Effects of Exenatide (Exendin-4) on Glycemic Control and Weight Over 30 Weeks in Metformin-Treated Patients With Type 2 Diabetes

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OBJECTIVE — This study evaluates the ability of the incretin mimetic exenatide (exendin-4) to improve glycemic control in patients with type 2 diabetes failing to achieve glycemic control with maximally effective metformin doses.

RESEARCH DESIGN AND METHODS — A triple-blind, placebo-controlled, 30-week study at 82 U.S. sites was performed with 336 randomized patients. In all, 272 patients completed the study. The intent-to-treat population baseline was 53 ± 10 years with BMI of 34.2 ± 5.9 kg/m^2 and HbA_{1c} of 8.2 ± 1.1%. After 4 weeks of placebo, subjects self-administered 5 μg exenatide or placebo subcutaneously twice daily for 4 weeks followed by 5 or 10 μg exenatide, or placebo subcutaneously twice daily for 26 weeks. All subjects continued metformin therapy.

RESULTS — At week 30, HbA_{1c} changes from baseline ± SE for each group were −0.78 ± 0.10% (10 μg), −0.40 ± 0.11% (5 μg), and +0.08 ± 0.10% (placebo; intent to treat; adjusted $P < 0.002$). Of evaluable subjects, 46% (10 μg), 32% (5 μg), and 13% (placebo) achieved HbA_{1c} ≤7% ($P < 0.01$ vs. placebo). Exenatide-treated subjects displayed progressive dose-dependent weight loss (−2.8 ± 0.5 kg [10 μg], −1.6 ± 0.4 kg [5 μg]; $P < 0.001$ vs. placebo). The most frequent adverse events were gastrointestinal in nature and generally mild to moderate. Incidence of mild to moderate hypoglycemia was low and similar across treatment arms, with no severe hypoglycemia.

CONCLUSIONS — Exenatide was generally well tolerated and reduced HbA_{1c} with no weight gain and no increased incidence of hypoglycemia in patients with type 2 diabetes failing to achieve glycemic control with metformin.

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In most individuals with type 2 diabetes, hyperglycemia results from a failure of insulin secretion from the β-cells to adequately compensate for insulin resistance in peripheral tissues (1). Results from the U.K. Prospective Diabetes Study (UKPDS) indicate that β-cell failure is a progressive phenomenon and probably explains why the therapeutic need increases with time despite therapy with diet, metformin, sulfonylureas, or insulin (2,3). Although reductions in HbA_{1c} lower the risk of vascular complications, glycemic control is often inadequate with average HbA_{1c} values well above 8% (4,5). Moreover, many available therapeutic agents have undesirable side effects (such as weight gain, hypoglycemia, and edema) that can impede the attainment of glycemic control and discourage patient compliance (6,7).

Metformin, a commonly prescribed first-line antidiabetic drug, has proven to be safe and efficacious when used as monotherapy or in combination with other oral antidiabetic agents or insulin in patients with type 2 diabetes (7–10). However, for patients failing to achieve optimal glycemic control with metformin, many of the currently available treatment choices come with the above-mentioned undesirable side effects and the likelihood of eventual loss of glycemic control (2,3,7–10).

Exenatide (exendin-4) is a 39–amino acid peptide incretin mimetic that exhibits glucoregulatory activities similar to the mammalian incretin hormone glucagon-like peptide 1 (GLP-1) (11–22). These actions include glucose-dependent enhancement of insulin secretion, suppression of inappropriately high glucagon secretion, and slowing of gastric emptying. Exenatide's glucose-dependent enhancement of insulin secretion may be mediated by exenatide binding to the pancreatic GLP-1 receptor (23). In animal models of diabetes and in insulin-secreting cell lines, exenatide and GLP-1 reportedly improve β-cell function by increasing the expression of key genes involved in insulin secretion, increasing insulin biosynthesis, and augmenting β-cell mass through multiple mechanisms (17). Data obtained in animal models also indicate that exenatide and GLP-1 reduce food intake, cause weight loss, and have an insulin-sensitizing effect (13,14,17,24,25). This study evaluated

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Abbreviations: GLP-1, glucagon-like peptide 1.

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

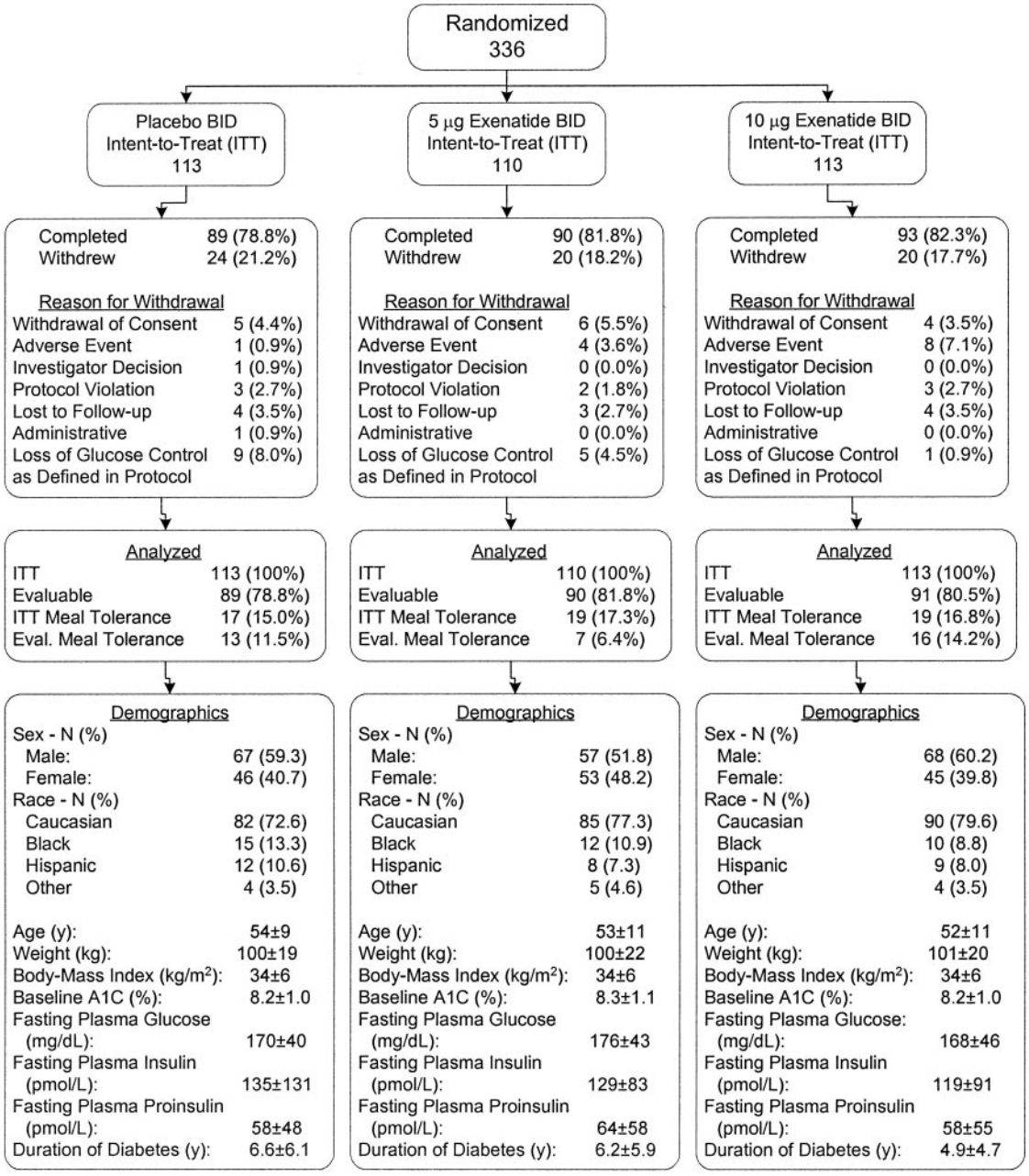

Figure 1—*Subject disposition and baseline demographics (mean ± SD). ITT, intent to treat.*

the effects of exenatide on glycemic control over a 30-week period in patients with type 2 diabetes failing to achieve glycemic control with metformin.

RESEARCH DESIGN AND METHODS

— Subjects were 19–78 years of age with type 2 diabetes treated with metformin monotherapy. General inclusion criteria were screening fasting plasma glucose concentration of <13.3 mmol/l (<240 mg/dl), BMI of 27–45 kg/m^2, and HbA_{1c} of 7.1–11.0%. The metformin dose was ≥1,500 mg/day for 3 months before screening. Subjects were weight stable (±10%) for 3 months before screening with no clinically significant (for a type 2 diabetes population) abnormal laboratory test values (>25% outside normal laboratory values). Female subjects were postmenopausal, surgically sterile, or using contraceptives for 3 months before screening and continuing throughout the study. Exclusion criteria included use of sulfonylureas, meglitinides, thiazolidinediones, α-glucosidase inhibitors, exogenous insulin therapy, weight loss drugs, corticosteroids, drugs known to affect gastrointestinal motility, transplantation medications, or any investigational drug, or evidence of clinically significant comorbid conditions for 3 months before screening.

Adults (n = 336) with type 2 diabetes treated with metformin participated at 82 sites in the U.S. (January 2002 to June 2003). A common clinical protocol was approved for each site by an institutional

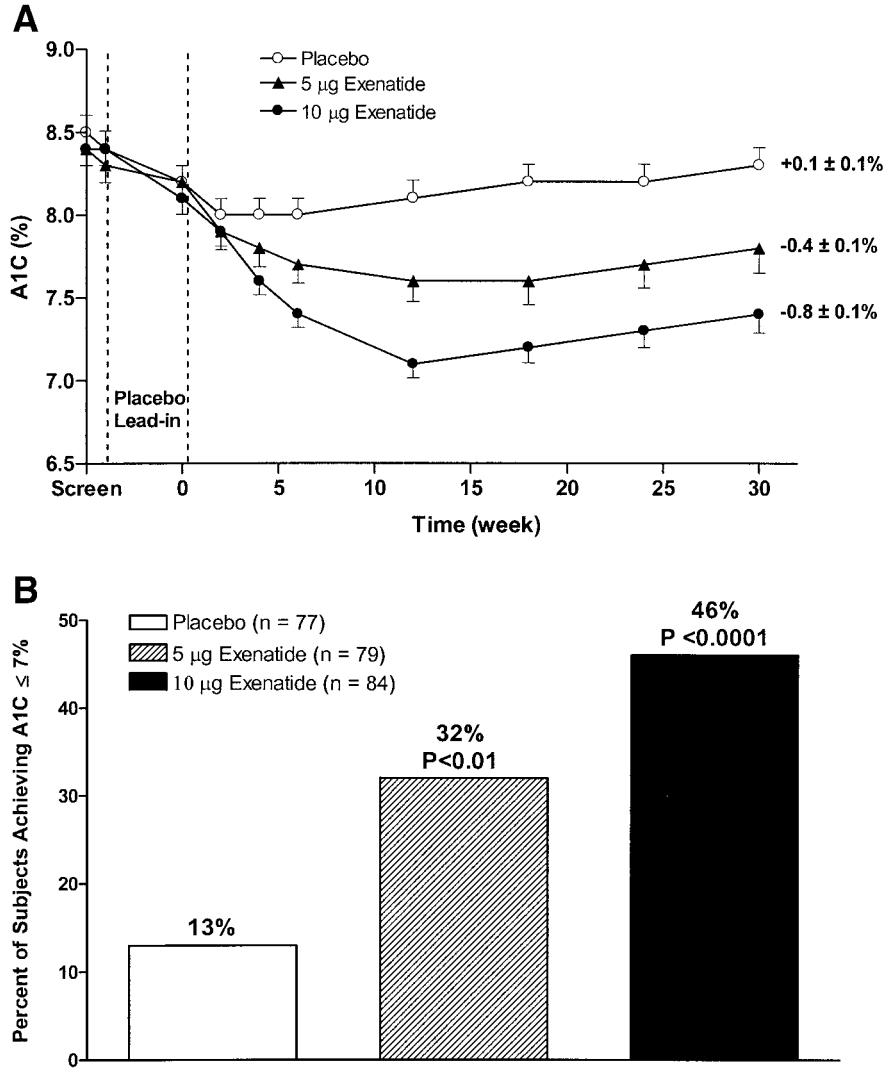

Figure 2—*Glycemic control in subjects with type 2 diabetes treated with metformin and exenatide or placebo.* A: *HbA_{1c} values over the course of the study in the intent-to-treat population. Baseline HbA_{1c} values (mean ± SE) were 8.18 ± 0.09% in the 10-μg exenatide arm, 8.26 ± 0.11% in the 5-μg exenatide arm, and 8.20 ± 0.10% in the placebo arm.* B: *Percentage of evaluable subjects achieving HbA_{1c} ≤7% at week 30. Subjects in the 10-μg exenatide arm received 5 μg exenatide twice daily during weeks 0–4. Subjects in all treatment arms were maintained on a stable metformin dose.*

review board in accordance with the principles described in the Declaration of Helsinki, including all amendments through the 1996 South Africa revision (26). All subjects provided written informed consent before participation.

This was a balanced, randomized, triple-blind, placebo-controlled, parallel-group clinical study (30-week duration) designed after consultation with the U.S. Food and Drug Administration to evaluate glycemic control, as assessed by HbA_{1c}, and safety. The study commenced with a 4-week, single-blind, lead-in period with subcutaneous injection of placebo twice daily. Thereafter, subjects were randomly assigned to one of four treatment arms. Nausea had been the most frequent treatment-emergent adverse event in earlier clinical trials, but gradual dose escalation has been shown to attenuate this side effect (27). Therefore, the present study design included an acclimation period (4 weeks) at a lower exenatide fixed dose (5 μg twice daily) in treatment arms A and B before the fixed dose of exenatide was either increased to 10 μg twice daily (arm B) or kept at 5 μg twice daily (arm A) for the duration of the study. Volumes of placebo equivalent to those administered to arms A and B were administered in treatment arms C and D. Study medication was self-injected subcutaneously in the abdomen within 15 min before meals in the morning and evening. All subjects continued their current regimen of metformin treatment (≥1,500 mg/day).

Subjects were instructed to fast overnight during the study. Any subject with either an HbA_{1c} change of +1.5% from baseline at any clinic visit or an HbA_{1c} ≥11.5% at week 18 or 24 could be terminated from the study for safety reasons at the investigator's discretion (loss of glucose control). Similarly, subjects could be withdrawn if fasting plasma glucose values were >13.3 mmol/l (>240 mg/dl) on two consecutive study visits or if recorded fingerstick fasting blood glucose values were >14.4 mmol/l (>260 mg/dl) for at least 2 weeks, not secondary to a readily identified illness or pharmacological treatment.

A subset of subjects (meal cohort) underwent a standardized meal tolerance test on weeks 0, 4, and 30. After an overnight fast (≥8 h), subjects took their morning dose of metformin within 1 h of their clinic visit. Exenatide or placebo was injected 15 min before a standardized breakfast. Meal size was calculated individually at screening to provide 20% of a subject's total daily caloric requirements with a macronutrient composition of 55% carbohydrate, 15% protein, and 30% fat based on body weight and activity level. The size of the standardized breakfast was the same on each test day for each individual subject.

Study end points

Primary end points included glycemic control, as assessed by HbA_{1c}, and safety. Secondary end points included percentage of patients achieving HbA_{1c} ≤7% by week 30, effect of exenatide on fasting and postprandial (meal cohort only) plasma glucose concentrations, body weight, fasting and postprandial concentrations of blood insulin, fasting proinsulin, and lipids.

Statistical analysis

Randomization was stratified according to screening HbA_{1c} values (<9.0% and ≥9.0%) to achieve a balanced distribution of subjects across treatment arms (A,

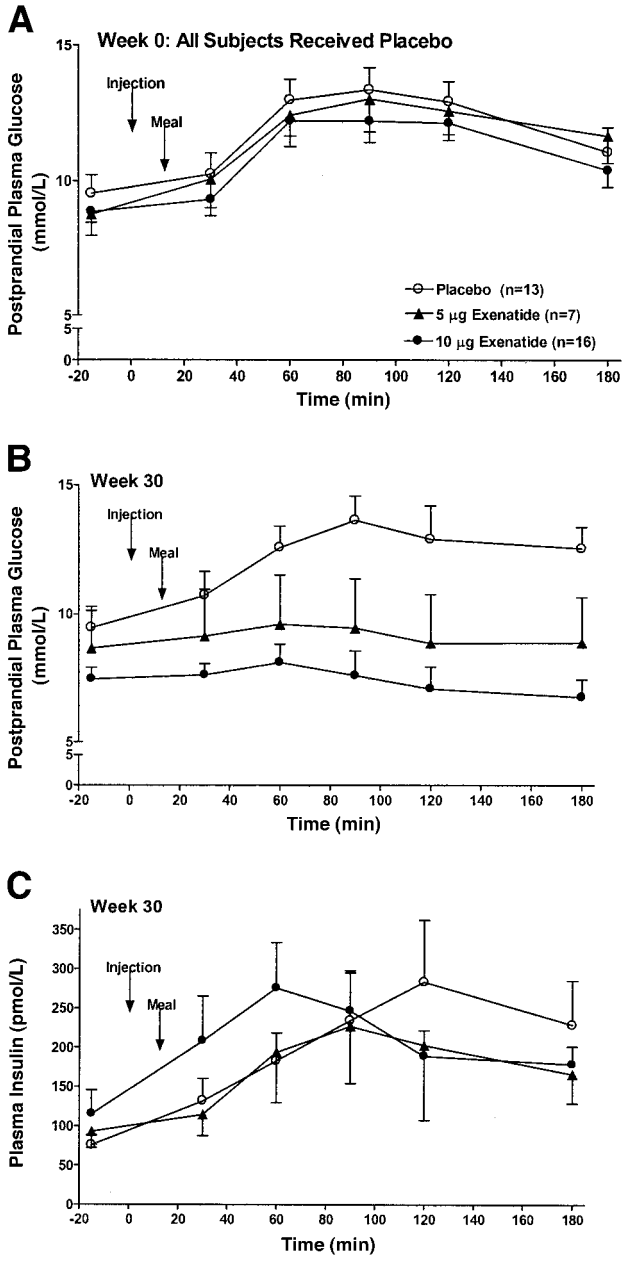

Figure 3—*Meal tolerance subgroups. Postprandial plasma glucose concentrations after a standardized meal at week 0* (A) *and at week 30* (B) *and postprandial plasma insulin levels at week 30* (C)*. Exenatide or placebo were administered at time zero. Evaluable population: 10 μg exenatide,* n = *16; 5 μg exenatide,* n = *7; placebo,* n = *13. Data are mean ± SE.*

B, C, or D in a 2:2:1:1 ratio). A minimum sample size of 300 subjects with at least one postbaseline HbA_{1c} measurement was estimated to provide ~90% power to detect a difference of 0.6% in the change from baseline in HbA_{1c} measurement between at least one exenatide treatment arm and placebo ($\alpha = 0.05$; Fisher's protected testing procedure). Placebo arms C and D were combined for all analyses.

All inferential statistical tests were conducted at a significance level of 0.05 (two-sided). A general linear model was used to test for differences in the change from baseline to each visit in HbA_{1c} and weight across treatments (28,29). Factors in the model included treatment (placebo and two active treatment arms), strata of baseline HbA_{1c} (<9.0% and ≥9.0%), and study site as fixed effects. Before data analysis, sites were pooled according to geographic location to prevent loss of too many degrees of freedom in the model. This pooling took into account the number of endocrinologists, patient accessibility to specialty diabetes care, and quality of managed care in the geographic locations.

The intent-to-treat population was defined as all randomized subjects who received at least one injection of medication starting from the evening of day 1. All efficacy and safety analyses were performed on the intent-to-treat population with the exception of the percentage of subjects achieving HbA_{1c} ≤7% (evaluable population) and the meal tolerance cohort. For intent-to-treat subjects, missing data (including missing values at intermediate visits) were imputed from scheduled visits using the last-observation-carried-forward method. The least square means and SE were derived from the general linear model for each treatment. Pairwise comparisons of the treatment effects were performed using Fisher's protected testing procedure to control type I errors due to multiple comparisons (30). Similar analyses were performed for each fasting metabolic parameter and for postprandial plasma glucose concentrations without adjusting for the multiple comparisons. Post hoc evaluation of change in body weight versus duration of nausea was performed using regression analysis. The proportion of subjects achieving HbA_{1c} ≤7% was compared across treatment groups using the Cochran-Mantel-Haenszel test, wherein strata of baseline HbA_{1c} values served as the stratification factor. Results are given as means ± SE unless otherwise indicated.

The evaluable population was defined as all randomized subjects who completed treatment through week 30 and received at least 80% of the study medication injections. Subjects who missed 7 consecutive days of injections during the last 2 months of the study were excluded.

Safety analysis

All safety analyses were performed using the intent-to-treat population. Safety end points included adverse events, clinical laboratory tests, physical examination, 12-lead electrocardiogram, vital signs, and titering of anti-exenatide antibodies. Treatment-emergent adverse events were defined as those occurring upon or after receiving the first randomized dose. The intensity of hypoglycemic episodes was

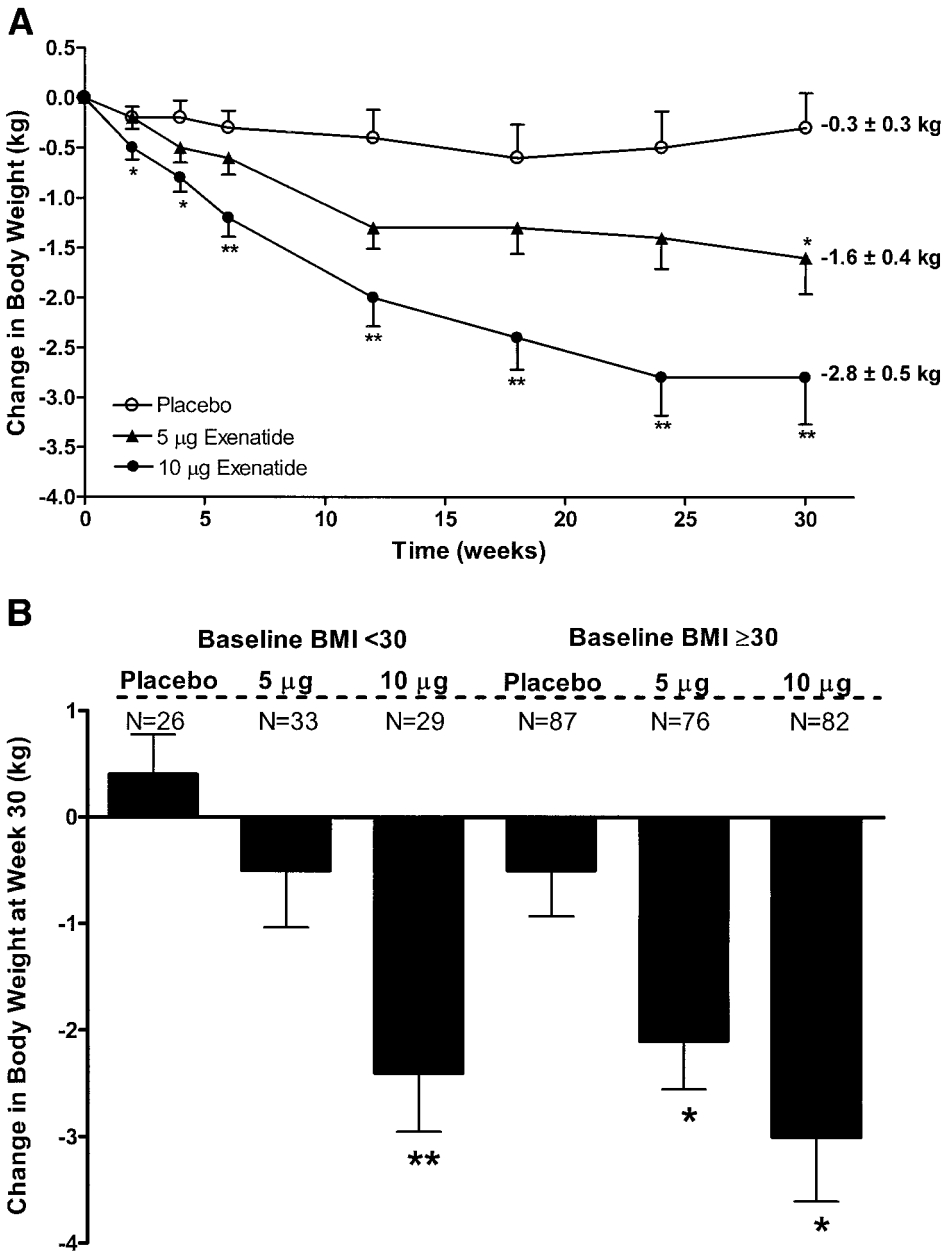

Figure 4—*Body weight in the intent-to-treat population.* A*: Change in body weight from baseline. Baseline weights were 101 ± 2 kg in the 10-μg exenatide arm, 100 ± 2 kg in the 5-μg exenatide arm, and 100 ± 2 kg in the placebo arm.* B*: Change in weight from baseline stratified by baseline BMI <30 and ≥30 kg/m^2. For baseline BMI <30 kg/m^2, baseline body weights were 84.0 ± 1.9 kg in the 10-μg exenatide arm, 80.8 ± 2.0 kg in the 5-μg exenatide arm, and 80.3 ± 2.2 kg in the placebo arm. For baseline BMI ≥30 kg/m^2, baseline body weights were 106.9 ± 2.1 kg in the 10-μg exenatide arm, 108.3 ± 2.3 kg in the 5-μg exenatide arm, and 105.8 ± 1.8 kg in the placebo arm. *P ≤ 0.05 compared with placebo treatment. **P ≤ 0.001 compared with placebo treatment. Data are mean ± SE.*

defined as mild/moderate or severe. For mild/moderate hypoglycemia, subjects reported symptoms consistent with hypoglycemia that may have been documented by a plasma glucose concentration value <3.3 mmol/l. For severe hypoglycemia, subjects required the assistance of another person to obtain treatment for their hypoglycemia, including intravenous glucose or intramuscular glucagon.

Assays

Plasma analytes and HbA_{1c} were quantitated by Quintiles Laboratories (Smyrna, GA) using standard methods. HbA_{1c} was measured using a high-performance liquid chromatography methodology (31,32). Serum insulin and proinsulin were quantitated by Esoterix Endocrinology (Calabasas Hills, CA) by two-site immunochemiluminometric assays. Intra-assay variability ranged from 3 to 12% and interassay variability from 7 to 14%. Cross-reactivities for the insulin assay were <0.001% with IGF-I and IGF-II, <0.01% with C-peptide, and <0.1% with proinsulin. There was no significant cross-reaction for the proinsulin assay with IGF-I, IGF-II, C-peptide, or insulin. Plasma exenatide and anti-exenatide antibodies were measured as described previously (12).

RESULTS

Study population demographics were evenly balanced across treatment arms (Fig. 1). The intent-to-treat population comprised 336 subjects with 272 subjects completing the study (81%) and 64 withdrawing early (19%). Withdrawal rates were equally distributed across treatment arms. Other than metformin, the most frequently used concomitant medications were ACE inhibitors (114 subjects, 34%), hydroxymethylglutaryl-CoA reductase

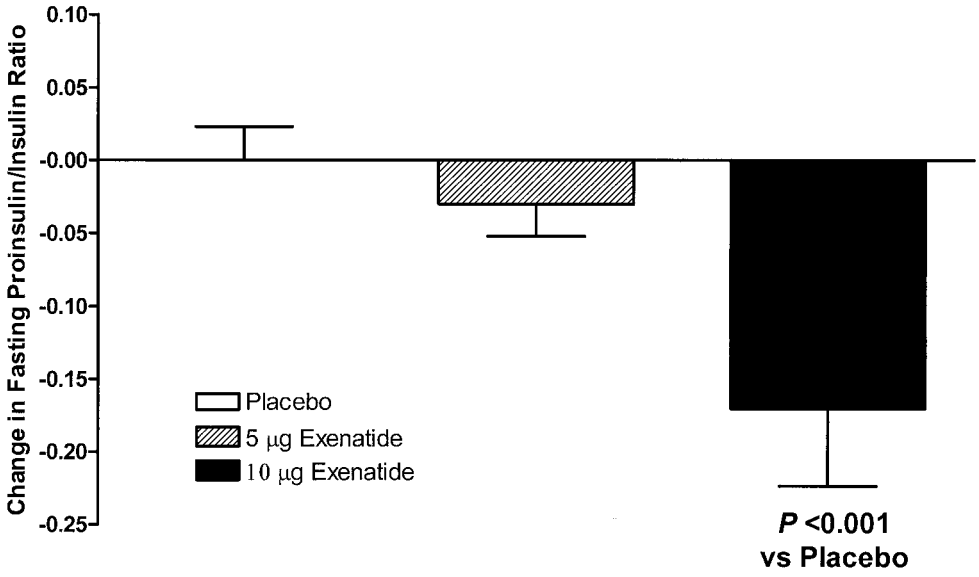

Figure 5—*Week 30 change in fasting proinsulin–to–insulin ratio from baseline in the intent-to-treat population. Data are mean ± SE.*

inhibitors (112 subjects, 33%), and platelet aggregation inhibitors, excluding heparin (101 subjects, 30%).

HbA_{1c} and plasma glucose

HbA_{1c} values declined in all treatment arms during the placebo lead-in period and the initial 2 weeks of the study after randomization (Fig. 2*A*). At week 4, significant reductions in HbA_{1c} from baseline were observed in both exenatide treatment arms compared with placebo ($P < 0.0005$). At week 30, a significant dose-dependent reduction in HbA_{1c} was observed in both exenatide-treated arms compared with placebo ($P < 0.001$, overall *F* test).

For intent-to-treat subjects at week 30 with baseline HbA_{1c} >7%, 40% (41 subjects) in the 10-μg exenatide arm and 27% (27 subjects) in the 5-μg exenatide arm reached an HbA_{1c} ≤7%. This proportion of the population was significantly greater than in the placebo arm (11% [11 subjects]; $P < 0.01$ for pairwise comparisons). Similarly, for the evaluable population with baseline HbA_{1c} values >7%, 46% (39 subjects) in the 10-μg exenatide arm and 32% (25 subjects) in the 5-μg exenatide arm achieved an HbA_{1c} ≤7% by week 30. These proportions of the evaluable population were significantly greater than in the placebo arm (13% [10 subjects]; $P < 0.0001$ and $P < 0.01$, respectively) (Fig. 2*B*).

Fasting plasma glucose concentrations were equivalent among treatment arms at baseline (Fig. 1). At week 30, fasting plasma glucose concentrations were −0.6 ± 0.2 mmol/l (−10.1 ± 4.4 mg/dl; $P = 0.0001$) and −0.4 ± 0.3 mmol/l (−7.2 ± 4.6 mg/dl; $P < 0.005$) for the 10- and 5-μg exenatide arms, respectively, compared with +0.8 ± 0.2 mmol/l (+14.4 ± 4.2 mg/dl) for the placebo arm. The end of study difference from placebo averaged −1.4 mmol/l (−25 mg/dl) in the 10-μg exenatide arm ($P = 0.0001$).

In subjects who underwent a standardized meal tolerance test, baseline data at week 0 (all arms received placebo) showed a similar rise in postprandial plasma glucose concentrations across treatment arms (Fig. 3*A*). Geometric mean area under the curve 15–180 min values at baseline were similar. At week 4, postprandial plasma glucose concentrations were reduced in both exenatide arms compared with placebo ($P = 0.006$). Postprandial plasma glucose geometric mean area under the curve 15–180 min values averaged 34% lower than baseline in each exenatide arm, compared with only 9% lower than baseline in the placebo arm. This pattern was sustained to week 30 with a robust lowering of postprandial glucose concentrations in the 10-μg ($P = 0.004$) and 5-μg exenatide arms ($P = 0.03$; Fig. 3*B*). At week 30, there was a rise in plasma insulin in response to the meal in all three arms, with a greater early increment noted in the 10-μg exenatide arm compared with placebo, despite lower baseline and postprandial glucose concentrations (Fig. 3*C*).

Body weight

Body weight averaged 100 kg across all treatment arms at baseline (Fig. 1). During the study, exenatide arms had progressive weight loss from baseline (Fig. 4*A*). Reductions in body weight were observed regardless of baseline BMI (Fig. 4*B*).

Insulin and proinsulin

Baseline fasting insulin and proinsulin concentrations were similar across treatment arms (Fig. 1). Despite the reduction in fasting plasma glucose concentrations in the exenatide arms, there were no significant differences in fasting plasma insulin concentrations from baseline in any treatment arm (+2.1 ± 7.8 pmol/l [10 μg], −3.5 ± 14.7 pmol/l [5 μg], −5.6 ± 10.4 pmol/l [placebo]). There was a trend toward a decline in fasting plasma proinsulin concentrations from baseline (−9.6 ± 3.8 pmol/l [10 μg], −5.2 ± 5.9 pmol/l [5 μg], −0.9 ± 4.5 pmol/l [placebo]) and a significant decrease in the proinsulin-to-insulin ratio toward more physiological proportions in the 10-μg exenatide arm ($P < 0.001$), with a similar trend observed in the 5-μg exenatide arm (Fig. 5).

Clinical laboratory findings and safety

Exenatide treatment was not associated with an increased incidence of cardiovascular, hepatic, or renal adverse events. No changes in plasma lipids, laboratory safety parameters, heart rate, blood pres-

Table 1—*Treatment-emergent adverse events*

	Placebo	5-μg exenatide	10-μg exenatide
n	113	110	113
Nausea	26 (23)	40 (36)	51 (45)
Diarrhea	9 (8)	13 (12)	18 (16)
Upper respiratory tract infection	12 (11)	15 (14)	11 (10)
Vomiting	4 (4)	12 (11)	13 (12)
Dizziness	7 (6)	10 (9)	5 (4)
Sinusitis	6 (5)	5 (5)	7 (6)
Hypoglycemia	6 (5)	5 (5)	6 (5)
Back pain	3 (3)	3 (3)	7 (6)

Data are *n* (%). Adverse events had an overall incidence ≥5% in any treatment arm and a higher incidence in an exenatide arm for the intent-to-treat population.

sure, or electrocardiogram variables were observed between treatment arms.

The incidence of serious (2.7, 4.5, and 3.5% for 10-μg, 5-μg, and placebo arms, respectively) and severe (9.7, 11.8, and 8.8% in the 10-μg, 5-μg, and placebo arms, respectively) treatment-emergent adverse events was low and evenly distributed across treatment arms. The most frequent adverse events were mild or moderate and were gastrointestinal in nature (Table 1). Nausea was the most frequent severe adverse event, and it was higher in exenatide-treated subjects than in placebo-treated subjects. Nausea was generally mild or moderate in intensity, with the incidence of severe nausea (3.5, 2.7, and 1.8% in the 10-μg, 5-μg, and placebo arms, respectively) and withdrawals due to nausea low (4 of 11 withdrawals [1.8%] in the exenatide arms). Nausea was reported at a higher incidence during the initial weeks of therapy (weeks 0–8) and declined thereafter (Fig. 6). There was no correlation between change in body weight and duration of nausea. Post hoc analysis of nausea and body weight change showed a lack of correlation between change in body weight and nausea duration (10 μg exenatide: $Y = -0.006X - 3.538$, $R^2 = 0.009$; 5 μg exenatide: $Y = +0.004X - 2.182$, $R^2 = 0.004$; placebo: $Y = +0.002X - 0.435$, $R^2 = 0.0002$). Moreover, subjects who never experienced nausea also lost weight: −2.2 ± 0.7 kg (10-μg exenatide arm) and −1.4 ± 0.4 kg (5-μg exenatide arm).

There were no cases of severe hypoglycemia. The overall incidence of mild to moderate hypoglycemia was 5.3% (six subjects) in the 10-μg exenatide arm, 4.5% (five subjects) in the 5-μg exenatide arm, and 5.3% (six subjects) in the placebo arm. The incidence of anti-exenatide antibodies (43% at 30 weeks) had no predictive effect on glycemic control or adverse events. Most treatment-emergent anti-exenatide antibodies were low titer (1/125) and of unknown biological relevance.

CONCLUSIONS — The data demonstrate that when exenatide at doses of 5 and 10 μg twice daily is added to a background of metformin for 30 weeks in a group of type 2 diabetic patients with less-than-optimal glycemic control (baseline HbA_{1c} ~8.2%), there was an overall improvement in glycemia (end of study HbA_{1c} ~7.4%), with nearly 50% of patients able to reach an HbA_{1c} treatment goal of ≤7% when treated with the 10-μg dose. The magnitude of HbA_{1c} reduction was notable, as the baseline HbA_{1c} was relatively low (8.2%). Many previous trials in this disease population have studied patients with higher baseline HbA_{1c} levels, where it is possible to exert a greater HbA_{1c}-lowering effect (33,34). Reduction of HbA_{1c} was the result of a modest decrease in fasting plasma glucose concentrations in keeping with the pharmacokinetic profile of exenatide and, more importantly, a sustained robust glucose-lowering effect postprandially, as indicated by the meal challenge cohort.

It is also noteworthy that the improvement in glycemia was coupled with overall weight loss and no increase in hypoglycemia. Exenatide treatment elicited dose-dependent reductions in body weight (~3% at the 10-μg dose) that did not appear to fully plateau by week 30. This occurred in the setting of a significant improvement in overall glycemia, where one would ordinarily see weight gain with most other therapies. Weight loss occurred in subjects who had not experienced nausea and was independent of nausea in the cohort at large, as weight loss was sustained over the course of the study but nausea was more pronounced during the first weeks of therapy.

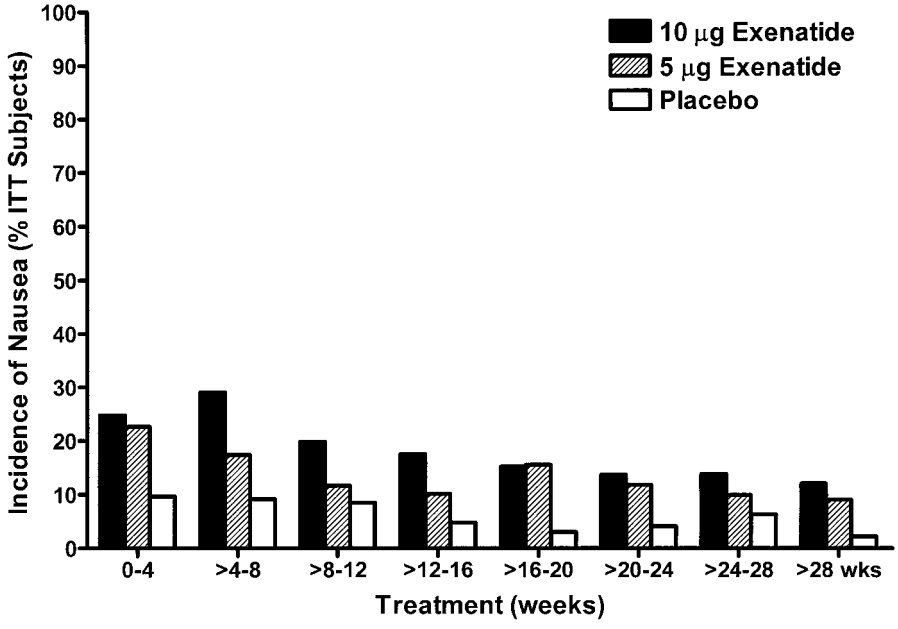

Figure 6—*Time-dependent incidence of subjects experiencing treatment-emergent nausea in the intent-to-treat (ITT) population.*

The improvement in the proinsulin-to-insulin ratio noted in the exenatide-treated patients is an indication of a beneficial effect on the β-cell. In addition, the meal challenge data indicate a robust insulin secretory response to the meal stimulus despite lower fasting and postprandial glucose concentrations. More detailed analysis of pancreatic β-cell function in long-term treatment with exenatide will be necessary to better characterize the potential positive effects of exenatide on the β-cell.

These results are consistent with those reported in a similar 30-week placebo-controlled phase III study of the effects of exenatide on glycemic control and safety in subjects with type 2 diabetes failing to achieve glycemic control with sulfunonylureas (35). In that study, at week 30 the 10-μg exenatide arm had significant placebo-adjusted reductions of −1.0% in HbA_{1c} and −1.0 kg in weight. In addition, a reduction in the proinsulin-to-insulin ratio in the 10-μg exenatide arm indicated that exenatide had a beneficial effect on the β-cell (32). In a parallel, 30-week placebo-controlled phase III study in subjects with type 2 diabetes failing to achieve glycemic control with metformin and a sulfonylurea, the 10-μg exenatide arm had significant placebo-adjusted reductions of −1.0% in HbA_{1c} and −0.7 kg in weight at week 30 (36). Thus, exenatide appears to elicit similar glycemic effects whether patients are on background metformin or sulfonylurea or a combination of both.

Combining exenatide with metformin did not increase the risk of hypoglycemia. It is acknowledged that metformin is antihyperglycemic in its action and has little or no hypoglycemic potential. That noted, although there was a background incidence of hypoglycemia in the metformin-plus-placebo group, it was mild or moderate in nature and of questionable clinical significance. Importantly, despite a decrease of nearly 1% in HbA_{1c} with exenatide, there was no increase in hypoglycemia above that seen in the placebo arm and no severe hypoglycemic events. This is a clear representation of the glucose-dependent action of exenatide and offers a potential advantage over other therapies in this area, such as the oral insulin secretagogues and exogenously administered insulin.

The most common treatment-emergent adverse event was dose-related nausea. Nausea was mostly mild-to-moderate in intensity with a low incidence of severe nausea; only 3% of subjects in the 10-μg exenatide arm withdrew from the clinical trial due to nausea. The incidence of treatment-emergent nausea was highest at initiation of the maintenance dose (weeks 4–8 for 10 μg and weeks 0–4 for 5 μg) and became less frequent with subsequent dosing. Lastly, anti-exenatide antibodies were detected in a subset of patients but this was not associated with any apparent loss of efficacy or increased incidence of immune system-associated adverse events.

In summary, in patients treated with metformin who are not achieving adequate glycemic control, exenatide elicited a substantial reduction in HbA_{1c} with no increase in the incidence of hypoglycemia and was associated with significant and sustained weight loss. This combination of beneficial effects suggests that long-term use of exenatide at subcutaneous doses of 5 μg and 10 μg twice daily has potential for the treatment of patients with type 2 diabetes not adequately controlled with metformin.

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References

1. Weyer C, Bogardus C, Mott DM, Pratley RE: The natural history of insulin secretory dysfunction and insulin resistance in the pathogenesis of type 2 diabetes mellitus. *J Clin Invest* 104:787–794, 1999
2. UK Prospective Diabetes Study Group: UK Prospective Diabetes Study 16: Overview of 6 years' therapy of type II diabetes: a progressive disease. *Diabetes* 44:1249–1258, 1995
3. UK Prospective Diabetes Study Group: Intensive blood-glucose control with sulfonylureas or insulin compared with conventional treatment and risk of complications in subjects with type 2 diabetes (UKPDS 33). *Lancet* 352:837–853, 1998
4. Koro CM, Bowlin SJ, Bourgeois N, Fedder DO: Glycemic control from 1988 to 2000 among U.S. adults diagnosed with type 2 diabetes. *Diabetes Care* 27:17–20, 2004
5. Harris MI, Eastman RC, Cowie CC, Flegal KM, Eberhardt MS: Racial and ethnic differences in glycemic control of adults with type 2 diabetes. *Diabetes Care* 22:403–408, 1999
6. Inzucchi SE: Oral antihyperglycemic therapy for type 2 diabetes: scientific review. *JAMA* 287:360–372, 2002
7. DeFronzo RA: Pharmacologic therapy for type 2 diabetes mellitus. *Ann Intern Med* 131:281–303, 1999
8. DeFronzo RA, Goodman AM: Efficacy of metformin in patients with non-insulin-dependent diabetes mellitus. *N Engl J Med* 333:541–549, 1995
9. Kirpichnikov D, McFarlane SI, Sowers JR: Metformin: an update. *Ann Intern Med* 137:25–33, 2002
10. Nathan DM: Initial management of glycemia in type 2 diabetes mellitus. *N Engl J Med* 347:1342–1348, 2002
11. Kolterman OG, Buse JB, Fineman MS, Gaines E, Heintz S, Bicsak TA, Taylor K, Kim D, Aisporna M, Wang Y, Baron AD: Synthetic exendin-4 (exenatide) signifi-

cantly reduces postprandial and fasting plasma glucose in subjects with type 2 diabetes. *J Clin Endocrinol Metab* 88:3082–3089, 2003
12. Fineman MS, Bicsak TA, Shen LZ, Taylor K, Gaines E, Varns A, Kim D, Baron AD: Effect on glycemic control of exenatide (synthetic exendin-4) additive to existing metformin and/or sulfonylurea treatment in patients with type 2 diabetes. *Diabetes Care* 26:2370–2377, 2003
13. Nielsen LL, Baron AD: Pharmacology of exenatide (synthetic exendin-4) for the treatment of type 2 diabetes. *Curr Opinion Investig Drugs* 4:401–405, 2003
14. Young AA, Gedulin BR, Bhavsar S, Bodkin N, Jodka C, Hansen B, Denaro M: Glucose-lowering and insulin-sensitizing actions of exendin-4: studies in obese diabetic (*ob/ob, db/db*) mice, diabetic fatty Zucker rats, and diabetic rhesus monkeys (*Macaca mulatta*). *Diabetes* 48:1026–1034, 1999
15. Parkes DG, Pittner R, Jodka C, Smith P, Young A: Insulinotropic actions of exendin-4 and glucagon-like peptide-1 in vivo and in vitro. *Metabolism* 50:583–589, 2001
16. Edwards CM, Stanley SA, Davis R, Brynes AE, Frost GS, Seal LJ, Ghatei MA, Bloom SR: Exendin-4 reduces fasting and postprandial glucose and decreases energy intake in healthy volunteers. *Am J Physiol Endocrinol Metab* 281:E155–E161, 2001
17. Nielsen LL, Young AA, Parkes D: Pharmacology of exenatide (synthetic exendin-4): a potential therapeutic for improved glycemic control of type 2 diabetes. *Regul Pept* 117:77–88, 2004
18. Egan JM, Clocquet AR, Elahi D: The insulinotropic effect of acute exendin-4 administered to humans: comparison of nondiabetic state to type 2 diabetes. *J Clin Endocrinol Metab* 87:1282–1290, 2002
19. Holst JJ: Therapy of type 2 diabetes mellitus based on the actions of glucagon-like peptide-1. *Diabetes Metab Res Rev* 18: 430–441, 2002
20. Holst JJ, Gromada J: Role of incretin hormones in the regulation of insulin secretion in diabetic and nondiabetic humans. *Am J Physiol Endocrinol Metab* 287:E199–E206, 2004
21. Nauck MA, Kleine N, Orskov C, Holst JJ, Willms B, Creutzfeldt W: Normalization of fasting hyperglycaemia by exogenous glucagon-like peptide 1 (7–38 amide) in type 2 (non-insulin-dependent) diabetic patients. *Diabetologia* 36:741–744, 1993
22. Zander M, Madsbad S, Madsen JL, Holst JJ: Effect of 6-week course of glucagon-like peptide 1 on glycaemic control, insulin sensitivity, and β-cell function in type 2 diabetes: a parallel-group study. *Lancet* 359:824–830, 2002
23. Göke R, Fehmann HC, Linn T, Schmidt H, Krause M, Eng J, Göke B: Exendin-4 is a high potency agonist and truncated exendin-(9–39)-amide an antagonist at the glucagon-like peptide 1-(7–36)-amide receptor of insulin-secreting β-cells. *J Biol Chem* 268:19650–19655, 1993
24. Szayna M, Doyle ME, Betkey JA, Holloway HW, Spencer RGS, Greig NH, Egan JM: Exendin-4 decelerates food intake, weight gain, and fat deposition in Zucker rats. *Endocrinology* 141:1936–1941, 2000
25. Gedulin BR, Nikoulina SE, Smith PA, Gedulin G, Nielsen LL, Baron AD, Parkes D, Young AA: Exenatide (exendin-4) improves insulin sensitivity and β-cell mass in insulin-resistant obese *fa/fa* Zucker rats independent of glycemia and body weight. *Endocrinology* 146:2069–2076, 2005
26. Declaration of Helsinski: Recommendations guiding medical physicians in biomedical research involving human subjects. *JAMA* 277:925–926, 1997
27. Fineman MS, Shen LZ, Kristin Taylor T, Kim DD, Baron AD: Effectiveness of progressive dose-escalation of exenatide (exendin-4) in reducing dose-limiting side-effects in subjects with type 2 diabetes. *Diabetes Metab Res Rev* 20:411–417, 2004
28. Neter J, Wasserman W, Kutner MH: *Applied Linear Statistical Models.* 3rd ed. Momewood, IL, Irwin, 1990
29. Milliken GA, Johnson DE: *Analyses of Messy Data. Vol I. Designed Experiments.* New York, Van Nostrand Reinhold, 1984
30. Hayter AJ: The maximum familywise error rate of Fisher's least significant difference test. *J Am Stat Assoc* 396:1000–1004, 1986
31. Davis JE, McDonald JM, Jarret L: A high performance liquid chromatogaraphy method for hemoglobin A1c. *Diabetes* 27: 102–107, 1978
32. Cole RA, Soeldner JS, Dunn PJ, Bunn HF: A rapid method for the determination of glycosylated hemoglobins using high pressure liquid chromatography. *Metabolism* 27:289–301, 1978
33. Fonseca V, Rosenstock J, Patwardhan R, Salzman A: Effect of metformin and rosiglitazone combination therapy in patients with type 2 diabetes mellitus: a randomized controlled trial. *JAMA* 13: 1695–1702, 2000
34. Rendell MS, Glazer NB, Ye Z: Combination therapy with pioglitazone plus metformin or sulfonylurea in patients with type 2 diabetes: influence of prior antidiabetic drug regimen. *J Diabetes Complications* 17:211–217, 2003
35. 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
36. Kendall DM, Riddle MC, Zhuang D, Kim DD, Fineman MS, Baron AD: Effects of exenatide (exendin-4) on glycemic control and weight in patients with type 2 diabetes treated with metformin and a sulfonylurea. Late-breaking abstract presented at the 64th Annual Meeting of the American Diabetes Association, 4–8 June 2004, at the Orange County Convention Center, Orlando, Florida