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

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OBJECTIVE — This study evaluated the ability of the incretin mimetic exenatide (exendin-4) to improve glycemic control in patients with type 2 diabetes failing maximally effective doses of a sulfonylurea as monotherapy.

RESEARCH DESIGN AND METHODS — This was a triple-blind, placebo-controlled, 30-week study conducted at 101 sites in the U.S. After a 4-week, single-blind, placebo lead-in period, 377 subjects were randomized (60% men, age 55 ± 11 years, BMI 33 ± 6 kg/m^2, HbA_{1c} 8.6 ± 1.2% [±SD]) and began 4 weeks at 5 μg subcutaneous exenatide twice daily (before breakfast and dinner; arms A and B) or placebo. Subsequently, subjects in arm B were escalated to 10 μg b.i.d. exenatide. All subjects continued sulfonylurea therapy.

RESULTS — At week 30, HbA_{1c} changes from baseline were −0.86 ± 0.11, −0.46 ± 0.12, and 0.12 ± 0.09% (±SE) in the 10-μg, 5-μg, and placebo arms, respectively (adjusted $P <$ 0.001). Of evaluable subjects with baseline $HbA_{1c} > 7\%$ ($n = 237$), 41% (10 μg), 33% (5 μg), and 9% (placebo) achieved $HbA_{1c} \leq 7\%$ ($P < 0.001$). Fasting plasma glucose concentrations decreased in the 10-μg arm compared with placebo ($P < 0.05$). Subjects in the exenatide arms had dose-dependent progressive weight loss, with an end-of-study loss in the 10-μg exenatide arm of −1.6 ± 0.3 kg from baseline ($P < 0.05$ vs. placebo). The most frequent adverse events were generally mild or moderate and gastrointestinal in nature. No severe hypoglycemia was observed.

CONCLUSIONS — Exenatide significantly reduced HbA_{1c} in patients with type 2 diabetes failing maximally effective doses of a sulfonylurea. Exenatide was generally well tolerated and was associated with weight loss.

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Sulfonylureas, a class of commonly prescribed antidiabetic drugs, are generally safe and efficacious in monotherapy and in combination with other oral agents and insulin in patients with type 2 diabetes. However, hypoglycemia and weight gain often accompany their use (1–3), and sulfonylurea therapy eventually fails to provide adequate glycemic control in the majority of patients with type 2 diabetes (4–6).

Exenatide (exendin-4) is a 39–amino acid peptide incretin mimetic that exhibits glucoregulatory activities similar to those observed with the mammalian incretin hormone glucagon-like peptide (GLP)-1 (7–12). The present study was undertaken to evaluate the ability of exenatide to improve glycemic control over a 30-week period in patients with type 2 diabetes failing maximally effective doses of a sulfonylurea.

RESEARCH DESIGN AND METHODS

— Subjects were 22–76 years of age and had type 2 diabetes treated with at least the maximally effective dose of a sulfonylurea as monotherapy (defined below) for at least 3 months before screening. General inclusion criteria were a screening fasting plasma glucose concentration <240 mg/dl, BMI 27–45 kg/m^2, and HbA_{1c} 7.1–11.0%, inclusive. In addition, subjects had stable weight (±10%) for 3 months before screening and had no clinically relevant (for a type 2 diabetic population) abnormal laboratory test values (>25% outside normal laboratory values). Female subjects were postmenopausal or surgically sterile or using contraceptives for at least 3 months before screening and continuing throughout the study. Subjects were excluded if they had used metformin, thiazolidinediones, meglitinides, α-glucosidase inhibitors, exogenous insulin therapy, or weight-loss drugs within the prior 3 months. Further exclusion criteria included therapy with corticoste-

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Abbreviations: GLP, glucagon-like peptide; ITT, intent to treat.

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

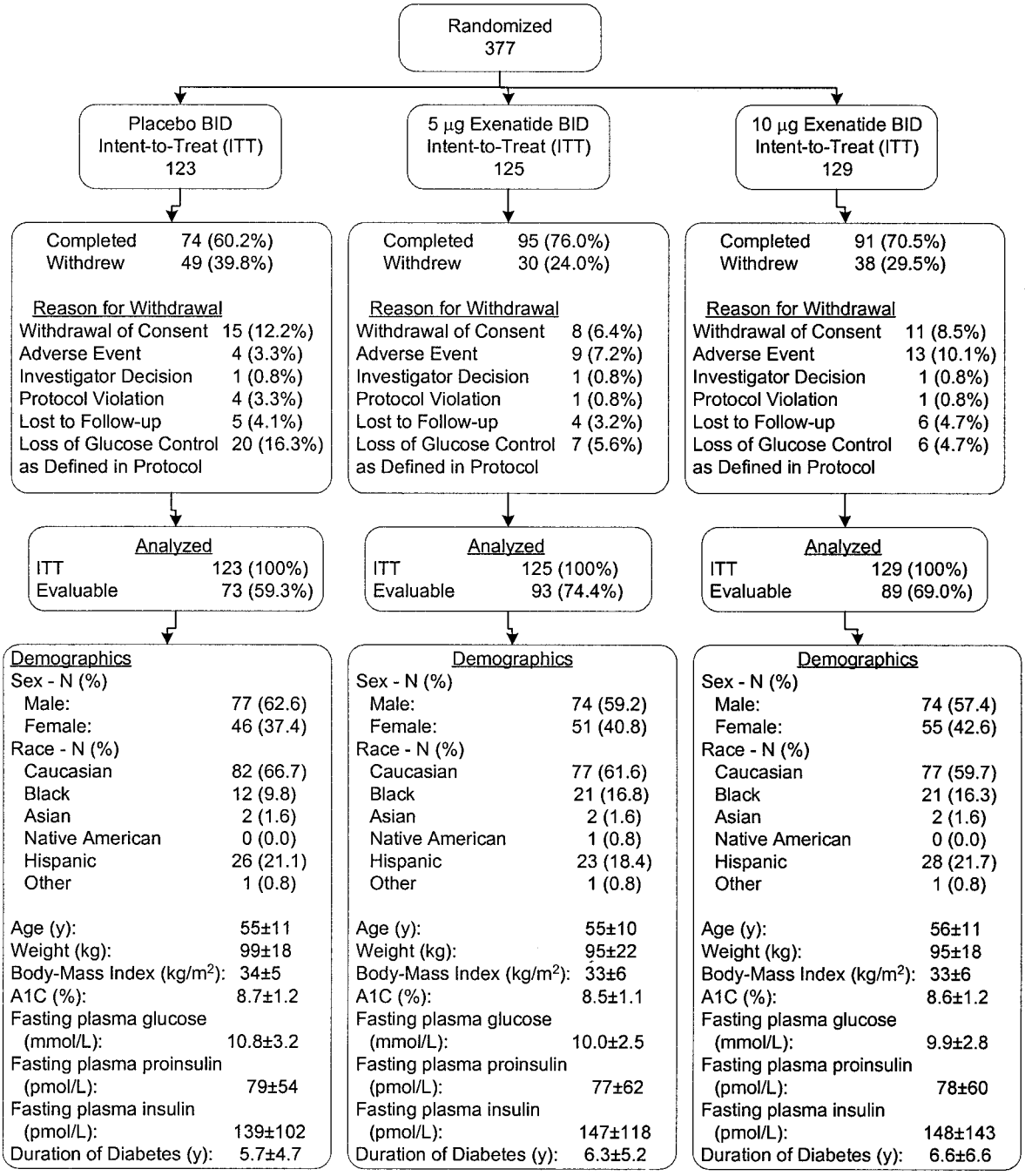

Figure 1— *Study flow chart and subject baseline demographics. Values are means ± SD or n (%).*

roids, drugs known to affect gastrointestinal motility, transplantation medications, or any investigational drug. Subjects were excluded if they had evidence of clinically significant comorbid conditions.

Three hundred seventy-seven adults with sulfonylurea-treated type 2 diabetes participated at 101 sites in the U.S. (February 2002 to August 2003). Data from 100 sites were used in statistical analyses (1 site was closed during study conduct due to protocol noncompliance). A common clinical protocol was approved for each site by an institutional review board and in accordance with the principles described in the Declaration of Helsinki, including all amendments through the 1996 South Africa revision (13). All subjects provided written informed consent before participation.

This was a balanced, randomized, triple-blind, placebo-controlled, parallel-group, pivotal clinical study 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 randomized 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 (14). Therefore, the present study design included an acclimation period (4 weeks) at a lower exenatide fixed dose (5 μg b.i.d.) in treatment arms A and B, before the fixed dose of exenatide was either increased to 10 μg b.i.d. (arm B) or remained at 5 μg b.i.d. (arm A) for the duration of the study. Equivalent volumes of placebo 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.

In an effort to standardize sulfonylurea use at study initiation, if required, subjects had their sulfonylurea dose adjusted before the placebo lead-in period to the maximally effective dose (4 mg/day glimepiride, 20 mg/day glipizide, 10 mg/day glipizide XL, 10 mg/day glyburide, 6 mg/day micronized glyburide, 350 mg/day chlorpropamide, or 500 mg/day tolazamide) (15–17). To address the risk of hypoglycemia, the protocol recommended progressive 50% reductions in sulfonylurea dose, eventual discontinuation (depending on the recurrence of hypoglycemia) in the event of a documented episode of hypoglycemia (glucose <60 mg/dl), or two undocumented but suspected episodes of hypoglycemia.

Any subject with either an HbA_{1c} change of 1.5% from baseline at any clinic visit before study termination or an HbA_{1c} ≥11.5% at week 18 or 24 could be withdrawn from the study (loss of glucose control). Similarly, subjects could be withdrawn if they had fasting plasma glucose values >240 mg/dl on two consecutive study visits or consistently recorded finger-stick fasting blood glucose values >260 mg/dl for at least 2 weeks, not secondary to a readily identified illness or pharmacological treatment.

Study end points

Primary objectives were to evaluate glycemic control, primarily as assessed by HbA_{1c}, and safety. Secondary objectives included examining the effects of exenatide on fasting plasma glucose concentrations, body weight, and fasting concentrations of circulating insulin, proinsulin, and lipids. Safety end points included adverse events, clinical laboratory tests, physical examination, 12-lead electrocardiogram, and vital signs. Treatment-emergent adverse events were defined as those occurring upon or after receiving the first randomized dose. The emergence of anti-exenatide antibodies was also assessed.

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 minimum sample size of 300 subjects who had 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} values 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 the 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} across treatments (18,19). 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 the 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 managed care in the geographic locations.

The intent-to-treat (ITT) population was defined as all randomized subjects who received at least one injection of randomized medication starting from the evening of day 1. All efficacy and safety analyses were performed on the ITT population, with the exception of the percentage of subjects achieving HbA_{1c} ≤7% by week 30. For the latter analysis, the more clinically relevant population of evaluable subjects was used (see below). For ITT subjects who had recorded values for at least one scheduled visit subsequent to the baseline measurement, 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 SEs 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 (20). Similar analyses were performed for body weight, each fasting metabolic parameter, and postprandial plasma glucose concentrations without adjusting for the multiple comparison. 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 ITT population. Treatment-emergent adverse events were defined as those occurring upon or after receiving the first randomized dose. The intensity of hypoglycemic episodes was 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 (<60 mg/dl). 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 were quantitated by Quintiles Laboratories (Smyrna, GA) or Esoterix Endocrinology (Calabasas Hills, CA) using standard methods. Serum insulin was quantitated by a two-site sandwich chemiluminescent immunoassay, and serum proinsulin was quantitated by a two-site immunochemiluminometric assay. HbA_{1c} was measured using a high-performance liquid chromatography methodology (21,22). Plasma exenatide and anti-exenatide antibodies were measured as described previously (8).

RESULTS

— Three hundred seventy-seven subjects were randomized to treatment and received at least one dose of study medication (ITT population), 260 subjects completed the entire study (69%), and 117 withdrew early (31%)

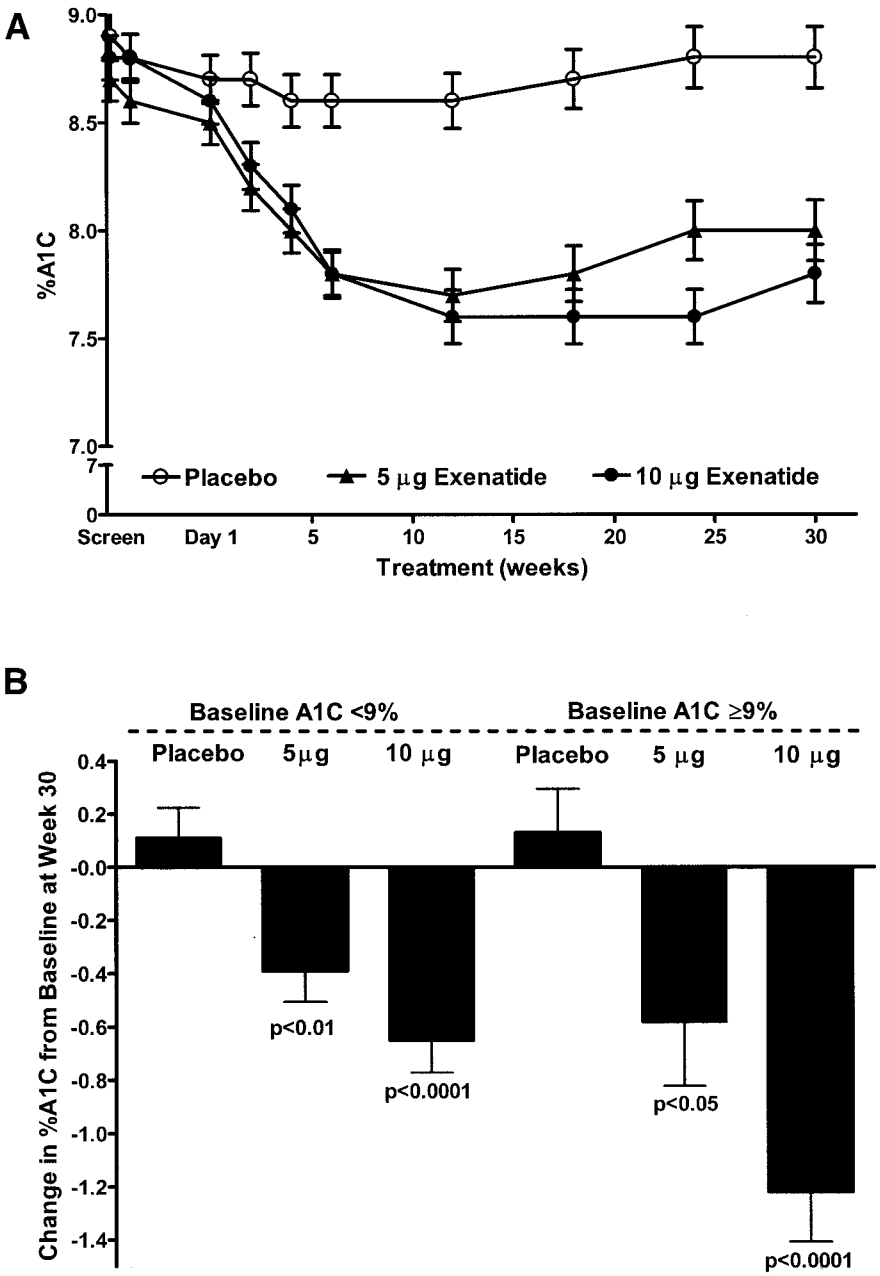

Figure 2— *Glycemic control in subjects with type 2 diabetes treated with a sulfonylurea and exenatide or placebo.* A: *HbA_{1c} values over the course of the study (ITT population). Baseline HbA_{1c} values were 8.6 ± 0.1% in the 10-μg exenatide arm (●, n = 129), 8.5 ± 0.1% in the 5-μg exenatide arm (▲, n = 125), and 8.7 ± 0.1% in the placebo arm (○, n = 123). Data are means ± SE.* B: *Change in HbA_{1c} values at week 30 stratified by baseline HbA_{1c} (ITT population). Baseline HbA_{1c} values were 7.9 ± 0.1% (10 μg), 7.8 ± 0.1% (5 μg), and 7.9 ± 0.1% (placebo) in subjects with baseline HbA_{1c} <9%. Baseline HbA_{1c} values were 10.0 ± 0.1% (10 μg), 9.7 ± 0.1% (5 μg), and 10.1 ± 0.1% (placebo) in subjects with baseline HbA_{1c} ≥9%. Data are means ± SE. The adjusted* P *values shown are with placebo as the reference arm. Subjects in the 10-μg b.i.d. exenatide treatment arm received 5 μg b.i.d. exenatide during weeks 0–4. Subjects in all treatment arms were maintained on a sulfonylurea.*

(Fig. 1). All subjects were treated with a sulfonylurea (45% glipizide, 33% glyburide, 20% glimepiride, 1% tolazamide, and 0.3% chlorpropamide). Thirty-nine percent of ITT subjects were also treated with an ACE inhibitor, 34% with an antithrombotic agent, and 37% with a serum lipid–reducing agent.

HbA_{1c} and plasma glucose

HbA_{1c} values declined in all treatment arms during the period between screening and randomization, averaged 8.6% at baseline, and were comparable across treatment arms (Fig. 2*A*). HbA_{1c} values declined in both exenatide arms during the initial 12 weeks of the study, in contrast to relatively little change in the placebo arm. Thereafter, HbA_{1c} values in the exenatide arms plateaued, followed by a slight rise toward baseline by the end of the study in parallel with a similar change in the placebo arm. At week 30, the HbA_{1c} change from baseline was −0.86 ± 0.11% in the 10-μg exenatide arm and −0.46 ± 0.12% in the 5-μg exenatide arm compared with an increase of 0.12 ± 0.09% in the placebo arm (adjusted $P \leq 0.0002$ for pairwise comparisons). For the ITT population at week 30 with baseline HbA_{1c} >7% ($n = 353$), 41 subjects (34.2%) in the 10-μg exenatide arm and 31 subjects (26.7%) in the 5-μg exenatide arm reached an HbA_{1c} ≤7%, and these proportions of the population were significantly greater than in the placebo arm (9 subjects [7.7%]; $P < 0.0001$ for pairwise comparisons). For the evaluable population at week 30 with baseline HbA_{1c} >7% ($n = 237$), 33 subjects (41.3%) in the 10-μg exenatide arm and 28 subjects (32.6%) in the 5-μg exenatide arm reached an HbA_{1c} ≤7%, and these proportions of the evaluable population were significantly greater than in the placebo arm (6 subjects [8.8%]; $P \leq 0.0002$ for pairwise comparisons).

When stratified by baseline HbA_{1c} ≥9%, the 10- and 5-μg exenatide arms had changes in HbA_{1c} from baseline of −1.22 ± 0.19% ($n = 46$) and −0.58 ± 0.24% ($n = 46$), respectively, compared with an increase of 0.13 ± 0.17% in the placebo arm at week 30 ($n = 46$; adjusted $P < 0.05$ for pairwise comparisons) (Fig. 2*B*). For subjects with baseline HbA_{1c} <9%, the 10- and 5-μg exenatide arms had changes in HbA_{1c} from baseline of −0.65 ± 0.12% ($n = 83$) and −0.39 ± 0.12% ($n = 79$), respectively, compared with an increase of 0.11 ± 0.12% in the placebo arm at week 30 ($n = 77$; adjusted $P < 0.01$ for pairwise comparisons).

Baseline fasting plasma glucose concentrations were similar across treatment arms (Fig. 1). By week 30, fasting plasma

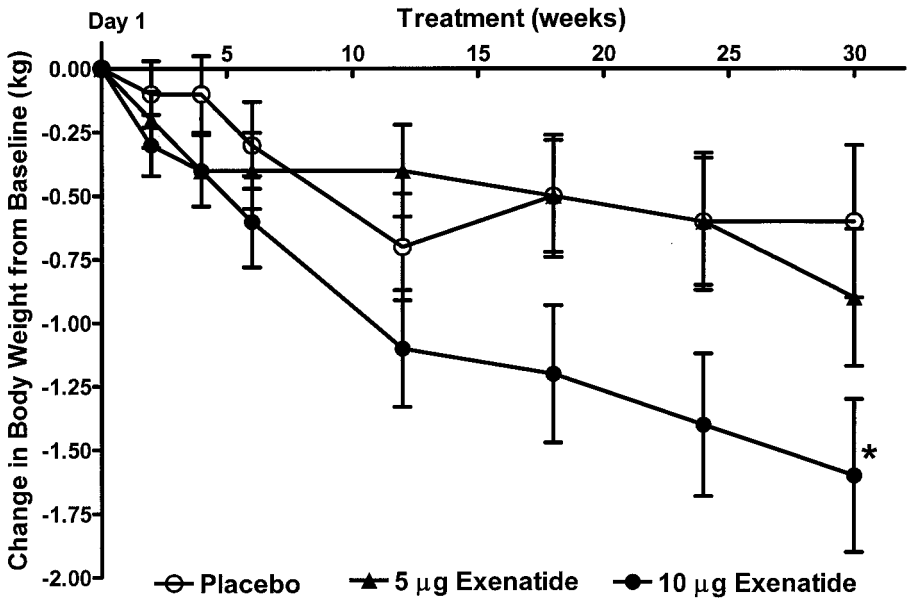

Figure 3— *Change in body weight from baseline over time in ITT subjects with type 2 diabetes treated with a sulfonylurea and exenatide or placebo. Baseline weights were 95.2 ± 1.6 kg in the 10-μg exenatide arm (●, n = 129), 94.9 ± 1.9 kg in the 5-μg exenatide arm (▲, n = 125), and 99.1 ± 1.7 kg in the placebo arm (○, n = 123). Subjects in the 10-μg b.i.d. exenatide treatment arm received 5 μg b.i.d. exenatide during weeks 0–4. Subjects in all treatment arms were maintained on a sulfonylurea. Data are means ± SE.* *P ≤ *0.05 compared with placebo treatment.*

glucose concentrations in the 10- and 5-μg exenatide arms were reduced by −0.6 ± 0.3 and −0.3 ± 0.2 mmol/l from baseline, respectively, compared with an increase of 0.4 ± 0.3 mmol/l in the placebo arm ($P < 0.05$ vs. placebo for the 10-μg arm only).

Body weight

Body weights averaged ~96 kg at baseline (Fig. 1) and were slightly higher in the placebo arm than in the exenatide arms. Subjects in the 10-μg exenatide arm had progressive weight loss over the entire 30 weeks, with an end-of-study loss of −1.6 ± 0.3 kg from baseline ($P < 0.05$ vs. placebo) (Fig. 3). Subjects in the 5-μg exenatide arm had an end-of-study weight loss of −0.9 ± 0.3 kg from baseline (NS vs. placebo), and subjects in the placebo arm had an end-of-study weight loss of −0.6 ± 0.3 kg from baseline.

Insulin and proinsulin

Baseline fasting insulin and proinsulin concentrations were similar across treatment arms (Fig. 1), and there were no significant differences in fasting plasma insulin concentrations across treatment arms over the course of the study. However, there was a significant reduction in fasting proinsulin concentrations in the 10-μg exenatide arm compared with baseline (−16 pmol/l, 95% CI −26.1 to −6.0) and with placebo ($P < 0.01$), with a similar trend noted in the 5-μg exenatide arm. Overall, there was a dose-dependent decrease in the proinsulin-to-insulin ratio toward more physiological proportions. Baseline proinsulin-to-insulin ratios were 0.66 ± 0.04, 0.59 ± 0.03, and 0.64 ± 0.04 in the 10-μg exenatide, 5-μg exenatide, and placebo arms, respectively. In the 10-μg exenatide arm at week 30, the mean proinsulin-to-insulin ratio was reduced −0.13 compared with baseline and was significantly lower than that in placebo ($P = 0.001$). There was a similar trend in the 5-μg exenatide arm.

Clinical laboratory findings and safety

There were no adverse trends apparent in vital sign measurements, physical examination findings, heart rate, or blood pressure between the treatment arms. Twelve subjects had mild-to-moderate abnormalities in their blood creatine phosphokinase concentrations; however, all changes were transient, with no consistent pattern. There were small reductions in LDL ($P < 0.05$ for pairwise comparisons) and apolipoprotein B ($P < 0.05$ for pairwise comparisons) concentrations in exenatide arms compared with placebo. However, other lipid parameters (total cholesterol, triglycerides, LDL-to-HDL ratios) did not differ significantly among treatment arms.

The incidence of serious treatment-emergent adverse events was low, with no discernable treatment pattern (4% in the 10-μg exenatide arm, 3% in the 5-μg exenatide arm, and 8% in the placebo arm). One subject in the 10-μg arm and one subject in the placebo arm experienced a myocardial infarction, and one subject in the placebo arm experienced clinical manifestations of coronary artery disease.

The most frequent adverse events were generally mild or moderate in intensity and gastrointestinal in nature (Table 1). The incidence of treatment-emergent

Table 1—*Treatment-emergent adverse events related to the gastrointestinal tract and hypoglycemia*

		Exenatide		
Adverse event	Placebo	5 μg	10 μg	All
n	123	125	129	254
Nausea	9 (7)	49 (39)	66 (51)	115 (45)
Hypoglycemia	4 (3)	18 (14)	46 (36)	64 (25)
Dizziness	8 (7)	19 (15)	19 (15)	38 (15)
Feeling jittery	2 (2)	15 (12)	19 (15)	34 (13)
Vomiting	3 (2)	12 (10)	17 (13)	29 (11)
Diarrhea	5 (4)	14 (11)	11 (9)	25 (10)
Headache	8 (7)	11 (9)	10 (8)	21 (8)
Constipation	4 (3)	2 (2)	12 (9)	14 (6)
Sweating increased	1 (1)	3 (2)	10 (8)	13 (5)
Weakness	4 (3)	7 (6)	2 (2)	9 (4)

Data are *n* (%).

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