

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

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OBJECTIVE — This study evaluated the effects of exenatide, a novel incretin mimetic, in hyperglycemic patients with type 2 diabetes unable to achieve glycemic control with metformin-sulfonylurea combination therapy.

RESEARCH DESIGN AND METHODS — A 30-week, double-blind, placebo-controlled study was performed in 733 subjects (aged 55 ± 10 years, BMI 33.6 ± 5.7 kg/m², A1C $8.5 \pm 1.0\%$; means \pm SD) randomized to 5 μ g subcutaneous exenatide b.i.d. (arms A and B) or placebo for 4 weeks. Thereafter, arm A remained at 5 μ g b.i.d. and arm B escalated to 10 μ g b.i.d. Subjects continued taking their dose of metformin and were randomized to either maximally effective (MAX) or minimum recommended (MIN) doses of sulfonylurea.

RESULTS — Week 30 A1C changes from baseline (\pm SE) were $-0.8 \pm 0.1\%$ (10 μ g), $-0.6 \pm 0.1\%$ (5 μ g), and $+0.2 \pm 0.1\%$ (placebo; adjusted $P < 0.0001$ vs. placebo), yielding placebo-adjusted reductions of -1.0% (10 μ g) and -0.8% (5 μ g). In the evaluable population, exenatide-treated subjects were more likely to achieve A1C $\leq 7\%$ than placebo-treated subjects (34% [10 μ g], 27% [5 μ g], and 9% [placebo]; $P < 0.0001$). Both exenatide arms demonstrated significant weight loss (-1.6 ± 0.2 kg from baseline each exenatide arm, -0.9 ± 0.2 kg placebo; $P \leq 0.01$ vs. placebo). Mild or moderate nausea was the most frequent adverse event. The incidence of mild/moderate hypoglycemia was 28% (10 μ g), 19% (5 μ g), and 13% (placebo) and appeared lower with MIN than with MAX sulfonylurea treatment.

CONCLUSIONS — Exenatide significantly reduced A1C in patients with type 2 diabetes unable to achieve adequate glycemic control with maximally effective doses of combined metformin-sulfonylurea therapy. This improvement in glycemic control was associated with no weight gain and was generally well tolerated.

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Abbreviations: AUC, area under the curve; GLP-1, glucagon-like peptide 1; ITT, intent to treat.

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

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In most individuals with type 2 diabetes, hyperglycemia results from a failure of β -cell insulin secretory capacity to adequately compensate for insulin resistance in peripheral tissues (1,2). Results from the U.K. Prospective Diabetes Study indicate that β -cell failure is a progressive defect even in the setting of effective glucose-lowering therapy with diet, metformin, sulfonylureas, or insulin (3–5). Despite the use of traditional therapies, it is often difficult to both achieve and maintain adequate glycemic control in the majority of patients with type 2 diabetes. Indeed, population-based glycemic control has not improved substantially in the past decade, with current A1C values $\geq 8\%$ in many patients (6,7). In addition, many of the currently available therapeutic agents have treatment-limiting side effects, such as weight gain, hypoglycemia, gastrointestinal intolerance, and peripheral edema, any of which may limit the use of some agents, reduce treatment compliance, and make it difficult to achieve glycemic treatment targets (8,9).

Despite the introduction of a number of new classes of medication for managing type 2 diabetes, recent studies (6,8,10,11) suggest that even currently available multidrug therapies often do not allow patients to achieve adequate glycemic control. The most common combination of oral therapies used for patients with type 2 diabetes is metformin with a sulfonylurea. Both drugs are safe and effective when used either as monotherapy or in combination, albeit with a risk of significant, drug-associated side effects (6,8,10,11). Clinicians and researchers currently debate the question of which therapies are best when combination therapy no longer maintains acceptable glycemic control. Addition of insulin or a thiazolidinedione to the existing oral therapies are leading choices, but each is associated with characteristic side effects including weight gain (8,12,13).

Glucoregulatory peptides, such as in-

cretins, are currently being investigated as potential therapies for type 2 diabetes (14). 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) (15–19). The present study evaluated the ability of exenatide to improve glycemic control in patients with type 2 diabetes unable to achieve adequate glycemic control despite treatment with combined metformin-sulfonylurea therapy.

RESEARCH DESIGN AND METHODS

Subjects were 22–77 years of age with type 2 diabetes treated with metformin and a sulfonylurea. General inclusion criteria were a screening fasting plasma glucose concentration <13.3 mmol/l, BMI 27–45 kg/m², inclusive, and an A1C value of 7.5–11.0%. The metformin dose was \geq 1,500 mg/day, and the sulfonylurea dose was at least the maximally effective dose for 3 months before screening. In addition, subjects were weight stable (\pm 10%) for 3 months before screening and had no clinically relevant (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 at least 3 months before screening and continuing throughout the study. Subjects were excluded if they had evidence of other clinically significant medical conditions or had used thiazolidinediones, meglitinides, α -glucosidase inhibitors, exogenous insulin, or weight loss drugs within the prior 3 months. Further exclusion criteria included therapy with corticosteroids, drugs known to affect gastrointestinal motility, transplantation medications, or any investigational drug.

Seven hundred thirty-three adults with type 2 diabetes participated at 91 sites in the U.S. (May 2002 to August 2003). 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 (20). All subjects provided written informed consent before participation.

This was a balanced, randomized, double-blind, placebo-controlled, parallel-group clinical study designed after consultation with the U.S. Food and Drug

Administration to evaluate glycemic control, primarily as assessed by A1C, and safety. The study commenced with a 4-week, single-blind, lead-in period with injection of placebo twice daily. Thereafter, subjects were randomized to one of four treatment arms. As nausea had been the most frequent adverse event in earlier clinical trials (21) and gradual dose escalation attenuated this side effect, the current study included an acclimation period of 4 weeks at a lower fixed dose of exenatide (5 μ g b.i.d.) in the active treatment arms (A and B) before the fixed dose of exenatide was either increased to 10 μ g b.i.d. (arm B) or left at 5 μ g b.i.d. (arm A) for the duration of the study. Placebo injections with volumes equal those used in 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 prestudy metformin regimen. To standardize sulfonylurea use in the clinical trial, subjects were randomized (one for one) to either maximally effective sulfonylurea dose (MAX group; 4 mg/day glimepiride, 20 mg/day glipizide, 10 mg/day glipizide XL, 10 mg/day glibenclamide [glyburide], 6 mg/day micronized glibenclamide, 350 mg/day chlorpropamide, 500 mg/day tolazamide, or 1,500 mg/day tolbutamide) or to minimum recommended dose (MIN group; 1 mg/day glimepiride, 5 mg/day glipizide, 5 mg/day glipizide XL, 1.25 mg/day glibenclamide, 0.75 mg/day micronized glibenclamide, 100 mg/day chlorpropamide, 100 mg/day tolazamide, or 250 mg/day tolbutamide). This approach allowed assessment of the influence of concurrent sulfonylurea dosing on hypoglycemia risk. The assignment to the sulfonylurea management group was not blinded.

During the blinded phase of the study, sulfonylurea dose could be reduced by 50%, regardless of the subject's assigned sulfonylurea management group, in the event of one documented hypoglycemic event (blood glucose concentration <3.3 mmol/l) or two undocumented suspected hypoglycemic events. Further 50% reductions, including complete cessation of sulfonylurea dose, were allowed upon repetition of the previous criteria. In subjects assigned to the MIN group, if a majority of fasting plasma glucose readings exceeded 6.9 mmol/l

during weeks 4–6, 6–9, or 9–12, the investigator was to consider doubling the sulfonylurea dose. No further escalation of sulfonylurea dose was permitted after week 12. Any subject with either an A1C change of +1.5% from baseline at any clinic visit or an A1C \geq 11.5% at week 18 or 24 could be withdrawn from the study. Similarly, subjects could be withdrawn if they had fasting plasma glucose values >13.3 mmol/l on two consecutive study visits during weeks 18–24 or if a subject consistently recorded finger-stick fasting blood glucose values >14.4 mmol/l for at least 2 weeks during weeks 18–24, not secondary to a readily identified illness or pharmacological treatment.

A subset of subjects (meal cohort) underwent a standardized meal tolerance test on day 1 (placebo administered to all subjects), at week 4, and at week 30. After an overnight fast of \geq 8 h, subjects received their morning dose of metformin and sulfonylurea within 1 h of their clinic visit. Exenatide or placebo was injected 15 min before a standardized breakfast. The size of the meal 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

The primary outcome measures were glycemic control, as assessed by change in A1C, and safety. Secondary objectives included examining the effects of exenatide on fasting and postprandial (meal cohort only) plasma glucose concentrations, body weight, fasting plasma lipids, and exenatide pharmacokinetics (meal cohort only).

Statistical analysis

Randomization was stratified according to screening A1C values (<9.0 and \geq 9.0%) to achieve a balanced distribution of subjects across treatment arms. Within each arm, subjects were randomized in a one-for-one ratio to either remain on their maximally effective sulfonylurea dose or to decrease their sulfonylurea to the minimum recommended dose. A sample size of 600 subjects who were expected to complete treatment through week 30 were estimated to provide at least 90%

power to detect a difference of 0.5% in the change from baseline in A1C 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 A1C and weight across treatments (22,23). Factors in the model included treatment, strata of baseline A1C, sulfonylurea management group, and aggregate 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. Pairwise comparisons of the treatment effects were performed using Fisher's protected testing procedure to control type I errors due to multiple comparisons (24). Similar analyses were performed for each fasting metabolic parameter and for postprandial plasma glucose concentrations without adjusting for the multiple comparisons.

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 A1C $\leq 7\%$. For the latter analysis, the more clinically relevant population of evaluable subjects (all randomized subjects who completed treatment through week 30 and received at least 80% of the study medication injections) with baseline A1C $> 7\%$ was used. For ITT subjects who had recorded values for at least one scheduled visit subsequent to the baseline measurement, missing data were imputed from scheduled visits using the last-observation-carried-forward method. Results are given as means \pm SE for the ITT population, unless otherwise indicated. The proportion of subjects achieving A1C target values were compared using the Cochran-Mantel-Haenszel test. Post hoc evaluation of change in body weight versus duration of nausea was performed using regression analysis.

Safety analysis

All safety analyses were performed using the ITT population. Safety end points included adverse events, clinical laboratory

tests, physical examination, 12-lead electrocardiogram, vital signs, and titration 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 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 (< 3.33 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 A1C were quantitated by Quintiles Laboratories (Smyrna, GA) or Esoterix Endocrinology (Cabasas Hills, CA) using standard methods. A1C was measured using a high-performance liquid chromatography methodology (25,26). Plasma exenatide and anti-exenatide antibodies were measured as described previously (16).

RESULTS

Baseline characteristics of subjects

Baseline demographics demonstrating balanced randomization are given in Fig. 1. Seven hundred thirty-three subjects were randomized to treatment and received at least one dose of study medication (ITT population); 593 subjects (81%) completed the entire study. All subjects were treated with metformin and a sulfonylurea during the course of the study (43% glipizide, 42% glibenclamide, 14% glimepiride, 3% glibenclamide combination with metformin, $< 1\%$ tolazamide, and $< 1\%$ chlorpropamide). Fifty percent of ITT subjects were treated with an ACE inhibitor, 38% with an anti-thrombotic agent, and 53% with a serum lipid-reducing agent.

A1C and plasma glucose

There was a modest decline in A1C values in all treatment arms during the placebo run-in period and the initial 2 weeks of the study after randomization (ITT population; Fig. 2). Thereafter, A1C values in the exenatide arms continued to decline for another 12 weeks of observation, while A1C values in the placebo arm remained stable and then gradually in-

creased such that these values returned to baseline by the end of the study. Exenatide treatment arms had significant reductions in A1C from baseline compared with placebo ($P < 0.0001$; Fig. 1A).

When stratified by baseline A1C $\geq 9\%$, significant reductions in A1C from baseline in each exenatide arm compared with placebo were observed (adjusted $P \leq 0.0002$ for pairwise comparisons). Similarly, for subjects with baseline A1C $< 9\%$, exenatide treatment at 5 or 10 μg resulted in significant reductions from baseline in A1C, compared with an increase in the placebo arm, at week 30 (adjusted $P < 0.0001$ for pairwise comparisons).

Of ITT subjects at week 30 with baseline A1C $> 7\%$, 30% (70 of 230 subjects) in the 10- μg exenatide arm and 24% (56 of 235 subjects) in the 5- μg exenatide arm reached an A1C $\leq 7\%$, and this proportion was significantly greater than that observed in the placebo arm (7% [16 of 238 subjects]; $P < 0.0001$ for pairwise comparisons). Of subjects evaluable at week 30 with baseline A1C $> 7\%$ ($n = 554$), 34% (60 of 179 subjects) in the 10- μg exenatide arm and 27% (54 of 197 subjects) in the 5- μg exenatide arm reached an A1C $\leq 7\%$, and this proportion was significantly greater than in the placebo arm (9% [16 of 174 subjects]; $P < 0.0001$ for pairwise comparisons).

At baseline, fasting plasma glucose concentrations were similar among treatment arms (Fig. 1). At week 30, fasting plasma glucose concentrations were reduced -0.6 ± 0.2 mmol/l in the 10- μg exenatide arm and -0.5 ± 0.2 mmol/l in the 5- μg arm compared with an increase of $+0.8 \pm 0.2$ mmol/l in the placebo arm ($P < 0.0001$ for pairwise comparisons; ITT population).

Postprandial plasma glucose concentrations were evaluated in the subset of subjects who underwent a standardized meal tolerance test (Fig. 1). At baseline, all subjects received a placebo injection, and postprandial plasma glucose geometric mean area under the curve (AUC)_(15–180 min) values were similar across treatment arms (Fig. 3A). At week 4, there was a significant decrease in postprandial plasma glucose geometric mean AUC_(15–180 min) in both exenatide arms compared with the placebo arm ($P < 0.001$), and this pattern was sustained at week 30 (Fig. 3B; $P < 0.001$ for pairwise comparisons). Exenatide also reduced in-

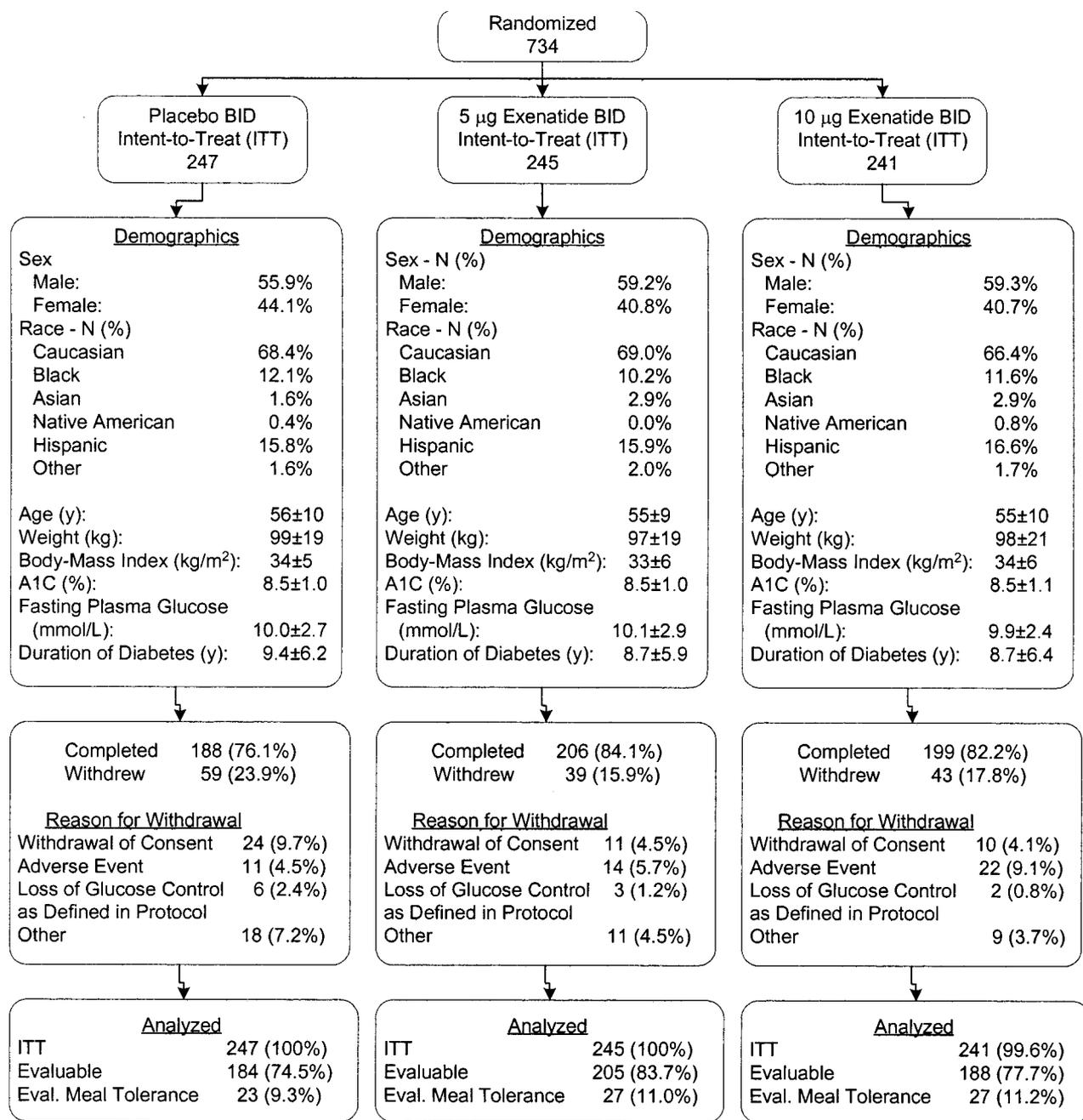


Figure 1—Protocol flow chart. One subject was randomized twice. Both screening numbers were counted in the randomized population, but only one was counted in the ITT population. Subjects in the 10-µg exenatide b.i.d. arm received 5 µg exenatide b.i.d. during weeks 0–4. Subjects in all treatment arms were maintained on metformin and a sulfonylurea. Data are means ± SD.

cremental postprandial plasma glucose concentrations at weeks 4 and 30, as measured by incremental AUC_(15–180 min) and incremental C_{ave} (average concentration; *P* < 0.01 vs. placebo). At week 30, changes from baseline for AUC_(15–180 min) were $-474 \pm 87 \text{ mmol} \cdot \text{min} \cdot \text{l}^{-1}$ (10-µg arm), $-318 \pm 49 \text{ mmol} \cdot \text{min} \cdot \text{l}^{-1}$ (5-µg arm), and $-3 \pm 72 \text{ mmol} \cdot \text{min} \cdot \text{l}^{-1}$ (placebo arm) and for C_{ave} were -2.9 ± 0.76

mmol/l (10-µg-arm), $-1.9 \pm 0.3 \text{ mmol/l}$ (5-µg arm), and $0.0 \pm 0.4 \text{ mmol/l}$ (placebo arm). Thus, incremental plasma glucose AUC values were reduced by 59% (5-µg arm) and 87% (10-µg arm) compared with a <1% decrease in the placebo arm.

Body weight

Subjects in the exenatide arms had progressive weight loss over the entire 30-

week treatment period: week 30 reduction of $-1.6 \pm 0.2 \text{ kg}$ from baseline in each exenatide arm compared with $-0.9 \pm 0.2 \text{ kg}$ from baseline in the placebo arm (*P* ≤ 0.01 vs. placebo; ITT population; Fig. 2C).

Safety

There was no evidence of cardiovascular, pulmonary, hepatic, or renal toxicity with

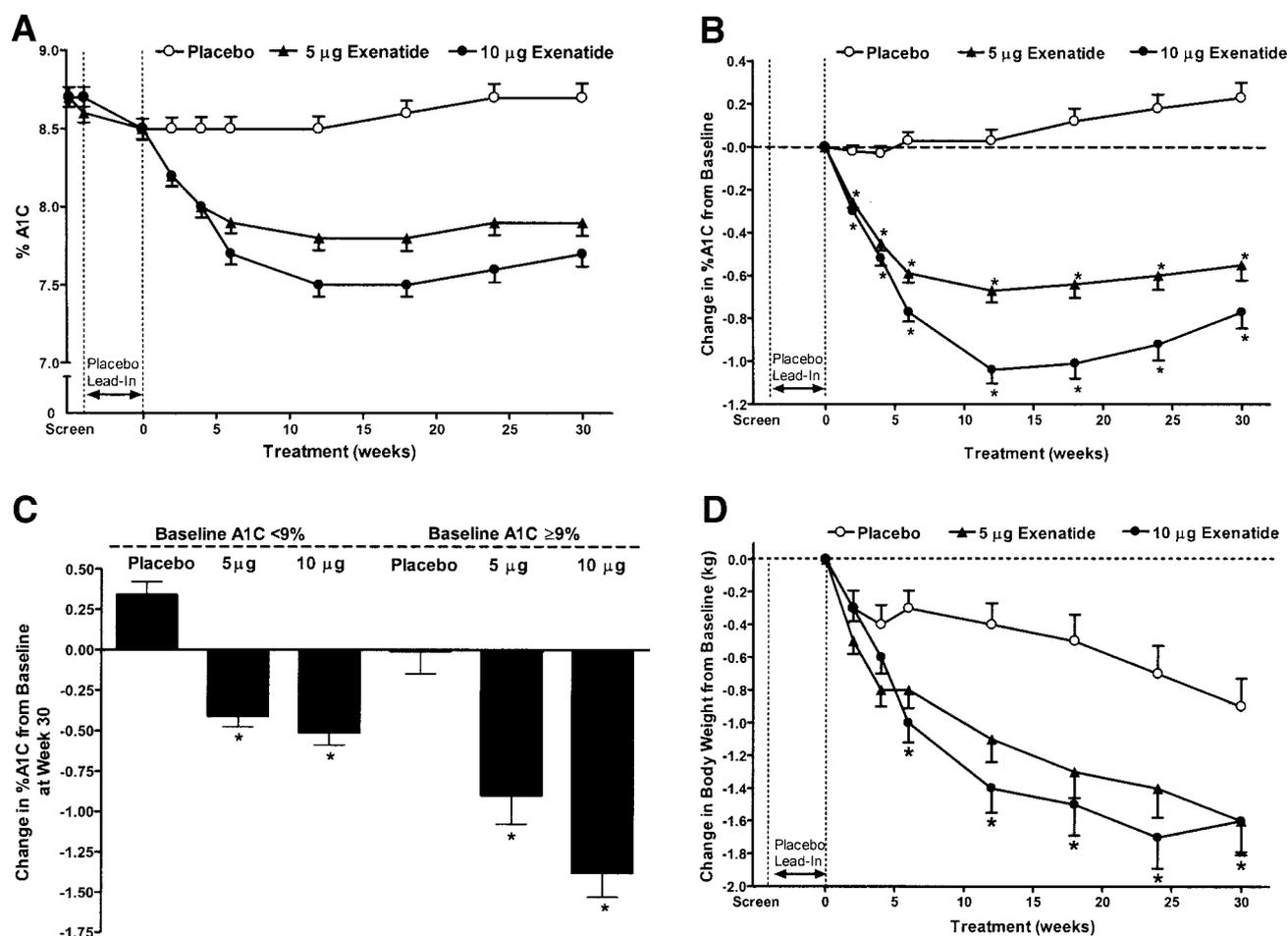


Figure 2—Glycemic control in subjects with type 2 diabetes treated with metformin and a sulfonylurea plus exenatide or placebo (ITT population) A: A1C values over the course of the study (raw data). B: Change in A1C over 30 weeks. *Adjusted $P < 0.0001$ compared with placebo. Week 30 changes in A1C values from baseline were $-0.77 \pm 0.08\%$ (10- μg arm; adjusted $P < 0.0001$ vs. placebo), $-0.55 \pm 0.07\%$ (5- μg arm; adjusted $P < 0.0001$ vs. placebo), and $+0.23 \pm 0.07\%$ (placebo arm). C: Week 30 change in A1C stratified by baseline A1C. For subjects with baseline A1C $< 9\%$, baseline A1C values were $7.92 \pm 0.04\%$ ($n = 169$), $7.91 \pm 0.04\%$ ($n = 172$), and $7.94 \pm 0.04\%$ ($n = 172$) for the 10- μg exenatide, 5- μg exenatide, and placebo arms, respectively. The corresponding values for subjects with baseline A1C $\geq 9\%$ were $9.86 \pm 0.07\%$ ($n = 72$), $9.75 \pm 0.07\%$ ($n = 73$), and $9.75 \pm 0.07\%$ ($n = 75$). D: Effects of exenatide on body weight. Subjects in the 10- μg exenatide b.i.d. treatment arm received 5 μg exenatide b.i.d. during weeks 0–4. Subjects in all treatment arms were maintained on metformin-sulfonylurea therapy. * $P \leq 0.001$ compared with placebo treatment. Data are means \pm SE.

exenatide treatment or of drug-related idiosyncratic side effects associated with its use. The incidence of serious (5% in 10- μg arm, 6% in 5- μg arm, and 6% in the placebo arm) and severe (12% in 10- μg arm, 14% in 5- μg arm, and 8% in the placebo arm) adverse events was low and evenly distributed across treatment arms. The most frequent adverse events were mostly mild or moderate and gastrointestinal in nature (Table 1). Nausea was the most frequent severe adverse event (3% in 10- μg arm, 5% in 5- μg arm, and $< 1\%$ in the placebo arm), with a low incidence of withdrawals due to nausea (4% in 10- μg arm, 2% in 5- μg arm, and $< 1\%$ in the placebo arm). Nausea was reported at a higher incidence during the initial weeks of therapy (weeks 0–8) and

declined thereafter (Fig. 4). 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: $Y = -0.013 \times -1.625$; $R^2 = 0.056$; 5 μg exenatide: $Y = -0.003 \times -1.273$; $R^2 = 0.003$; placebo: $Y = 0.013 \times -1.596$; $R^2 = 0.028$). Subjects who never experienced nausea still lost weight: -1.1 ± 0.3 kg (10- μg arm) and -1.7 ± 0.2 kg (5- μg arm).

The overall incidence of hypoglycemia was higher in each exenatide treatment arm compared with the placebo arm (Table 1). One case of hypoglycemia requiring assistance from another individ-

ual (severe hypoglycemia), but no medical intervention, occurred in the 5- μg arm. All other hypoglycemic events were mild or moderate in intensity, and there were no withdrawals due to hypoglycemia.

At week 30, 49% of exenatide-treated subjects (193 of 398) had detectable anti-exenatide antibody titers, with the majority of titers in the low range (1/5 to 1/125 titer). The anti-exenatide antibodies had no predictive effect on the magnitude of an individual's glycemic response or the incidence of adverse events.

Management of sulfonylurea dosing

In the MAX group, all treatment arms maintained relatively constant dosage levels of sulfonylurea throughout the study.

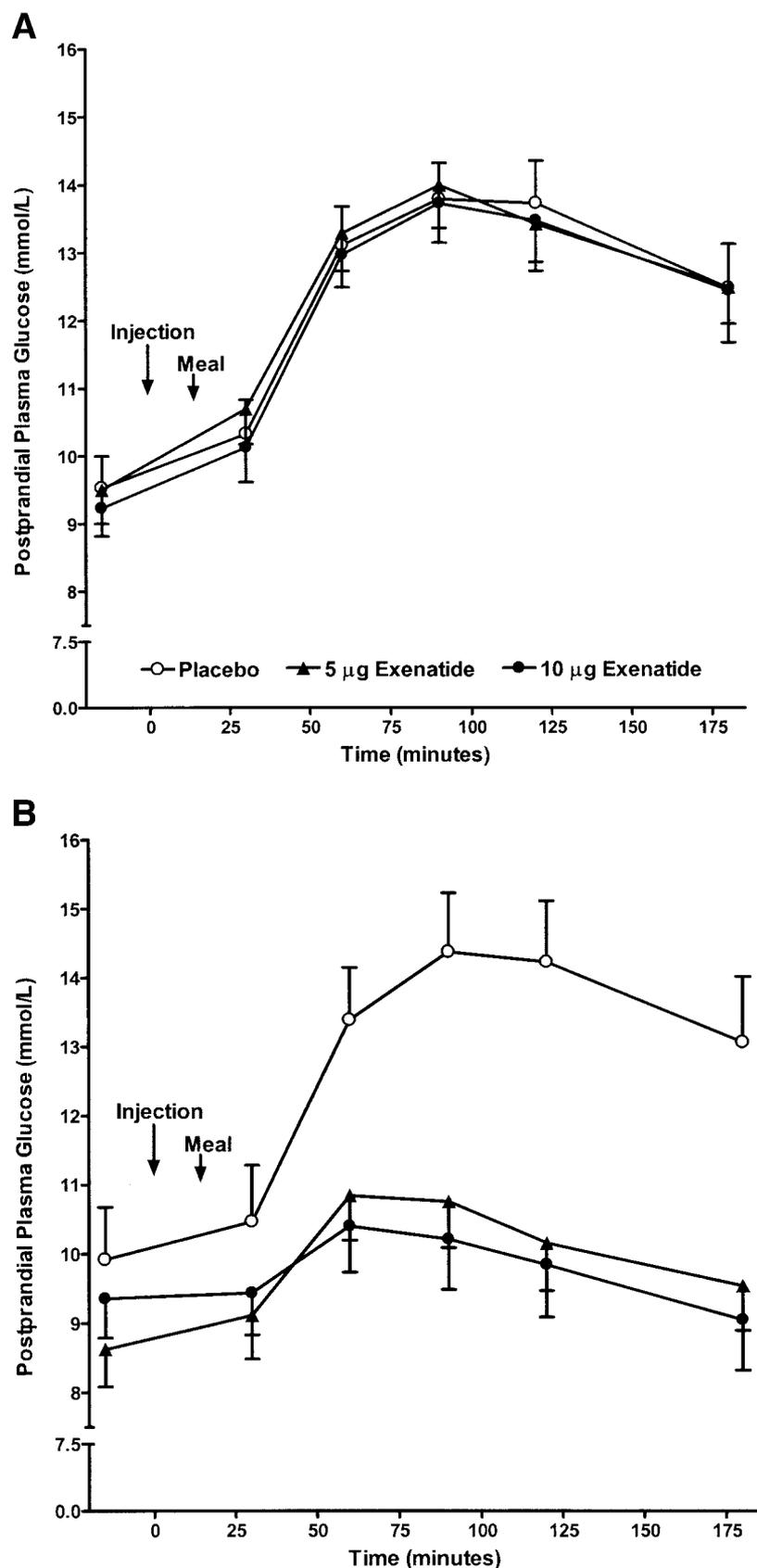


Figure 3—Postprandial plasma glucose concentrations in the meal tolerance test subpopulation. A: Postprandial plasma glucose concentrations after a standardized meal at day 1. Subjects in all treatment arms received placebo. Postprandial plasma glucose geometric mean $AUC_{(15-180 \text{ min})}$ values were $2,033 \text{ mmol} \cdot \text{min} \cdot \text{l}^{-1}$ in the $10\text{-}\mu\text{g}$ exenatide arm, $2,089 \text{ mmol} \cdot \text{min} \cdot \text{l}^{-1}$ in the $5\text{-}\mu\text{g}$ exenatide arm, and $2,090 \text{ mmol} \cdot \text{min} \cdot \text{l}^{-1}$ in the placebo arm. B: Postprandial plasma glucose concentrations after a standardized meal at week 30. Geometric mean $AUC_{(15-180 \text{ min})}$ values were $1,539 \text{ mmol} \cdot \text{min} \cdot \text{l}^{-1}$ in the $10\text{-}\mu\text{g}$ exenatide arm ($P = 0.0004$ vs. placebo), $1,584 \text{ mmol} \cdot \text{min} \cdot \text{l}^{-1}$ in the $5\text{-}\mu\text{g}$ exenatide arm ($P = 0.0009$ vs. placebo), and $2,087 \text{ mmol} \cdot \text{min} \cdot \text{l}^{-1}$ in the placebo arm. Exenatide or placebo were administered at time zero. Evaluable population: $10\text{-}\mu\text{g}$ exenatide, $n = 27$; $5\text{-}\mu\text{g}$ exenatide, $n = 27$; placebo, $n = 23$. Subjects in the $10\text{-}\mu\text{g}$ exenatide b.i.d. arm received $5\text{-}\mu\text{g}$ exenatide b.i.d. during weeks 0–4. Subjects in all treatment arms were maintained on metformin-sulfonylurea therapy. Data are means \pm SE.

Table 1—Most frequent adverse events with incidence $\geq 10\%$ in any treatment arm (ITT)*

Preferred term	Placebo	5 μg exenatide	10 μg exenatide
<i>n</i>	247	245	241
Nausea	51 (20.6)	96 (39.2)	117 (48.5)
Hypoglycemia	31 (12.6)	47 (19.2)	67 (27.8)
Upper respiratory tract infection	48 (19.4)	28 (11.4)	42 (17.4)
Vomiting	11 (4.5)	36 (14.7)	33 (13.7)
Diarrhea	16 (6.5)	25 (10.2)	42 (17.4)
Feeling jittery	17 (6.9)	21 (8.6)	28 (11.6)
Headache	12 (4.9)	27 (11.0)	18 (7.5)

Data are *n* (%). *Treatment emergent.

In the MIN group, sulfonylurea dose was $\sim 64\%$ of MAX sulfonylurea dose across all treatment arms at study outset (baseline). By week 2, MIN subjects reduced the dose of sulfonylurea to a nadir of 30% of MAX dose across treatment arms. This low dose was maintained for several weeks, then sulfonylurea doses gradually increased throughout the remainder of the study. At week 30, subjects on placebo reached $\sim 94\%$ of MAX dose compared with $\sim 79\%$ of MAX dose in the exenatide arms. For the two sulfonylurea dosing groups, there were similar overall effects on A1C when comparing exenatide treatment arms with placebo, but the MAX group had a slightly greater reduction in A1C from baseline ($P \leq 0.0001$ for pairwise comparisons; Table 2). However, the overall incidence of hypoglycemia was lower in the MIN group, with a small attenuation of the effects on glycemic control.

CONCLUSIONS— This study, conducted in a large subject population, demonstrated that exenatide therapy improved glycemic control in patients with type 2 diabetes inadequately controlled on maximal doses of combined metformin-sulfonylurea therapy. Exenatide added to metformin-sulfonylurea therapy was associated with weight loss and was generally well tolerated. The addition of exenatide resulted in similar beneficial effects in patients whose sulfonylurea dose was initially reduced to minimally effective doses, with later titration, when compared with patients using fixed maximally effective doses of sulfonylurea throughout the study.

The glucoregulatory activities of the novel incretin mimetic exenatide include glucose-dependent enhancement of insulin secretion, suppression of inappropri-

ately high glucagon secretion, and slowing of gastric emptying (15–18,27–30). These effects together may explain the reduction in postmeal glucose excursions observed in the meal challenge tests presented in our report. The ability of exenatide to enhance glucose-dependent insulin secretion may be mediated by exenatide binding to the pancreatic GLP-1 receptor (31). In animal models of diabetes and in insulin secretory cell lines, exenatide and GLP-1 reportedly improve β -cell function by increasing the expression of key genes involved in β -cell function, by increasing insulin biosynthesis and processing, and by augmenting β -cell mass through multiple mechanisms (18). Data obtained in animal and human studies also indicate that exenatide and GLP-1

reduce food intake, cause weight loss, and may have an insulin-sensitizing effect (18,27,32,33). The latter effect has been shown in some but not all studies, and there is some question as to whether the apparent insulin sensitizing effect, if observed, is an indirect consequence of overall improved metabolic control and therefore reduced glucotoxicity or an actual direct effect.

In the current trial, the observation of a modest reduction in fasting plasma glucose, in keeping with the pharmacokinetic profile of exenatide, and yet a significant drop in A1C strongly suggests a robust effect of exenatide on postprandial plasma glucose concentrations. This is confirmed by the sustained reductions in postprandial glucose concentrations observed in the meal challenge test at weeks 4 and 30. Incremental plasma glucose AUC and average concentration during the postprandial period were reduced by $\sim 60\%$ (5- μg arm) and 90% (10- μg arm) by exenatide treatment.

Because the magnitude of any fall in A1C is dependent upon a number of factors (e.g., baseline A1C, background therapy, and endogenous β -cell function), it is not possible to directly compare the efficacy of exenatide in this population to the effects of other agents, as no comparable trial data are currently available. Perhaps a better measure of efficacy is to examine the

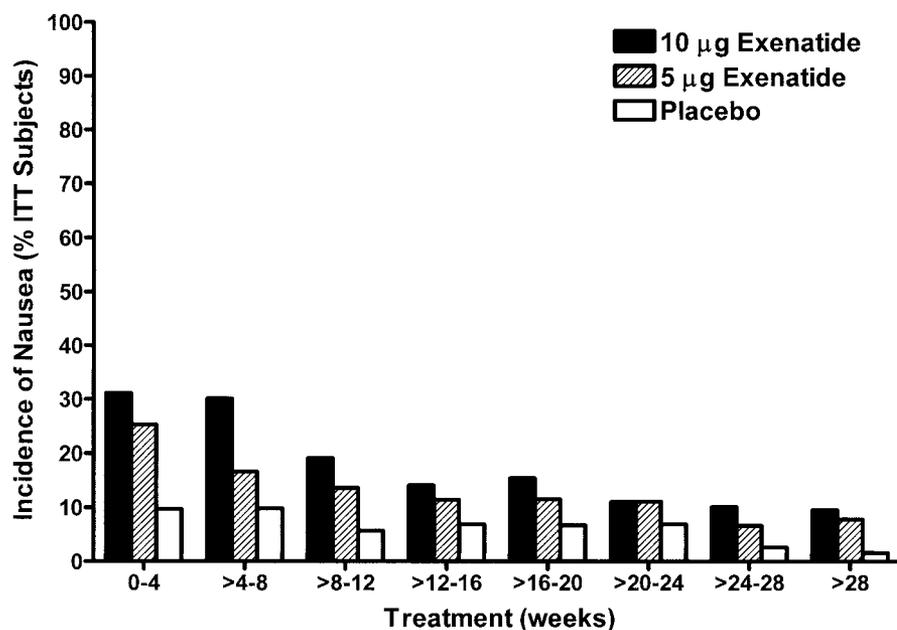


Figure 4—Time-dependent incidence of subjects experiencing treatment-emergent nausea (ITT population).

Table 2—Change in A1C from baseline to week 30 and incidence of hypoglycemia stratified by sulfonylurea management group (ITT)

Sulfonylurea management group	Change in A1C (%)			Incidence of hypoglycemia (%)		
	Placebo	5 μ g exenatide	10 μ g exenatide	Placebo	5 μ g exenatide	10 μ g exenatide
MAX	+0.2 \pm 0.1	-0.7 \pm 0.1; $P < 0.0001^*$	-0.9 \pm 0.1; $P < 0.0001^*$	15%	22%	35%
MIN	+0.3 \pm 0.1	-0.4 \pm 0.1; $P < 0.0001^*$	-0.6 \pm 0.1; $P < 0.0001^*$	10%	16%	21%

Data are means \pm SE, unless otherwise noted. *A1C change comparison for exenatide treatment versus placebo.

proportion of subjects in each specific treatment arm who were able to achieve an A1C $\leq 7\%$ at the 10- and 5- μ g fixed doses of exenatide, which was 34 and 27% of subjects who completed the study, respectively, compared with 9% of subjects who received placebo.

These results are consistent with those reported in another 30-week, placebo-controlled, phase 3 study (34) of the effects of exenatide on glycemic control and safety in subjects with type 2 diabetes failing to achieve glycemic control with sulfonylureas. In that study, at week 30, the 10- μ g exenatide b.i.d. arm had significant placebo-adjusted reductions of $\sim 1.0\%$ in A1C and 1.0 kg in weight. In addition, a reduction in the proinsulin-to-insulin ratio in the 10- μ g exenatide b.i.d. arm indicated that exenatide had a beneficial effect on the β -cell (34). In a parallel 30-week, placebo-controlled, phase 3 study in subjects with type 2 diabetes failing to achieve glycemic control with metformin, the 10- μ g exenatide b.i.d. arm had significant placebo-adjusted reductions of -0.9% in A1C and -2.5 kg in weight at week 30 (35).

Importantly, exenatide treatment was not associated with the weight gain ordinarily seen with the glycemic improvement achieved by other therapies (6,8,10,11), even though no program of behavior modification was included in the protocol. The progressive weight loss observed is consistent with the known action of exenatide to reduce food intake (29,32). The most common adverse event associated with exenatide treatment was dose-dependent mild to moderate nausea. Nausea was reported most commonly during the initial 8 weeks of therapy and was reported less frequently as the study progressed. Although nausea was reported most frequently in the initial weeks after starting therapy, weight loss was progressive over 30 weeks, thus supporting the dissociation of the two effects.

Across all three treatment arms, there

was a significant incidence of hypoglycemia, but the vast majority of events were mild or moderate in severity. Occurrence of hypoglycemia appeared to be influenced by three factors: background sulfonylurea dose, exenatide dose, and ambient level of glycemia. For example, a higher incidence of hypoglycemia was observed for the MAX group taking the higher dose of exenatide with an ambient glycemia closer to 7% A1C. Associated studies suggest that exenatide's action is glucose dependent and would therefore present minimal hypoglycemic risk. Under controlled clamped condition, exenatide's insulinotropic effect on the β -cell is not observed once plasma glucose is lowered to ~ 3.9 mmol/l (36). Also, when exenatide is administered to metformin-treated patients, where you would expect minimal background hypoglycemia risk, no increase in hypoglycemia is observed despite a lowering of A1C (35). In the present study, the hypoglycemia observed seems most likely the result of an exenatide-induced improvement in glycemia superimposed upon the nonglucose-dependent actions of sulfonylurea treatment. The findings further suggest that a proactive approach to sulfonylurea dose management will likely limit the incidences of hypoglycemia in exenatide-treated patients. That is, initial reduction of dosage of a sulfonylurea may limit the risk of hypoglycemia associated with such therapies upon initiation of exenatide treatment.

In summary, exenatide therapy significantly improved glycemic control in patients with type 2 diabetes and was associated with significant sustained weight loss when added to the commonly used combination of metformin and sulfonylurea. The main adverse events were dose-dependent nausea and mild to moderate hypoglycemia that was ameliorated by appropriate adjustments of sulfonylurea dosage. This novel therapy may offer another potential treatment option when

two-drug oral therapy fails to maintain adequate glycemic control.

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APPENDIX

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