Effects of Once-Weekly Dosing of a Long-Acting Release Formulation of Exenatide on Glucose Control and Body Weight in Subjects With Type 2 Diabetes

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OBJECTIVE — In patients with type 2 diabetes, exenatide reduces A1C, postprandial and fasting glucose, and weight. In this study we investigated the effects of continuous exenatide administration from a long-acting release (LAR) formulation.

RESEARCH DESIGN AND METHODS — In this randomized, placebo-controlled phase 2 study, exenatide LAR (0.8 or 2.0 mg) was administered subcutaneously once weekly for 15 weeks to subjects with type 2 diabetes ($n = 45$) suboptimally controlled with metformin (60%) and/or diet and exercise (40%): 40% female, A1C (mean ± SD) 8.5 ± 1.2%, fasting plasma glucose 9.9 ± 2.3 mmol/l, weight 106 ± 20 kg, and diabetes duration 5 ± 4 years.

RESULTS — From baseline to week 15, exenatide LAR reduced mean ± SE A1C by −1.4 ± 0.3% (0.8 mg) and −1.7 ± 0.3% (2.0 mg), compared with +0.4 ± 0.3% with placebo LAR ($P <$ 0.0001 for both). A1C of ≤7% was achieved by 36 and 86% of subjects receiving 0.8 and 2.0 mg exenatide LAR, respectively, compared with 0% of subjects receiving placebo LAR. Fasting plasma glucose was reduced by −2.4 ± 0.9 mmol/l (0.8 mg) and −2.2 ± 0.5 mmol/l (2.0 mg) compared with +1.0 ± 0.7 mmol/l with placebo LAR ($P < 0.001$ for both). Exenatide LAR reduced self-monitored postprandial hyperglycemia. Subjects receiving 2.0 mg exenatide LAR had body weight reductions (−3.8 ± 1.4 kg) ($P < 0.05$), whereas body weight was unchanged with both placebo LAR and the 0.8-mg dose. Mild nausea was the most frequent adverse event. No subjects treated with exenatide LAR withdrew from the study.

CONCLUSIONS — Exenatide LAR offers the potential of 24-h glycemic control and weight reduction with a novel once-weekly treatment for type 2 diabetes.

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In the U.S., diabetes affects >21 million people, with combined direct and indirect costs of $132 billion annually (1). Treatment of this chronic, progressive disease often requires daily blood glucose monitoring and multiagent treatment regimens. However, despite the many medications available, the majority of people with type 2 diabetes are unable to maintain long-term glycemic control (2). The high prevalence of obesity in this population compounds this problem, as obesity is a risk factor for developing type 2 diabetes and worsens hyperglycemia and insulin resistance (3,4). Furthermore, use of many antihyperglycemic medications is associated with weight gain (5).

Incretin hormones, intestinally derived hormones that stimulate glucose-dependent insulin secretion in response to food intake, play an important role in glucose homeostasis (6). Glucagon-like peptide-1 (GLP-1) is an incretin hormone with multiple glucoregulatory actions, including enhancement of glucose-dependent insulin secretion, suppression of inappropriately elevated glucagon secretion, slowing of gastric emptying, and reduction of food intake and body weight (6–9). Postprandial secretion of GLP-1 is reduced in patients with type 2 diabetes (10), suggesting that the GLP-1 signaling pathway is an attractive therapeutic target. However, GLP-1 is rapidly degraded by the enzyme dipeptidyl peptidase-IV and has a relatively short half-life (~2 min) (6). The therapeutic potential of the GLP-1 pathway has led to the development of a class of compounds called incretin mimetics that share several glucoregulatory actions with GLP-1 but are resistant to dipeptidyl peptidase-IV degradation.

Exenatide, with a half-life of 2.4 h and clinical effects lasting up to 8 h, is the first clinically available incretin mimetic (10–16). Compared with GLP-1 in preclinical studies, exenatide has a 20- to 30-fold longer half-life and 5,500-fold greater potency in lowering plasma glucose (7,17). In placebo-controlled clinical trials in patients not achieving adequate glycemic control with metformin, a sulfonylurea, or a combination of both, 30 weeks of 10 μg subcutaneous exenatide twice daily (BID) resulted in statistically significant reductions in mean A1C, body weight, fasting plasma glucose, and postprandial plasma glucose excursions (18–20). Patients who continued in open-label extension studies for a total of 1.5 years (82 weeks) of BID exenatide treatment had sustained A1C reductions and progressive body weight reductions (21). In

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Abbreviations: BID, twice daily; GLP-1, glucagon-like peptide-1; ITT, intention to treat; LAR, long-acting release.
A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

glargine or 70/30 insulin aspart, exenatide treatment resulted in A1C reductions that were similar to those with insulin but with better postprandial glucose control and body weight reduction instead of weight gain (22,23). Mild-to-moderate nausea, which decreased over time, was the most common adverse event associated with exenatide in all of these trials.

A long-acting release (LAR) exenatide formulation for subcutaneous injection in patients with type 2 diabetes is under development to determine whether superior glycemic control can be achieved when exenatide is continuously present, compared with BID exenatide, which may not provide complete coverage after midday meals and overnight. In this report, we describe the effects of once-weekly subcutaneous administration of exenatide LAR for 15 weeks on glycemic parameters, weight, pharmacokinetics, safety, and tolerability in patients with type 2 diabetes.

RESEARCH DESIGN AND METHODS

— Subjects enrolled in this study were 18–75 years of age, had type 2 diabetes treated for at least 3 months before screening with diet modification with exercise (i.e., taking no antidiabetes agent) and/or metformin, A1C of 7.1–11.0%, fasting plasma glucose <14.4 mmol/l, and BMI 25–45 kg/m^2. All of the subjects treated with metformin (total daily dose ranging from 500 to 2,550 mg) continued to receive the same dose throughout the study, with the exception of a subject in the 2.0 mg exenatide LAR arm who discontinued metformin and added insulin lispro and insulin glargine to her regimen 6 weeks after the last dose of study medication. Another change in antidiabetes treatment occurred when, after 9 weeks of placebo LAR, a subject initiated treatment with glimepiride (this subject subsequently withdrew from the study because of loss of glucose control). Subjects who had previously received exenatide treatment in a clinical trial were excluded from the study. Additionally, no subjects were treated with exenatide during the trial. A common clinical protocol was approved for each site by an institutional review board. All subjects provided written informed consent before participation, and the study was conducted in accordance with the principles described in the Declaration of Helsinki, including all amendments through the 1996 South Africa revision (24).

In this multicenter subject- and investigator-blinded phase 2 study, subjects (n = 45) were equally randomized to placebo LAR or 0.8 or 2.0 mg exenatide LAR. Blinded, randomized study medication kits with unique package numbers were prepared separately and shipped to each clinical site. The study-site pharmacist contacted an interactive voice response system to randomly assign subjects to a treatment group and find out which medication kit to dispense to each subject. Doses were targeted to result in concentrations previously found to be therapeutic with exenatide BID. Subjects underwent a 3-day lead-in of 5 μg exenatide or placebo subcutaneous BID to determine whether any subjects randomly assigned to exenatide LAR had an acute exenatide sensitivity. Then, once-weekly subcutaneous injections of 0.8 or 2.0 mg exenatide LAR or placebo LAR were administered at the study sites by study personnel for 15 weeks, with no changes in preexisting antidiabetes regimens. Subjects were monitored for adverse events and pharmacokinetics during a subsequent 12-week follow-up period during which time no study medications were administered. Generally, visits were conducted at weekly intervals. Study recruitment began 16 February 2005 and follow-up continued through 17 October 2005.

For self-monitored blood glucose profiles, subjects were given blood glucose meters and instructed to perform measurements by fingerstick at the fingertip. Preprandial glucose was measured 15 min before each meal, postprandial glucose was measured 1.5–2 h after each meal, and an additional glucose measurement was taken at 0300 h. Measurements were recorded on 3 separate days for both baseline and week 15.

Exenatide LAR consists of microspheres composed of exenatide and a poly(lactide-coglycolide) polymeric matrix. Poly(lactide-coglycolide) is a common biodegradable medical polymer with an extensive history of human use in absorbable sutures and extended-release pharmaceuticals. After injection, exenatide is slowly released from the microspheres through diffusion and erosion. Placebo LAR contained 0.5% ammonium sulfate instead of exenatide.

End points

Objectives of this study were to evaluate the safety, tolerability, and pharmacokinetics of exenatide LAR. Additional objectives were to evaluate pharmacodynamic (i.e., glucose), A1C, and weight effects of exenatide LAR. Safety was assessed by adverse events, clinical laboratory values, physical examination, and electrocardiograms. Adverse events, as reported by the subjects or noted by study-site staff incidentally or as a result of nondirected questioning, were categorized as mild if transient, requiring no special treatment, and not interfering with daily activities and as moderate if causing a low level of inconvenience, possibly interfering with daily activities, and ameliorated by simple therapeutic measures. An adverse event was categorized as severe if it interrupted a subject's usual daily activities and required systemic drug therapy or other treatment.

Laboratory values

Blood to measure plasma exenatide was drawn before study medication injection. Plasma exenatide concentrations were quantitated by a validated enzyme-linked immunosorbent assay (25) at LINCO Diagnostic Services (St. Charles, MO). A1C was quantitated by Quintiles Laboratories (Smyrna, GA) using high-performance liquid chromatography (26,27). Anti-exenatide antibodies were measured in a fashion similar to that described previously (25) at LINCO Diagnostic Services.

Statistical analysis

A sample size of 36 subjects was estimated to provide 95% CIs of ~65–115 and 170–290 pg/ml for the mean exenatide concentrations at steady state for 0.8 and 2.0 mg exenatide LAR, respectively. The intent-to-treat (ITT) population comprised all randomized subjects who received at least one injection of lead-in medication (n = 45), whereas the evaluable population consisted of subjects from the ITT population who completed the study procedures through week 15 in compliance with the protocol (n = 43). Descriptive statistics on demographics, safety, glycemic end points, and weight (i.e., mean values with either SE or SD, as appropriate) were provided for the ITT population. Descriptive statistics for self-monitored blood glucose measurements, which contained week 15 measurements, were performed for the evaluable population. The proportion of subjects achieving

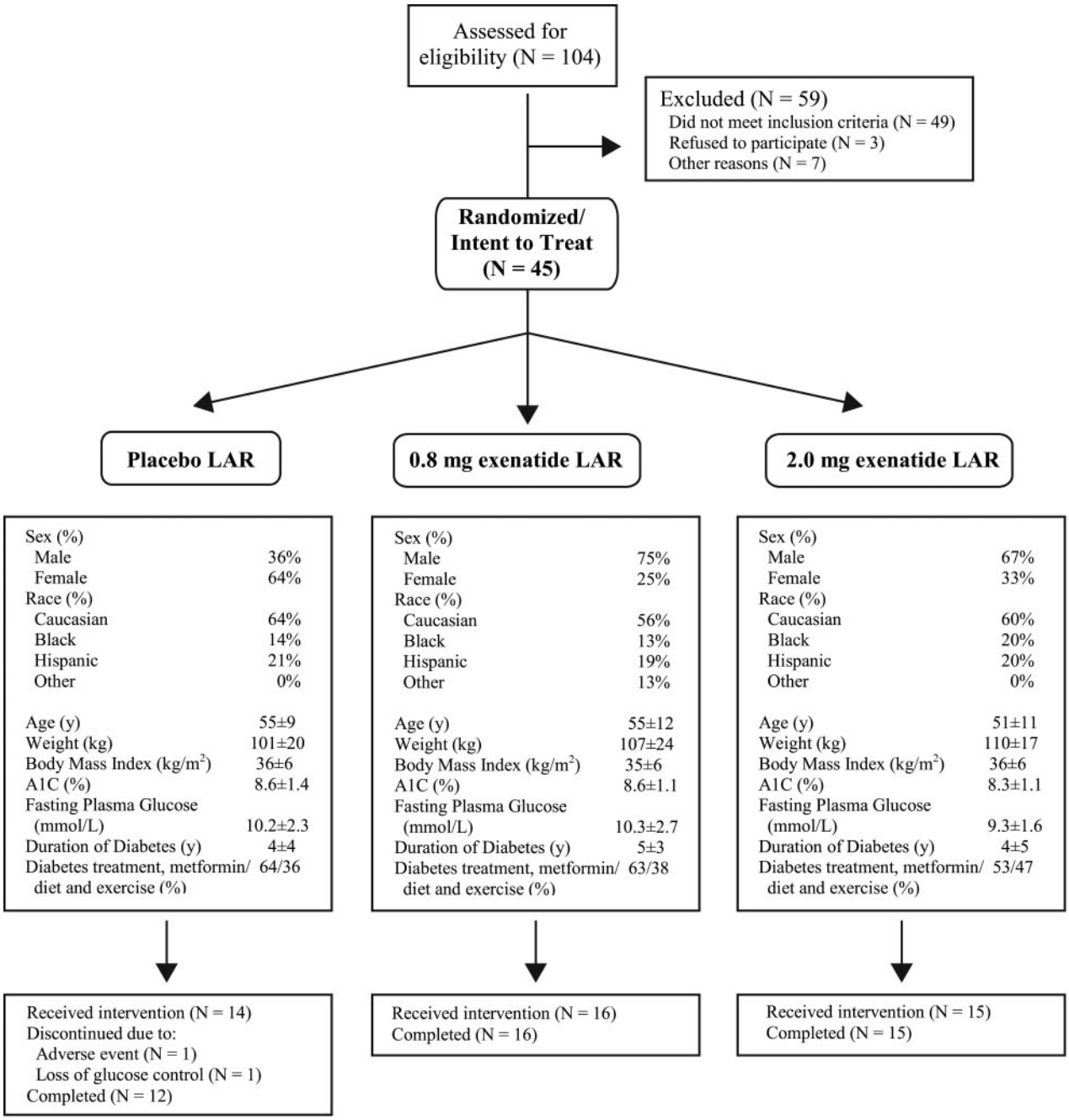

Figure 1— *Study flowchart. Disposition of patients throughout the study, with baseline demographics. Demographic data are means ± SD, except for sex, race, and diabetes treatment. Percentages may not add up to 100 because of rounding.*

A1C ≤7.0% also depended on week 15 measurements. The A1C target analysis was performed on the subset of evaluable patients with baseline A1C >7% ($n = 41$).

Plasma exenatide concentrations by treatment and time were provided for those subjects who received exenatide LAR and completed the study. Exenatide pharmacokinetics were analyzed by standard noncompartmental methods and summarized descriptively. Post hoc analyses were performed to compare the 0.8- and 2.0-mg exenatide LAR groups to the placebo LAR group with respect to the change from baseline for A1C, fasting plasma glucose, and body weight. Statistical significance was set at $P < 0.05$.

RESULTS

Subject demographics and disposition

Study subjects ($n = 45$) were 40% female and had the following mean ± SD baseline characteristics: A1C 8.5 ± 1.2%, fasting plasma glucose 9.9 ± 2.3 mmol/l, weight 106 ± 20 kg, and diabetes duration 5 ± 4 years. The different groups (Fig. 1) varied in their sex, with more women in the placebo LAR group and more men in the exenatide LAR groups, and glycemia, with lower A1C and fasting plasma glucose in the 2.0-mg exenatide LAR group. Most subjects in this study were receiving metformin ($n = 27$), whereas the remaining 18 subjects were

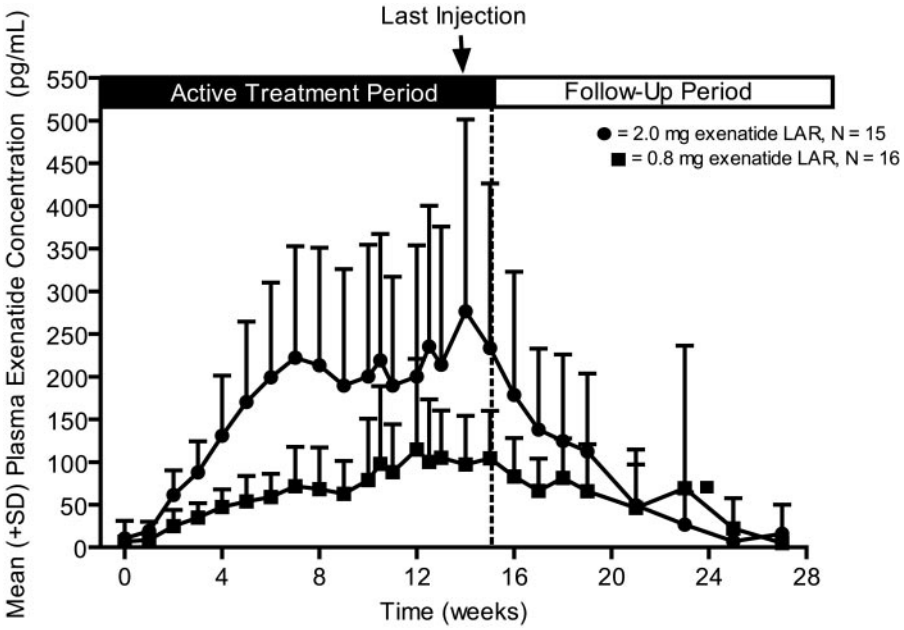

Figure 2— *Plasma exenatide concentrations (means ± SD) over time in subjects receiving exenatide LAR* (n = *31). Note that the last injection was administered at week 14.*

treated with diet modification and exercise. Two subjects withdrew from the study, both from the placebo LAR group. One subject withdrew during the lead-in period because of an adverse event, and one subject withdrew during the treatment period because of loss of glucose control (Fig. 1).

Pharmacokinetics

With once-weekly exenatide LAR injections, mean plasma exenatide concentrations rose steadily. By week 2, treatment with 2.0 mg exenatide LAR reached 50 pg/ml, a concentration previously shown to significantly reduce plasma glucose (Fig. 2) (28). After ~6 weeks of treatment with 2.0 mg exenatide LAR, plasma exenatide concentrations were maintained at concentrations similar to the maximum concentration achieved with a single injection of 10 μg exenatide (steady-state concentration of 232 pg/ml with 2.0 mg exenatide LAR compared with 211 pg/ml after a single injection of 10 μg exenatide) (16). The steady-state concentration with 0.8 mg exenatide LAR was 111 pg/ml. After completion of the treatment phase at week 15, exenatide concentrations decreased steadily to below those considered to have a therapeutic effect by week 21.

Glycemic end points

Fasting plasma glucose was reduced rapidly, with significant mean ± SE changes from baseline to week 15 of −2.4 ± 0.9 and −2.2 ± 0.5 mmol/l for the 0.8- and 2.0-mg exenatide LAR groups, respectively, compared with +1.0 ± 0.7 mmol/l for the placebo LAR group ($P < 0.001$ for both 0.8 and 2.0 mg vs. placebo LAR) (Fig. 3*A*).

All three groups had similar self-monitored blood glucose profiles and mean average daily blood glucose concentrations at baseline (placebo LAR 11.3 mmol/l, 0.8 mg exenatide LAR 11.4 mmol/l, and 2.0 mg exenatide LAR 10.8 mmol/l) (Fig. 3*B*). By week 15, the mean average daily blood glucose concentration decreased for both LAR treatment groups (week 15 values 9.2 mmol/l [0.8 mg] and 8.3 mmol/l [2.0 mg]) and rose for the placebo LAR group (12.2 mmol/l). Preprandial and postprandial plasma glucose concentrations decreased for both exenatide LAR groups, with the magnitude of postprandial excursions decreased by as much as fourfold with 2.0 mg exenatide LAR compared with placebo LAR.

A1C was reduced at the first postexenatide LAR measurement (week 3) for both exenatide LAR groups and progressively decreased throughout the treatment period (Fig. 3*C*). At week 15, significant mean ± SE A1C changes from baseline of −1.4 ± 0.3 and −1.7 ± 0.3% were observed for the 0.8- and 2.0-mg exenatide LAR groups, respectively, compared with +0.4 ± 0.3% for the placebo LAR group ($P < 0.0001$ for both 0.8 and 2.0 mg vs. placebo LAR), resulting in mean A1C values of 7.2 and 6.6% in the 0.8- and 2.0-mg exenatide LAR groups, respectively, compared with 9.0% for the placebo LAR group. Of evaluable subjects with baseline A1C >7% ($n = 41$), 86% in the 2.0-mg group and 36% of subjects in the 0.8-mg group achieved an A1C of ≤7% at week 15, compared with 0% of subjects in the placebo LAR group.

Weight

Body weight decreased progressively in the 2.0-mg exenatide LAR group, with a significant mean ± SE change from baseline at week 15 of −3.8 ± 1.4 kg (3.5% of total baseline body weight) (Fig. 3*D*) ($P < 0.05$ for 2.0 mg exenatide LAR vs. placebo LAR). Body weight was unchanged for the 0.8-mg exenatide LAR and placebo LAR groups.

Safety and tolerability

All adverse events were mild to moderate in intensity, except for one severe adverse event of urticaria and pruritus, which was considered to be related to shellfish ingestion not to exenatide treatment. Nausea was the most frequently reported adverse event among exenatide LAR-treated subjects (exenatide LAR 0.8 mg 19% and 2.0 mg 27% vs. placebo LAR 15%), followed by gastroenteritis (exenatide LAR 0.8 mg 19% and 2.0 mg 13% vs. placebo LAR 0%), and hypoglycemia (exenatide LAR 0.8 mg 25% and 2.0 mg 0% vs. placebo

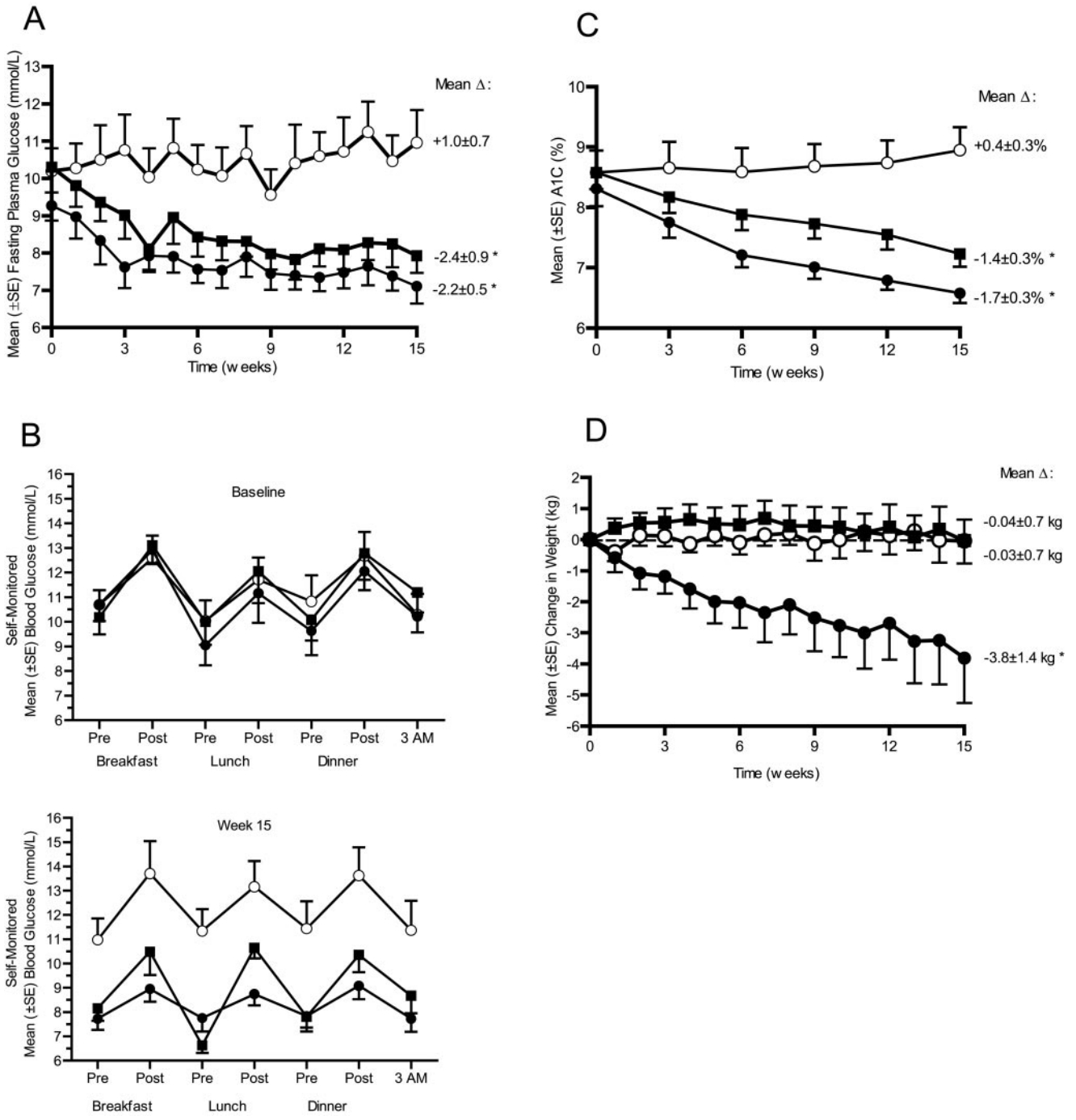

Figure 3— *Glycemic and weight parameters. Unless otherwise indicated:* ○*, placebo LAR,* n = *14;* ■*, 0.8 mg exenatide LAR,* n = *16;* ●*, 2.0 mg exenatide LAR,* n = *15. *Statistically significant results:* P < *0.05 compared with placebo LAR* (A, C, *and* D). A*: Fasting plasma glucose concentrations over time (ITT,* n = *45; mean ± SE).* B*: Self-monitored blood glucose concentration profiles at baseline and week 15 (evaluable,* n = *43; mean ± SE).* ○*, placebo LAR,* n = *12;* ■*, 0.8 mg exenatide LAR,* n = *16;* ●*, 2.0 mg exenatide LAR,* n = *15.* C*: A1C (%) over time (ITT,* n = *45; mean ± SE).* D*: Change in body weight from baseline over time (ITT,* n = *45; mean ± SE).*

LAR 0%). All episodes of nausea were mild, with no reports of vomiting. Hypoglycemic episodes, only one of which was confirmed with a blood glucose concentration (3.1 mmol/l), were mild in intensity and were not related to the dose of exenatide LAR (as all occurred in the 0.8-mg group). Injection site bruising occurred more frequently in exenatide LAR-treated patients (exenatide LAR 0.8 mg 13% and 2.0 mg 7% vs. placebo LAR 0%).

There were no withdrawals because of adverse events during exenatide LAR treatment. There were no clinically significant abnormal hematologic, chemistry, or urinalysis values reported during the study. Further, there were no clinically significant abnormalities in vital signs and electrocardiogram interpretations.

At week 15, 67% of subjects in the exenatide LAR treatment groups were positive for anti-exenatide antibodies. Individual subject profiles did not reveal a

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