdrawn before receiving treatment. Accordingly, the intent-to-treat and safety (all subjects exposed to study drug) populations comprised 1,087 subjects and are summarized by treatment group in Table 1. Baseline characteristics of the study population appeared to be balanced across treatment groups (Table 1). The majority (65%) of the randomly assigned subjects were treated with two OADs before the study.

Efficacy

At the end of the study, the mean A1C values for the overall population decreased by $0.7 \pm 0.1\%$ for the 0.6 mg liraglutide group and by $1.0 \pm 0.1\%$ for both the 1.2 and 1.8 mg liraglutide groups and for the glimepiride group and increased by $0.1 \pm 0.1\%$ for the placebo group (all values means ± SEM). The estimated treatment differences of all three

liraglutide groups compared with the placebo group and the resulting 95% CIs demonstrated that liraglutide-treated subjects had superior glycemic control compared with those in the placebo group (0.6 mg liraglutide versus placebo -0.8% [95% CI -1.0 to -0.6]; 1.2 mg liraglutide versus placebo -1.1% [-1.3 to -0.9]; and 1.8 mg liraglutide versus placebo -1.1% [-1.3 to -0.9]). Analysis of the estimated treatment difference in A1C between liraglutide and glimepiride demonstrated that 1.2 and 1.8 mg liraglutide treatments were noninferior to treatment with glimepiride (1.2 mg liraglutide versus glimepiride 0.0% [-0.2 to 0.2] and 1.8 mg liraglutide versus glimepiride -0.0% [-0.2 to 0.2]).

Within the first 12 weeks of the study, mean A1C values for the overall population decreased from baseline for all liraglutide treatment groups and for the glimepiride group whereas a slight increase was observed in the placebo group (Fig. 1A). The A1C profiles for subjects stratified by prestudy OAD therapy (monotherapy or combination therapy) were similar in appearance to those of the overall population (Fig. 1B and C). How-

ever, the baseline and end-of-study mean A1C values in the monotherapy group were slightly less than those in the combination therapy group, and the resulting change-from-baseline decreases appeared to be slightly greater in the monotherapy group than in the combination therapy group (Fig. 1D).

The percentages of subjects reaching the ADA and AACE A1C goals were dose-dependent for liraglutide treatment in overall subjects and in subjects with prestudy OAD monotherapy or combination therapy (Fig. 1E and F). For the overall population, a logistic regression analysis demonstrated that a significantly greater percentage of subjects in all of the liraglutide groups achieved the ADA and AACE A1C goals than subjects in the respective placebo groups ($P < 0.02$ for all comparisons of liraglutide to placebo for both A1C goals). The percentages of subjects in the 1.2 and 1.8 mg liraglutide treatment groups achieving the ADA and AACE A1C goals were comparable to the percentage achieving goals in the glimepiride group. However, for the overall population, the ADA target was achieved by significantly more subjects in

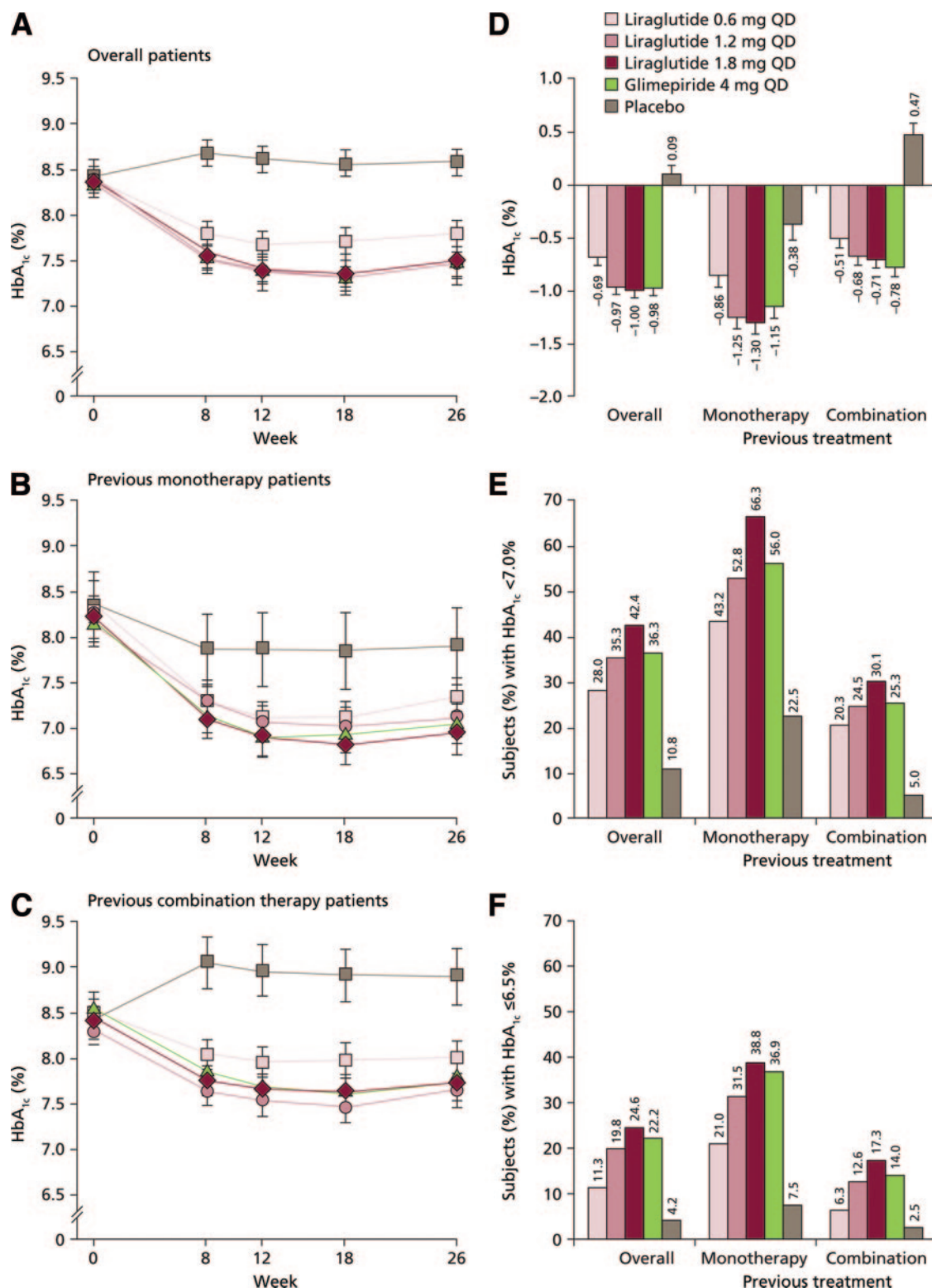


Figure 1— A1C profiles for the overall study population (A), for subjects with prestudy oral monotherapy (B), and for subjects with prestudy oral combination therapy (C). D: Change in A1C for the overall study population and for subjects treated by prestudy monotherapy or combination therapy. Error bars in A, B, C, and D represent $2 \times$ SEM. Percentages of subjects achieving ADA (E) and AACE (F) A1C goals at the end of the study were determined using a logistic regression analysis. Symbols for A–C: pink boxes, 0.6 mg/day liraglutide; circles, 1.2 mg/day liraglutide; diamonds, 1.8 mg/day liraglutide; triangles, 4 mg/day glimepiride; gray boxes, placebo. QD, every day.

the 1.8 mg liraglutide group than in the 1.2 mg liraglutide group (42.4 vs. 35.3%, $P = 0.0265$).

FPG values decreased within the 2 weeks of randomization in the liraglutide groups and in the glimepiride group and

increased in the placebo group, remaining relatively stable thereafter. At the end of the study, FPG values were 9.1 ± 2.5 ,

8.5 ± 2.6, 8.5 ± 2.4, 8.9 ± 2.5, and 10.7 ± 3.2 mmol/l in the 0.6 mg liraglutide, 1.2 mg liraglutide, 1.8 mg liraglutide, glimepiride, and placebo groups, respectively. The decreases in FPG from baseline for all of the liraglutide groups (−1.1, −1.6, and −1.7 mmol/l for 0.6, 1.2, and 1.8 mg liraglutide groups, respectively) were significantly greater than the increase observed for the placebo group (0.4 mmol/l, $P < 0.0001$) but were similar to the decrease observed for the glimepiride group (−1.3 mmol/l).

Mean postprandial glucose values (mean of three meals), from self-monitored 7-point plasma glucose measurements at the end of the study, decreased from baseline in all treatment groups (−1.7 mmol/l for 0.6 mg liraglutide, −2.3 mmol/l for 1.2 mg liraglutide, and −2.6 mmol/l for 1.8 mg liraglutide, −2.5 mmol/l for glimepiride, and −0.6 mmol/l for placebo; $P < 0.001$ for comparisons of all liraglutide groups to placebo; the decreases in the 1.2 and 1.8 mg liraglutide groups were comparable to those with glimepiride). The blood glucose values 90 min after breakfast, lunch, and dinner for the 1.8 mg liraglutide group at week 26 appeared to be similar across the three meals (9.9, 9.5, and 9.7 mmol/l, respectively) and appeared to be similar to the corresponding blood glucose values observed in the glimepiride group (10.0, 9.2, and 9.7 mmol/l, respectively) and slightly less than the corresponding values in the placebo group (11.0, 10.7, and 10.9 mmol/l, respectively).

Weight loss was dose dependent in the liraglutide treatment groups (1.8 ± 0.2, 2.6 ± 0.2, and 2.8 ± 0.2 kg for 0.6, 1.2, and 1.8 mg liraglutide groups, respectively) and was significantly different ($P < 0.0001$) from the weight gain in the glimepiride group (1.0 ± 0.2 kg). The weight losses in the 1.2 and 1.8 mg liraglutide groups were also significantly greater ($P \leq 0.01$) than the weight loss in the placebo group (1.5 ± 0.3 kg). The great majority of subjects either did not report nausea or reported nausea for ≤ 7 days during the first 8 weeks of treatment and did not report nausea or reported nausea for ≤ 7 days in weeks 8–26 of treatment (86–93% in the liraglutide groups and 98–99% in the placebo and glimepiride groups). As such, the occurrence of nausea did not appear to account for the weight loss.

The decreases in the proinsulin-to-insulin ratio from baseline (baseline of 0.4

across all groups) for the three liraglutide groups (decrease by 0.1) were comparable to those in the glimepiride group and were significantly different ($P < 0.0001$) than those in the placebo group, which increased from baseline by 0.1. No significant differences in the change-from-baseline fasting insulin and fasting C-peptide values were observed between the liraglutide treatment groups compared with either the glimepiride or placebo groups. The liraglutide treatment groups had improvements in HOMA-B of 63, 70, and 71% for the 0.6, 1.2, and 1.8 mg liraglutide groups from baseline values of 40, 47, and 43%, respectively. The glimepiride group had a similar improvement in the mean HOMA-B value to 68% from a baseline value of 43%. No improvement in HOMA-B was observed in the placebo group; baseline and end-of-study values were 45 and 43%, respectively. No significant differences were observed between treatments for the homeostasis model assessment index of insulin resistance.

The 1.2 and 1.8 mg liraglutide groups had significant reductions in systolic blood pressure (SBP) of 2–3 mmHg compared with the increase in SBP of 0.4 mmHg observed in the glimepiride group (treatment difference compared with glimepiride: 1.2 mg liraglutide, −3.2 mmHg, $P = 0.0128$; 1.8 mg liraglutide, −2.7 mmHg, $P = 0.0467$). The decreases in SBP in the 0.6 mg liraglutide and placebo groups were 0.6 and 1.8 mmHg, respectively. On the basis of the SBP and weight profiles over time, the reduction in SBP may not be fully explained by the reduction in body weight. Diastolic blood pressure did not appear to change from baseline for any groups.

Safety

Gastrointestinal disorders (nausea, vomiting, and diarrhea) were the most frequently reported adverse events in the liraglutide groups and were reported during the course of the study by 35, 40, and 44% of the subjects in the 0.6, 1.2, and 1.8 mg liraglutide groups, respectively, and by 17% in the placebo and glimepiride groups. Overall, nausea alone was experienced by 11, 16, and 19% of the subjects in the 0.6, 1.2, and 1.8 mg liraglutide groups, respectively; however, $< 10\%$ of the subjects were experiencing nausea on a weekly basis by week 4. Vomiting was experienced by 5–7% in the liraglutide groups and by 1% in the placebo and glimepiride groups; diarrhea

was experienced by 10, 8, and 15% in the 0.6, 1.2, and 1.8 mg liraglutide groups, respectively, and by 4% in the placebo and glimepiride groups.

The percentages of subjects withdrawn because of adverse events were generally greater in the liraglutide groups than in the glimepiride or placebo groups (Table 1). Nausea, vomiting, and/or diarrhea were the gastrointestinal events that led to the withdrawal of 36 liraglutide-treated subjects (5% of all liraglutide-treated subjects) in a dose-dependent manner (Table 1). Most of these adverse event withdrawals caused by gastrointestinal disorders occurred during the first month of therapy. One subject in the 1.2 mg liraglutide group and one in the glimepiride group were withdrawn for acute pancreatitis during the study. Neither subject had a prior history of pancreatitis, and both subjects were hospitalized for 7 days and subsequently recovered. One death (cardiorespiratory arrest) was reported during the trial and occurred during the metformin run-in period, before randomization to treatment. A second subject had liver cirrhosis and hepatocellular carcinoma during the trial and died after the trial had completed. Both deaths were unrelated to liraglutide treatment.

In general, minor hypoglycemia occurred at low incidence ($\sim 3\%$ of subjects in the placebo and liraglutide groups and 17% in the glimepiride group), resulting in a relatively low rate of reported minor hypoglycemia (0.03–0.14 events/year for the placebo and liraglutide groups and 1.23 events/year for the glimepiride group) that was significantly less for all three liraglutide groups than for the glimepiride group ($P < 0.001$). No major hypoglycemic events were reported.

No clinically relevant between-treatment differences were observed in physical examination findings, laboratory analyses (hematology and biochemistry analyses), electrocardiogram, or ophthalmoscopy. No significant differences in calcitonin laboratory values were found between the liraglutide groups and either the placebo or glimepiride group. Slight increases in pulse rate were observed in all treatment groups (2–3 bpm in the liraglutide groups and 1 bpm in the glimepiride and placebo groups). The increases in pulse in the 0.6 and 1.2 mg liraglutide groups were significantly greater than that in the glimepiride group ($P = 0.012$ and $P = 0.024$, respectively).

CONCLUSIONS— This trial demonstrated that treatment with liraglutide once daily (0.6, 1.2, or 1.8 mg) in combination with metformin provided improvement in A1C superior to that of metformin monotherapy (placebo group) and noninferior to that of combination therapy of glimepiride and metformin (glimepiride group). The improvements in A1C for liraglutide-treated subjects receiving prestudy OAD monotherapy were greater (decrease of 1.3% for 1.8 mg liraglutide) than the improvements for subjects with prestudy oral combination therapy (decrease of 0.8%, 1.8 mg liraglutide, significance not tested). The monotherapy group probably had greater improvement because they added liraglutide onto a monotherapy treatment whereas liraglutide was substituted for one of the prestudy oral therapies (other than metformin) in the subjects receiving prestudy combination therapy. The findings of the current study demonstrate that liraglutide is an effective treatment option for combination therapy with metformin when subjects are not achieving glycemic control with metformin therapy alone.

The decrease in A1C observed in the prestudy monotherapy group confirms the A1C decrease observed (1.45%) in subjects treated with liraglutide monotherapy in a prior 14-week study (10). Another recent liraglutide phase 3 study demonstrated that a subgroup of subjects previously treated with diet and exercise and then treated with 1.8 mg liraglutide monotherapy had a mean A1C decrease of 1.60% that was sustained over the 52-week trial period. In this subgroup, the decrease in A1C was significantly greater than the decrease achieved in the corresponding glimepiride control group in the same study (0.88%; $P < 0.05$) (13). A1C decreases by subjects previously treated with metformin monotherapy have also been observed with the GLP-1 agonist exenatide (decrease of 0.8%) or with the DPP-4 inhibitor sitagliptin (decrease of 0.65%) in populations of patients with type 2 diabetes inadequately controlled with previous metformin monotherapy (16,17).

The percentages of liraglutide-treated subjects achieving A1C targets are reflective of the decreases in A1C values for the overall population and for the subgroups stratified by prior OAD therapy. Greater percentages of subjects receiving prestudy monotherapy achieved the target compared with their respective counterparts receiving prestudy combination

therapy (66 and 39%, respectively, for 1.8 mg liraglutide) (compare Fig. 1E and F). This finding probably results from the addition of liraglutide as a second therapeutic agent in subjects whose type 2 diabetes may not be as advanced as that is those subjects entering the study with prestudy combination therapy.

In this study, liraglutide provided 24-h glycemic control as demonstrated by the similar postprandial blood glucose values after each of the three meals. The postprandial values of the 1.8 mg liraglutide group also appeared to be similar to those of the glimepiride group and less than those of the placebo group.

Nausea, vomiting, and diarrhea are known side effects of GLP-1 receptor agonists. The incidence of gastrointestinal effects in this study increased dose dependently during the first 2 weeks of liraglutide treatment but decreased thereafter. In studies with treatment of exenatide, subjects reported nausea that also decreased in incidence over time (16,18,19). The dose dependence and transient nature of gastrointestinal side effects in the current trial suggest that in clinical practice liraglutide should be titrated from a starting dose of 0.6 mg/day up to 1.2 mg/day and then up to 1.8 mg/day. Apart from the gastrointestinal side effects, liraglutide treatment was generally well tolerated and had a low incidence of hypoglycemia that was comparable to that of the placebo group (metformin monotherapy). A reduction in SBP was also observed in the 1.2 and 1.8 mg liraglutide groups (2–3 mmHg) within 2 weeks of treatment and could not be explained entirely by weight loss that occurred over a greater time frame.

Liraglutide was shown to be similar to glimepiride in improving HOMA-B values in the current study. Improvements in β -cell function with liraglutide treatment have been observed in several other studies with liraglutide (10,20,21). Furthermore, liraglutide has been shown to increase β -cell mass in animal models and decrease β -cell apoptosis in vitro (22,23). Such improvements in β -cell function have the potential to delay type 2 diabetes progression.

The liraglutide-treated subjects generally had improvements in glycemic parameters (decreases in A1C, FPG, and postprandial glucose from baseline) similar to those of glimepiride-treated subjects. However, the glimepiride group had a significant increase in weight compared with the liraglutide groups and experienced a

significantly greater rate of hypoglycemia. Thus, addition of once-daily liraglutide to metformin monotherapy is a viable treatment option if weight gain and hypoglycemia are a concern.

Acknowledgments— M.N. is a member on advisory boards for Amylin Pharmaceuticals, ConjuChem, Eli Lilly, GlaxoSmithKline, Hoffman-La Roche, Novartis Pharma, Novo Nordisk, Probiobdrug, Restoragen, and sanofi-aventis; has received consulting fees from AstraZeneca, Bayer Vital, Berlin-Chemie, Biovitrum, ConjuChem, Eli Lilly, Hoffman-La Roche, Merck, Merck Sharp & Dohme, Novartis Pharma, Novo Nordisk, Pfizer, Probiobdrug, Restoragen, sanofi-aventis, and Takeda; and has received research support from Amylin Pharmaceuticals, Bayer Vital, Eli Lilly, Lifescan Germany, Berlin-Chemie, Novartis Pharma, Novo Nordisk, sanofi-aventis, Probiobdrug, and Restoragen. K.H. has received honoraria for consultation and lecturing from Novo Nordisk, sanofi-aventis, and Merck. No other potential conflicts of interest relevant to this article were reported.

We acknowledge the assistance of the LEAD-2 study group, their staff, and clinical trial personnel and the subjects for participating in the study. We also thank Brian Hennigan, PhD, of Novo Nordisk for writing assistance.

Parts of this study were presented as a poster at the 68th annual meeting of the American Diabetes Association, San Francisco, California, 6–10 June 2008.

References

1. UK Prospective Diabetes Study 16: overview of 6 years' therapy of type II diabetes: a progressive disease. *Diabetes* 44:1249–1258, 1995
2. Drucker DJ, Nauck MA: The incretin system: glucagon-like peptide-1 receptor agonists and dipeptidyl peptidase-4 inhibitors in type 2 diabetes. *Lancet* 368:1696–1705, 2006
3. Holst JJ: The physiology of glucagon-like peptide 1. *Physiol Rev* 87:1409–1439, 2007
4. Meier JJ, Nauck MA, Kranz D, Holst JJ, Deacon CF, Gaeckle D, Schmidt WE, Gallwitz B: Secretion, degradation, and elimination of glucagon-like peptide 1 and gastric inhibitory polypeptide in patients with chronic renal insufficiency and healthy control subjects. *Diabetes* 53:654–662, 2004
5. Knudsen LB, Nielsen PF, Huusfeldt PO, Johansen NL, Madsen K, Pedersen FZ, Thogersen H, Wilken M, Agerso H: Potent derivatives of glucagon-like peptide-1 with pharmacokinetic properties suitable for once daily administration. *J Med Chem* 43:1664–1669, 2000

6. Deacon CF, Knudsen LB, Madsen K, Wiberg FC, Jacobsen O, Holst JJ: Dipeptidyl peptidase IV resistant analogues of GLP-1 which have extended metabolic stability and improved biological activity. *Diabetologia* 41:271–278, 1998
7. Agersø H, Jensen LB, Elbrønd B, Rolan P, Zdravkovic M: The pharmacokinetics, pharmacodynamics, safety and tolerability of NN2211, a new long-acting GLP-1 derivative, in healthy men. *Diabetologia* 45:195–202, 2002
8. Elbrønd B, Jakobsen G, Larsen S, Agersø H, Jensen LB, Rolan P, Sturis J, Hatorp V, Zdravkovic M: Pharmacokinetics, pharmacodynamics, safety and tolerability of a single dose of NN2211, a long-acting glucagon-like peptide 1 derivative, in healthy male patients. *Diabetes Care* 25:1398–1404, 2002
9. Degn KB, Juhl CB, Sturis J, Jakobsen G, Brock B, Chandramouli V, Rungby J, Landau BR, Schmitz O: One week's treatment with the long-acting glucagon-like peptide 1 derivative liraglutide (NN2211) markedly improves 24-h glycemia and α - and β -cell function and reduces endogenous glucose release in patients with type 2 diabetes. *Diabetes* 53:1187–1194, 2004
10. Vilsbøll T, Zdravkovic M, Le-Thi T, Krarup T, Schmitz O, Courreges J-P, Verhoeven R, Buganova I, Madsbad S: Liraglutide, a long-acting human glucagon-like peptide-1 analog, given as monotherapy significantly improves glycemic control and lowers body weight without risk of hypoglycemia in patients with type 2 diabetes. *Diabetes Care* 30:1608–1610, 2007
11. Madsbad S, Schmitz O, Ranstam J, Jakobsen G, Matthews DR: 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. *Diabetes Care* 27:1335–1342, 2004
12. Nauck MA, Hompesch M, Filipczak R, Le TD, Zdravkovic M, Gumprecht J: Five weeks of treatment with the GLP-1 analogue liraglutide improves glycemic control and lowers body weight in patients with type 2 diabetes. *Exp Clin Endocrinol Diabetes* 114:417–423, 2006
13. Garber A, Henry R, Ratner R, Garcia-Hernandez PA, Rodriguez-Pattzi H, Olvera-Alvarez I, Hale PM, Zdravkovic M, Bode B: Liraglutide versus glimepiride monotherapy for type 2 diabetes (LEAD-3 Mono): randomised, 52-week, phase III, double-blind, parallel-treatment trial. *Lancet*. 2008 [Epub ahead of print]. DOI: 10.1015/S0140-6736(08)61246-5
14. World Medical Association: Declaration of Helsinki: recommendations guiding physicians in biomedical research involving human subjects. *JAMA* 277:925–926, 1997
15. Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC: Homeostasis model assessment: insulin resistance and β -cell function from fasting plasma glucose and insulin concentrations in man. *Diabetologia* 28:412–419, 1985
16. DeFronzo RA, Ratner RE, Han J, Kim DD, Baron AD: Effects of exenatide (exendin-4) on glycemic control and weight over 30 weeks in metformin-treated patients with type 2 diabetes. *Diabetes Care* 28:1092–1100, 2007
17. Charbonnel B, Karasik A, Liu J, Wu M, Meininger G, Sitagliptin Study 020 Group: Efficacy and safety of the dipeptidyl peptidase-4 inhibitor sitagliptin added to ongoing metformin therapy in patients with type 2 diabetes inadequately controlled with metformin monotherapy. *Diabetes Care* 29:2638–2643, 2006
18. Buse JB, Henry RR, Han J, Kim DD, Fineman MS, Baron AD: Effects of exenatide (exendin-4) on glycemic control over 30 weeks in sulfonylurea-treated patients with type 2 diabetes. *Diabetes Care* 27:2628–2635, 2004
19. Kendall DM, Riddle MC, Rosenstock J, Zhuang D, Kim DD, Fineman MS, Baron AD: Effects of exenatide (exendin-4) on glycemic control over 30 weeks in patients with type 2 diabetes treated with metformin and a sulfonylurea. *Diabetes Care* 28:1083–1091, 2005
20. Mari A, Degn K, Brock B, Rungby J, Ferrannini E, Schmitz O: Effects of the long-acting human glucagon-like peptide-1 analog liraglutide on β -cell function in normal living conditions. *Diabetes Care* 30:2032–2033, 2007
21. Vilsbøll T, Brock B, Perrild H, Levin K, Lervang H-H, Kølendorf K, Krarup T, Schmitz O, Zdravkovic M, Le-Thi T, Madsbad S: Liraglutide, a once-daily human GLP-1 analogue, improves pancreatic B-cell function and arginine-stimulated insulin secretion during hyperglycaemia in patients with type 2 diabetes mellitus. *Diabet Med* 25:152–156, 2008
22. Rolin B, Larsen MO, Gotfredsen CF, Deacon CF, Carr RD, Wilken M, Knudsen LB: The long-acting GLP-1 derivative NN2211 ameliorates glycemia and increases β -cell mass in diabetic mice. *Am J Physiol Endocrinol Metab* 283:E745–E752, 2002
23. Bregenholt S, Moldrup A, Blume N, Karlsen AE, Friedrichsen BN, Tornhave D, Knudsen LB, Petersen JS: The long-acting glucagon-like peptide-1 analogue, liraglutide, inhibits β -cell apoptosis in vitro. *Biochem Biophys Res Commun* 330:577–584, 2005