

Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of Exenatide Once Weekly in Japanese Patients with Type 2 Diabetes

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Abstract. This randomized, placebo-controlled, double-blind, parallel study assessed the safety, tolerability, pharmacokinetics, and pharmacodynamics of exenatide once weekly (QW) in 30 Japanese patients with type 2 diabetes (T2D) suboptimally controlled by diet and exercise alone or combined with biguanide, sulfonylurea, thiazolidinedione, or combinations of these agents (58.6% male; 58±9 years; body mass index 26.3±2.9 kg/m²; hemoglobin A_{1c} [HbA_{1c}] 7.4±0.8%; fasting plasma glucose [FPG] 156.1±29.1 mg/dL; duration of T2D 6±5 years; means ± SD). Patients were randomized in a 1:1:1 ratio to subcutaneous placebo QW, exenatide QW 0.8 mg, or exenatide QW 2.0 mg for 10 weeks. All evaluable patients were analyzed (placebo QW, n=10; exenatide QW 0.8 mg, n=10; exenatide QW 2.0 mg, n=9), unless otherwise stated. Steady-state plasma exenatide concentrations were observed by Week 8 of the study. For the evaluable pharmacokinetic population, geometric mean (90% confidence interval) steady-state plasma concentrations (pg/mL) were 81.2 (68.3-96.4) and 344.5 (256.5-462.7) with exenatide QW 0.8 mg (n=8) and exenatide QW 2.0 mg (n=5), respectively. Baseline-to-Week 10 glycemic improvements with placebo QW, exenatide QW 0.8 mg, and exenatide QW 2.0 mg, respectively, were: HbA_{1c} (%): -0.4±0.3, -1.0±0.7, and -1.5±0.7; FPG (mg/dL): -20.5±20.4, -25.2±10.9, and -50.8±27.8; and 2-hour postprandial plasma glucose excursions (mg/dL): -8.8±26.9, -50.0±41.1, and -59.7±26.8 (means ± SD). No serious adverse events (AEs) were reported and no AEs led to study discontinuation in any group. The most frequent AE observed was mild-to-moderate injection site induration. No serious hypoglycemia was reported. Exenatide QW for 10 weeks was well tolerated and improved short-term glycemic control in Japanese patients with suboptimally controlled T2D.

Key words: Asia, Exenatide once weekly, Glycemic control, Japan, Type 2 diabetes

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DIABETES is a growing problem in Japan, a country estimated to have had 6.8 million people with diabetes in the year 2000 and predicted to have 8.9 million people with diabetes in the year 2030 [1]. Despite a low prevalence of obesity in Japan [2], Westernized lifestyle changes combined with the Japanese “thrifty” genotype – which can contribute to imbalances in energy expenditure, glucose homeostasis, and glucose

disposal efficiency in modernized societies – have been implicated in the increasing prevalence of diabetes in Japan [3-5].

Type 2 diabetes (T2D) is a complex, chronic disease that frequently requires treatment with more than one drug [6-9]. As such, development of pharmacological agents with novel mechanisms of action is of clinical interest for the treatment of Japanese patients with T2D.

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Exenatide is the first in a class of antidiabetic agents known as glucagon-like peptide-1 (GLP-1) receptor agonists. Exenatide shares several metabolic effects with the naturally occurring human incretin gut hormone GLP-1, including glucose-dependent enhancement of insulin secretion, suppression of elevated glucagon secretion, slowing of gastric emptying, and enhancement of satiety [10, 11].

Exenatide twice daily (BID), administered as a subcutaneous injection, has been shown to reduce hemoglobin A_{1c} (HbA_{1c}), fasting glucose, and postprandial glucose in Japanese patients with T2D [12, 13]. However, exenatide BID does not provide continuous activation of GLP-1 receptors. A once-weekly (QW)-dosed formulation of exenatide for subcutaneous injection is now being developed for the treatment of T2D, in order to evaluate whether additional benefits might be achieved with exenatide being continuously present in the systemic circulation. This new formulation consists of injectable microspheres of exenatide and poly (D, L lactic-co-glycolic acid), a biodegradable polymer that allows extended drug delivery at a controlled rate.

Exenatide QW has been shown to improve glycemic control and be well tolerated in previous studies of primarily Caucasian patients with T2D. A 15-week, randomized, placebo-controlled, multicenter, phase 2 study has shown that exenatide QW 0.8 mg and exenatide QW 2.0 mg improve glycemic control and reduce body weight in patients from the United States with T2D poorly controlled by metformin and/or diet and exercise [14]. Additionally, a 30-week, randomized, open-label, non-inferiority study has shown that exenatide QW 2.0 mg leads to greater improvements in glycemic control than exenatide 10 µg BID, with reductions in body weight and no increased risk of hypoglycemia, in patients with T2D from the United States and Canada naïve to drug therapy or treated with oral antidiabetic agent(s) [15]. This is the first clinical study to evaluate the safety, tolerability, pharmacokinetics, and pharmacodynamics of exenatide QW in Japanese patients with T2D.

Patients and Methods

Patients

Japanese patients with T2D were eligible for the

study if they were from 20-75 years of age, inclusive, and had a body weight ≥ 50 kg. Patients were required to have been managing their T2D with diet and exercise alone or in combination with a stable regimen of a biguanide (BG), a sulfonylurea (SU), a thiazolidinedione (TZD), a BG combined with an SU, a BG combined with a TZD, or an SU combined with a TZD for at least 2 months prior to screening. Patients taking an α -glucosidase inhibitor (α -GI) or a meglitinide derivative could be included in this study, but were required to discontinue these oral antidiabetic agents at least 7 days prior to initiation of study drug. Patients were required to have suboptimal glycemic control at screening, as evidenced by an HbA_{1c} value ranging from 6.5%-10%, inclusive, for patients treated with diet and exercise alone or in combination with a BG, an SU, a TZD, or combinations thereof, or from 6.5%-9.5%, inclusive, for patients treated with an α -GI or a meglitinide derivative.

Exclusion criteria included treatment with exogenous insulin or the continuous use of any drug directly affecting gastrointestinal motility within the 3 months prior to screening; clinically significant renal or hepatic disease; blood pressure $\geq 160/100$ mm Hg; hospitalization for cardiac disease within the year prior to inclusion in the study; clinically significant history of or active digestive disease within the year prior to inclusion in the study; active or untreated malignancy or remission from clinically significant malignancy for < 5 years; obvious hyperglycemia as evidenced by self-monitored blood glucose ≥ 250 mg/dL in the fasting state or ≥ 350 mg/dL measured at any time; or > 1 severe hypoglycemic episode requiring the assistance of another person within the 3 months prior to screening. Female patients of childbearing age were excluded if they were pregnant at the time of enrollment, intended to become pregnant during the study, had not practiced a reliable method of birth control for the 3 months prior to screening, or did not agree to continue practicing a reliable method of birth control during the study.

Study design

The study design and data collection schedule are shown in Figure 1. This was a Phase 1, randomized, placebo-controlled, double-blind, parallel study conducted at 5 centers in Japan. Patients, investigators, and the sponsor were unblinded to the injection volume but blinded to the distinction between exenatide

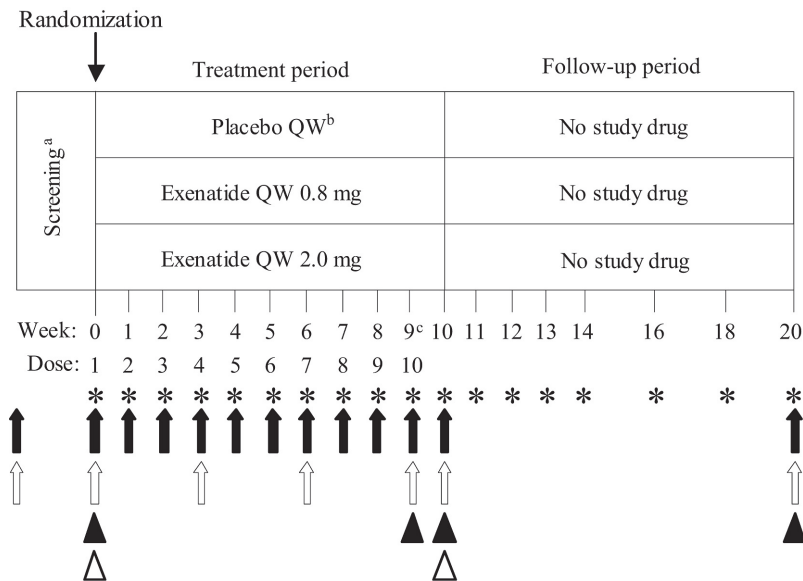


Fig. 1. Study design and data collection schedule. *Asterisks* = patient-reported AEs, vital signs, clinical laboratory evaluations, and pharmacokinetics; *black arrows* = FPG; *white arrows* = HbA_{1c}, body weight, and antibodies to exenatide (excluding at screening); *black triangles* = electrocardiograms (before and 2 hours after administration of study drug); *white triangles* = meal tolerance testing. ^aScreening was within 3 weeks of starting the study. During this period, α -GI and meglitinide derivatives had to be discontinued and washed out for a period of at least 7 days prior to initiation of study drug. ^bOne-half of the patients randomized to placebo received an injection volume equivalent to that of exenatide QW 0.8 mg, while the other one-half received an injection volume equivalent to that of exenatide QW 2.0 mg, with the placebo groups pooled for analysis. ^cPatients returned to the investigative site for pharmacokinetic blood sampling on any 4 days between Weeks 9 and 10. α -GI = α -glucosidase inhibitor; AEs = adverse events; FPG = fasting plasma glucose; HbA_{1c} = hemoglobin A_{1c}; QW = once weekly.

and placebo. Patients underwent screening within 3 weeks before starting the study. During this period, α -GI and meglitinide derivatives had to be discontinued and washed out for at least 1 week prior to initiation of study drug.

Thirty patients were enrolled and randomized in a ratio of 1:1:1 to receive placebo QW, exenatide QW 0.8 mg, or exenatide QW 2.0 mg. One-half of the patients randomized to placebo QW received an injection volume equivalent to that of exenatide QW 0.8 mg, while the other one-half received an injection volume equivalent to that of exenatide QW 2.0 mg, with the placebo groups pooled for analysis. Study drug was administered by site personnel to patients QW via subcutaneous injection into the abdomen after patients had fasted overnight for ≥ 8 hours.

Study drug was administered from baseline until Week 10, after which study drug was discontinued and patients were followed until Week 20. The 10 week durations of the treatment and follow-up periods were based on a previous study of exenatide QW [14] during which steady-state plasma exenatide concentra-

tions were achieved within 6-7 weeks, and the mean plasma exenatide concentration was below the lower limit of the therapeutic range (50 pg/mL) [16] within 10 weeks after discontinuation of study drug.

Patients were to continue their pre-study dose(s) of BG, SU, and/or TZD during the study. The doses of these drugs were not to have been changed during the study unless medically required. SU could be discontinued or the dose reduced, at the discretion of the investigator, in the event of hypoglycemic symptoms or a self-monitored blood glucose < 70 mg/dL. The SU dose could not be increased during the study.

Patients were not allowed to consume alcohol-containing products for 24 hours prior to each study visit. Additionally, smoking was prohibited for 1 hour prior to testing blood pressure, pulse rate, and electrocardiograms. Patients were to maintain their normal pre-study exercise regimen as directed by the investigator.

Institutional review boards provided written approval of the study protocol and the informed consent document. The study was conducted in accordance with the ethical principles of the Declaration of Helsinki

and was consistent with good clinical practices and applicable laws and regulations. Investigators obtained written informed consent from patients prior to administering study drug or performing protocol procedures.

Safety and tolerability evaluations

Safety and tolerability, the primary endpoints of this study, were evaluated based on patient-reported adverse events (AEs), vital signs including blood pressure and pulse rate, standard 12-lead electrocardiograms, and clinical laboratory evaluations. The effects of antibodies to exenatide on the incidence of hypoglycemia and change in HbA_{1c} were also evaluated.

Bioanalytical methods

Blood samples obtained during this study were analyzed using standard methods at the BioPharma Services Laboratory within Millipore, Inc. (Saint Charles, Missouri, United States). Plasma exenatide concentrations were measured using a validated enzyme-linked immunosorbent assay (ELISA) as previously described [17]. Antibodies to exenatide were also measured using ELISA [17], with titers <625 considered low and titers ≥625 considered higher. Antibodies to exenatide were considered treatment-emergent if they were detectable (titer ≥25) after a negative or missing baseline titer or if they had increased by at least 3 dilutions from a detectable baseline titer.

Pharmacokinetic evaluations

Plasma exenatide concentrations were analyzed using WinNonlin Professional, Version 5.0.1. Plasma exenatide trough concentrations throughout the treatment period were evaluated graphically to determine the time to reach the lower limit of the therapeutic range (50 pg/mL) [16] and the time to reach steady state. Additionally, key pharmacokinetic parameters were computed by noncompartmental methods: area under the concentration-versus-time curve of exenatide in the initial release period (AUC [0-8 hours]) for Day 1 (after a single subcutaneous injection), maximum observed plasma exenatide concentration (C_{max}) for Day 1, area under the concentration-versus-time curve of exenatide over a dosing interval at steady state for Weeks 9-10 (after QW dosing), and steady-state plasma exenatide concentration (C_{ave,ss}) for

Weeks 9-10.

Pharmacodynamic evaluations

Pharmacodynamic measures included HbA_{1c}, percent of patients achieving HbA_{1c} <7.0% and <6.5% at Week 10, fasting plasma glucose (FPG), postprandial plasma glucose and excursions measured during meal tolerance testing, and body weight.

Statistical Analyses

Thirty patients were enrolled with the expectation that at least 7 patients per group would complete the study. This number was estimated to provide sufficient information for the evaluation of safety and tolerability of exenatide QW.

Of the 30 patients who were randomized and received ≥1 dose of study drug, 1 received incorrect study drug (a protocol violation) and was excluded from analyses; therefore, the *evaluable population* was composed of the remaining 29 patients. The *pharmacokinetic evaluable population* additionally excluded 4 patients who had higher-titer antibodies to exenatide at any time during the study, as a previous *in vitro* study has shown that the presence of higher-titer antibodies to exenatide can affect the ELISA used to quantitate plasma exenatide [unpublished data].

Patient-reported AEs, including hypoglycemia, were categorized as mild, moderate, or severe based on the judgment of the investigator.

Analyses of HbA_{1c}, FPG, and body weight were performed using the last-observation-carried-forward approach. Descriptive statistics of means ± standard deviations (SD) or means (90% confidence intervals) are provided.

Results

Patients

Demographics and baseline characteristics for the individual groups are shown in Table 1. For the groups combined, patients were 58.6% male and had the following mean ± SD baseline characteristics: age, 58±9 years; HbA_{1c}, 7.4±0.8%; FPG, 156.1±29.1 mg/dL; body weight, 69.7±13.4 kg; body mass index, 26.3±2.9 kg/m²; and duration of T2D, 6±5 years.

Table 1. Demographics and baseline characteristics for the evaluable population

	Placebo QW (n=10)	Exenatide QW 0.8 mg (n=10)	Exenatide QW 2.0 mg (n=9)
Sex, n (%) male	4 (40.0)	5 (50.0)	8 (88.9)
Age, years	61±8	56±11	58±9
Weight, kg	68.2±14.2	69.1±15.1	71.9±11.4
Body mass index, kg/m ²	26.4±3.3	26.5±2.8	26.1±2.9
HbA _{1c} , %	7.5±0.9	7.4±0.7	7.3±0.8
FPG, mg/dL	164.5±38.0	145.0±16.5	159.2±28.1
Duration of T2D, years	7±5	6±6	5±4
Diabetes treatment, n (%)			
Diet and exercise	2 (20.0)	5 (50.0)	4 (44.4)
SU alone	3 (30.0)	2 (20.0)	3 (33.3)
SU + α -GI	0 (0)	0 (0)	1 (11.1)
SU + BG	2 (20.0)	0 (0)	0 (0)
SU + TZD	1 (10.0)	1 (10.0)	1 (11.1)
BG alone	1 (10.0)	1 (10.0)	0 (0)
BG + α -GI	0 (0)	1 (10.0)	0 (0)
TZD alone	1 (10.0)	0 (0)	0 (0)

Unless otherwise stated, data are means \pm SD. α -GI = α -glucosidase inhibitor; BG = biguanide; FPG = fasting plasma glucose; HbA_{1c} = hemoglobin A_{1c}; SD = standard deviations; SU = sulfonylurea; T2D = type 2 diabetes; TZD = thiazolidinedione; QW = once weekly.

One evaluable patient treated with exenatide QW 0.8 mg discontinued the study during the treatment period due to physician decision. The remaining 96.6% (28/29) of evaluable patients completed both the treatment and follow-up periods.

Safety and Tolerability

Safety and tolerability findings are presented for the 10-week treatment and 10-week follow-up periods combined. No serious AEs were reported and no patients discontinued the study due to an AE. All of the 29 patients in the evaluable population reported ≥ 1 AE during the treatment plus follow-up periods. The most common AEs were mild-to-moderate injection site induration (60.0% [6/10], 90.0% [9/10], and 88.9% [8/9] of patients) and mild-to-moderate injection site pruritus (20.0% [2/10], 40.0% [4/10], and 44.4% [4/9] of patients) for the placebo QW, exenatide QW 0.8 mg, and exenatide QW 2.0 mg groups, respectively.

Mild nausea was reported for 33.3% [3/9] of patients and mild vomiting for 11.1% [1/9] of patients in the exenatide QW 2.0 mg group during the treatment plus follow-up periods. Mild vomiting was also reported for 10.0% (1/10) of patients treated with placebo QW during the treatment plus follow-up periods.

Moderate hypoglycemia was reported for 10.0% (1/10) and 11.1% (1/9) of patients receiving exenatide

QW 0.8 mg and exenatide QW 2.0 mg, respectively, during the treatment plus follow-up periods. Both of these patients were taking a concomitant SU.

Increased blood amylase was reported as an AE for 2 patients in the exenatide QW 0.8 mg group. These events were not associated with any clinical symptoms in these patients. Mean (\pm SD) amylase changes from baseline to Week 10 were not clinically relevant for any group (placebo: +1 \pm 13 U/L; exenatide QW 0.8 mg: +17 \pm 17 U/L; and exenatide QW 2.0 mg: +13 \pm 14 U/L), and mean (\pm SD) Week 10 amylase values were within the normal reference range for all groups (placebo: 76 \pm 40 U/L; exenatide QW 0.8 mg: 89 \pm 34 U/L; and exenatide QW 2.0 mg: 80 \pm 28 U/L; normal reference range: 39-134 U/L). Moreover, mean amylase values remained within the normal reference range for all groups at all timepoints during the treatment and follow-up periods. No pancreatitis was reported during the study.

Treatment-emergent antibodies to exenatide were present in 60.0% (6/10) and 77.8% (7/9) of patients in the exenatide QW 0.8 mg and exenatide QW 2.0 mg groups, respectively, at any point during the study. Ten percent (1/10) and 33.3% (3/9) of patients receiving exenatide QW 0.8 mg and exenatide QW 2.0 mg, respectively, had higher-titer antibodies to exenatide at any point during the study. The presence of antibodies to exenatide had no clinically relevant effects on the

Table 2. Noncompartmental pharmacokinetic parameters for the pharmacokinetic evaluable population

Sampling period Parameter	Exenatide QW 0.8 mg	Exenatide QW 2.0 mg
Day 1 ^a		
N	8	6
AUC (0-8 hours) (pg*h/mL)	187.6 (133.7-263.3)	405.6 (278.4-590.8)
Cmax (pg/mL)	64.3 (38.3-107.8)	137.3 (74.6-252.6)
Week 9-10 ^b		
N	8	5
AUC (0- τ ,ss) (pg*h/mL)	13860 (11708-16408)	60823 (46385-79755)
Cave,ss (pg/mL) ^c	81.2 (68.3-96.4)	344.5 (256.5-462.7)

Data are geometric means (90% CI). ^aOne patient receiving exenatide QW 0.8 mg was excluded from analyses on Day 1 because the plasma exenatide concentrations were below the quantification limits at all timepoints on that day. The plasma exenatide concentration at the 6-hour timepoint on Day 1 for another patient receiving exenatide QW 0.8 mg was excluded as an outlier. This patient discontinued the study during the treatment period due to physician decision and was excluded from Week 9-10 analyses. ^bOne patient receiving exenatide QW 2.0 mg was excluded at Week 9 because the plasma exenatide concentrations from Weeks 8-11 were outliers. ^cFor the complete evaluable population (n=29), geometric mean (90% CI) Cave,ss values were greater (84.4 [71.5-99.6] pg/mL and 644.8 [368.2-1129.2] pg/mL for the exenatide QW 0.8 mg and exenatide QW 2.0 mg groups, respectively), likely due to an effect of higher-titer antibodies to exenatide on the ELISA used to quantitate plasma exenatide. AUC (0-8 hours) = area under the concentration-versus-time curve of exenatide in the initial release period; Cmax = maximum observed plasma exenatide concentration; AUC (0- τ ,ss) = area under the concentration-versus-time curve of exenatide over a dosing interval at steady state; Cave,ss = steady-state plasma concentration; Day 1 = after a single subcutaneous injection; Weeks 9-10 = after QW dosing; CI = confidence interval; ELISA = enzyme-linked immunosorbent assay; QW = once weekly.

incidence of hypoglycemia or change in HbA_{1c} (data not shown).

There were no clinically relevant alterations in vital signs, clinical laboratory measures, or electrocardiograms during the study.

Pharmacokinetics

Table 2 shows noncompartmental pharmacokinetic parameters for the pharmacokinetic evaluable population. Based on graphical evaluations of plasma exenatide trough concentrations, plasma exenatide concentrations reached 50 pg/mL, a concentration previously shown to significantly reduce plasma glucose [16], between Weeks 3-9 of the study for patients treated with exenatide QW 0.8 mg and between Weeks 2-5 of the study for patients treated with exenatide QW 2.0 mg. Steady state, at which point the mean pharmacokinetic profiles began to flatten, was achieved by Week 8 for both exenatide QW groups (Figure 2).

Pharmacodynamics

Changes in HbA_{1c} over time are shown in Figure 3 (A). Reductions in mean (\pm SD) HbA_{1c} from baseline to Week 10 were $-0.4\pm 0.3\%$, $-1.0\pm 0.7\%$, and $-1.5\pm 0.7\%$ with placebo QW, exenatide QW 0.8 mg, and exenatide QW 2.0 mg, respectively. At the end of the follow-up period, 10 weeks after study drug discontinuation, mean (\pm SD) HbA_{1c} changes from baseline were $-0.07\pm 0.4\%$, $-0.6\pm 0.7\%$, and $-0.7\pm 0.9\%$, respectively.

At Week 10, 44.4% (4/9), 71.4% (5/7), and 100% (5/5) of patients with a baseline HbA_{1c} $\geq 7.0\%$ achieved an HbA_{1c} $< 7.0\%$, and 0%, 62.5% (5/8), and 85.7% (6/7) of patients with a baseline HbA_{1c} $\geq 6.5\%$ achieved an HbA_{1c} $< 6.5\%$ in the placebo QW, exenatide QW 0.8 mg, and exenatide QW 2.0 mg groups, respectively.

Changes in FPG over time are shown in Figure 3 (B). Reductions in mean (\pm SD) FPG from baseline to Week 10 were -20.5 ± 20.4 mg/dL, -25.2 ± 10.9 mg/dL, and -50.8 ± 27.8 mg/dL with placebo QW, exenatide QW 0.8 mg, and exenatide QW 2.0 mg, respectively. At the end of the follow-up period, mean (\pm SD) FPG changes

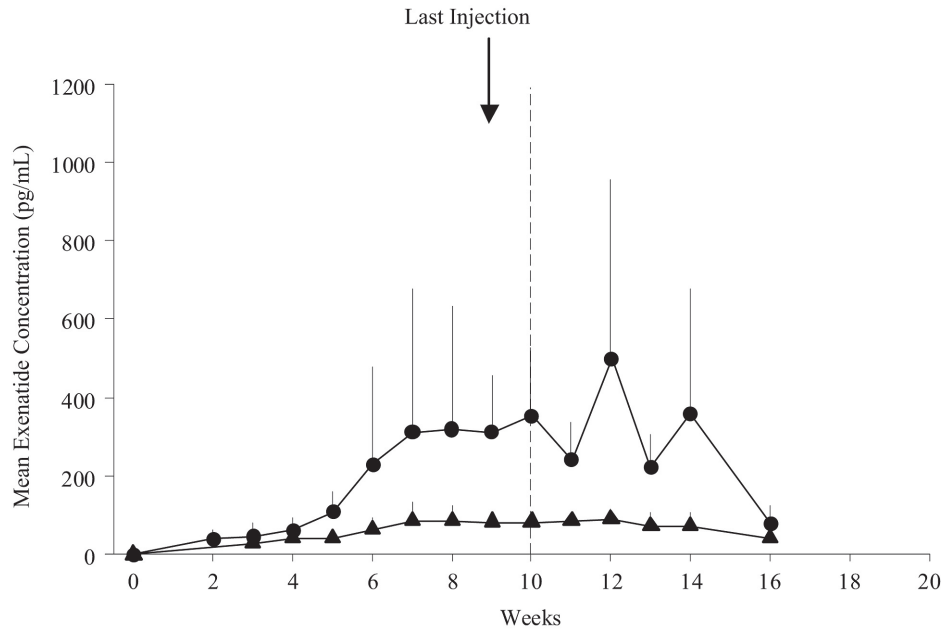


Fig. 2. Mean (\pm SD) plasma exenatide trough concentration-versus-time profiles in pharmacokinetic evaluable patients receiving exenatide QW 0.8 mg (closed triangles) ($n=8$) or exenatide QW 2.0 mg (closed circles) ($n=6$). One patient receiving exenatide QW 0.8 mg discontinued the study during the treatment period due to physician decision and was excluded from the analysis. Also excluded from the analysis as outliers were Week 2 plasma exenatide concentrations for a patient receiving exenatide QW 0.8 mg; Week 4 plasma exenatide concentrations for another patient receiving exenatide QW 0.8 mg; and Week 8-11 and 16 plasma exenatide concentrations for a patient receiving exenatide QW 2.0 mg. The dashed vertical line indicates the end of the treatment period at Week 10. Data are shown to Week 16 based on the 2/3 rule, according to which summary statistics for plasma exenatide concentrations were calculated and plotted only if $>2/3$ of the individual patient data at the timepoint had quantifiable plasma exenatide concentrations.

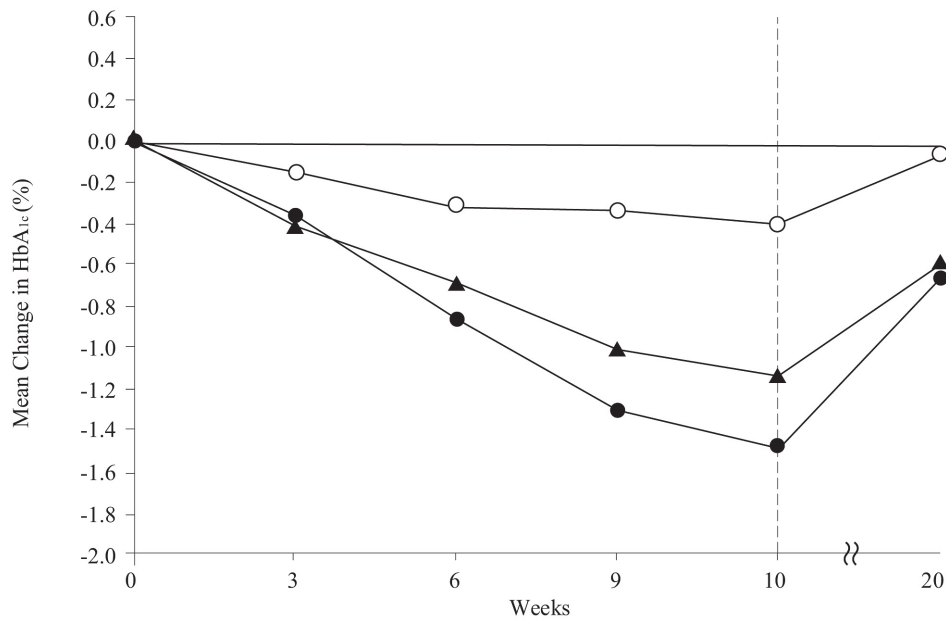


Fig. 3 (A). Mean change in HbA_{1c} over time in patients receiving placebo QW (open circles), exenatide QW 0.8 mg (closed triangles), or exenatide QW 2.0 mg (closed circles). Data are for the evaluable population ($n=29$). The dashed vertical line indicates the end of the treatment period at Week 10. HbA_{1c} = hemoglobin A_{1c}; QW = once weekly.

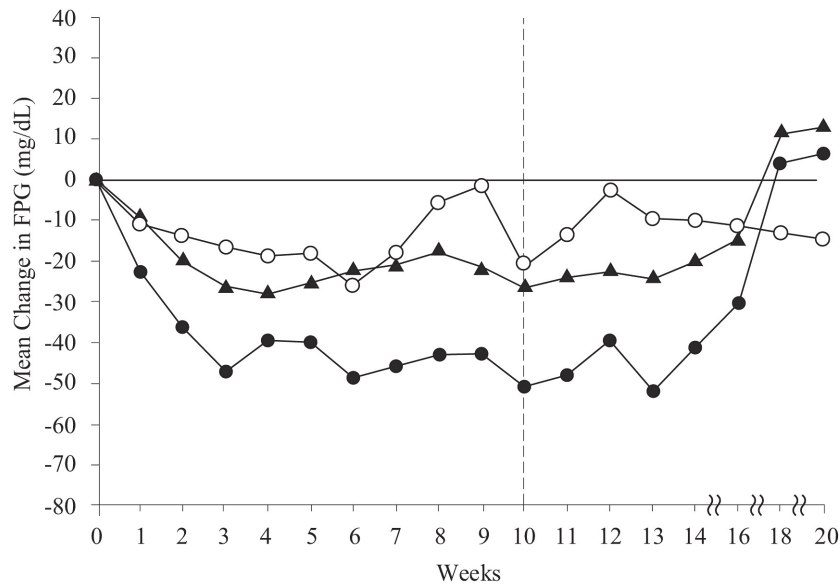


Fig. 3 (B). Mean change in FPG over time in patients receiving placebo QW (open circles), exenatide QW 0.8 mg (closed triangles), or exenatide QW 2.0 mg (closed circles). Data are for the evaluable population ($n=29$). The dashed vertical line indicates the end of the treatment period at Week 10. FPG = fasting plasma glucose; QW = once weekly.

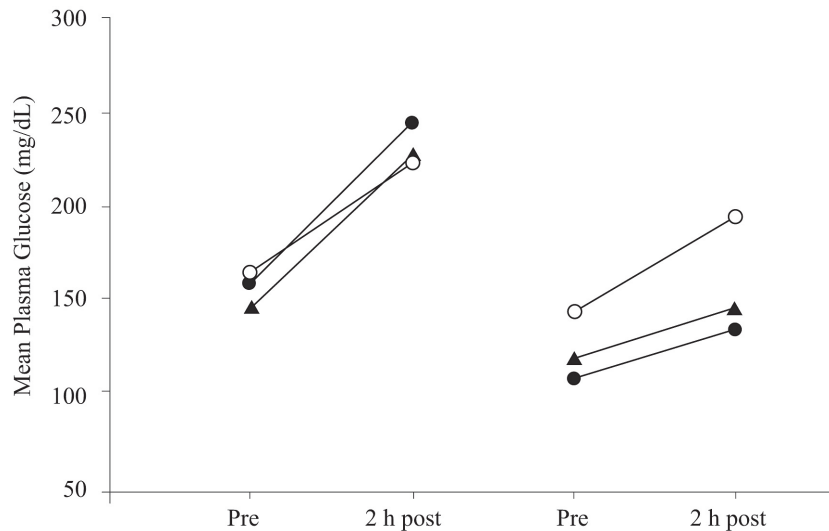


Fig. 3 (C). Mean pre- and 2-hour postprandial plasma glucose at baseline and Week 10 in patients receiving placebo QW (open circles), exenatide QW 0.8 mg (closed triangles), or exenatide QW 2.0 mg (closed circles). Data are for the evaluable population ($n=29$). h = hours; QW = once weekly.

from baseline were -14.9 ± 16.8 mg/dL, $+13.2 \pm 30.3$ mg/dL, and $+6.3 \pm 37.5$ mg/dL, respectively.

Mean pre- and 2-hour postprandial plasma glucose concentrations measured during meal tolerance testing at baseline and Week 10 are shown in Figure 3 (C). Reductions in mean (\pm SD) 2-hour postprandial plasma glucose from baseline to Week 10 were -28.5 ± 38.4 mg/

dL, -75.8 ± 42.9 mg/dL, and -111.1 ± 48.5 mg/dL with placebo QW, exenatide QW 0.8 mg, and exenatide QW 2.0 mg, respectively. Reductions in mean (\pm SD) 2-hour postprandial plasma glucose excursions from baseline to Week 10 were -8.8 ± 26.9 mg/dL, -50.0 ± 41.1 mg/dL, and -59.7 ± 26.8 mg/dL, respectively. Meal tolerance testing was not performed during follow-up.

Mean (\pm SD) body weight changes were -1.6 ± 1.6 kg, $+0.3\pm 2.2$ kg, and -0.8 ± 1.5 kg from baseline to Week 10 with placebo QW, exenatide QW 0.8 mg, and exenatide QW 2.0 mg, respectively. At the end of the follow-up period, mean (\pm SD) body weight changes from baseline were -2.0 ± 1.9 kg, -0.6 ± 2.9 kg, and -0.05 ± 1.3 kg.

Discussion

Exenatide QW, a new formulation which would provide 24-hour exposure to exenatide, is being evaluated as a potentially important new treatment for patients with T2D. This was the first clinical study to evaluate the safety, tolerability, pharmacokinetics, and pharmacodynamics of exenatide QW in Japanese patients with T2D suboptimally controlled with diet and exercise alone or in combination with oral antidiabetic agent(s).

Both exenatide QW doses were well tolerated and there were no unexpected safety findings during the study. AEs were exclusively mild-to-moderate in intensity, with mild-to-moderate injection site induration being reported with the greatest incidence. Injection site induration was reported more commonly in the current study than in previous studies of exenatide QW in primarily Caucasian populations [14, 15]. One reason may be that these Japanese patients were leaner than the non-Japanese patients (body mass indexes of $26\text{--}27$ kg/m² compared with $35\text{--}36$ kg/m²), which could have made induration more apparent in the Japanese.

Nausea and vomiting with exenatide QW were reported exclusively in the higher-dose group, with all cases being mild in intensity. The incidences of nausea and vomiting with exenatide QW in the current study were similar to those observed during previous studies of exenatide QW in primarily Caucasian populations [14, 15], and generally lower than those observed during previous studies of exenatide BID in Japanese and primarily Caucasian populations [13, 18–21]. Gradual dose escalation with exenatide BID has been shown to reduce the proportion of patients experiencing dose-limiting nausea and vomiting [22]. Therefore, generally lower incidences of nausea and vomiting with exenatide QW as compared with exenatide BID is consistent with a more gradual increase in plasma exenatide concentrations after initiation of exenatide QW.

Exenatide enhances the secretion of insulin from pancreatic β -cells in a glucose-dependent fashion. By

this mechanism, insulin secretion decreases as glucose levels normalize [10, 11], which reduces the potential for exenatide to cause hypoglycemia. In the current study, hypoglycemia was observed in two patients. Notably, both of these patients were taking a concomitant SU. In previous placebo-controlled studies of exenatide BID performed in primarily Caucasian populations, concomitant SUs have been implicated in increasing the incidence of hypoglycemia when coupled with lower ambient glycemia and increasing exenatide dose [18, 20]. A proactive approach to SU dose management has been suggested to reduce the incidence of hypoglycemia in patients receiving exenatide BID [20]. However, proactive SU dose adjustments were not performed in the current study of exenatide QW because the protocol specified that SU could be discontinued or the dose reduced only after a documented hypoglycemic episode.

Antibodies to exenatide were measured since any protein or peptide can have potentially immunogenic properties. In this study, the presence of antibodies to exenatide had no clinically relevant effects on the incidence of hypoglycemia or change in HbA_{1c}. Previous studies in primarily Caucasian populations have demonstrated that antibody titers diminish over time in most patients [23]; longer-term studies would be required to evaluate antibody titers over time in Japanese patients.

Pharmacokinetic parameters in this Japanese pharmacokinetic evaluable population were compared with those in non-Japanese to understand the impact of ethnic factors on exenatide pharmacokinetics following QW administration. Pharmacokinetic properties were expected to be similar between these Japanese patients and non-Japanese populations, since exenatide is a peptide that is administered subcutaneously and therefore would not be subject to polymorphic differences in gut or liver enzyme expression or dietary variations [24]. Consistent with expectations, C_{ave,ss} values in the Japanese patients in the current study (Table 2) were consistent with a previous study of exenatide QW in a primarily Caucasian population [14]. The current results are also consistent with earlier findings with the exenatide BID formulation, which demonstrated a lack of ethnic sensitivity in exenatide pharmacokinetics following subcutaneous administration [12].

Exenatide QW improved glycemic control in the current study, reducing HbA_{1c}, FPG, postprandial plasma glucose, and postprandial plasma glucose excursions. The improvements in HbA_{1c} and FPG were

clinically relevant and consistent with those from previous studies of exenatide QW in primarily Caucasian populations [14, 15], and are noteworthy given the shorter 10-week duration of this study compared with the previous studies, which lasted 15-30 weeks. Additionally, the improvements were generally greater than those from previous studies of similar or longer duration evaluating exenatide BID in Japanese and primarily Caucasian populations [13, 18-21]. The degree of HbA_{1c} reduction in the current study was also notable given the patients' relatively low mean HbA_{1c} values of 7.3%-7.5% at baseline. The greater effect on HbA_{1c} and FPG of exenatide QW, as compared with exenatide BID [13, 18-21], may be attributable to the 24-hour exposure with the QW formulation.

Improvements in 2-hour postprandial plasma glucose measured during meal tolerance testing that were observed during the current study were also clinically relevant and consistent with those from a previous study of exenatide QW in a primarily Caucasian population [15]. Reductions in 2-hour postprandial plasma glucose excursions with exenatide QW were clinically relevant as well. These effects with exenatide QW are noteworthy since postprandial glucose control is known to play an important role in overall glucose control [25, 26] and is recognized as an independent risk factor for macrovascular disease [27]. Furthermore, these effects with exenatide QW are important since the relative contribution to metabolic disequilibrium of postprandial glycemic excursions, as compared with fasting plasma glucose, is greater for patients with better glycemic control [28], such as those in the current study, who had mean baseline HbA_{1c} values from 7.3%-7.5%. Finally, reductions in postprandial glucose excursions with exenatide QW are important since they may help prevent oxidative stress that can be triggered by acute glucose fluctuations [29].

A combination of the effects of exenatide QW on fasting and postprandial plasma glucose may explain why generally larger percentages of patients reached target HbA_{1c} values of <6.5% and <7.0% in the current study as compared with previous studies of exenatide BID in Japanese and primarily Caucasian populations [13, 18-21].

Exenatide QW appeared to have a neutral effect on body weight in Japanese patients, as compared with placebo, in the current study. This apparent neutral effect of exenatide QW on body weight is important since other antidiabetic therapies, including

SU, TZDs, and insulins, can cause weight gain in patients with T2D [30]. The reasons for the unexpected weight loss (-1.6 kg at Week 10) with placebo observed in this study are not known; however, a similar placebo effect and apparent neutral effect of exenatide on body weight, as compared with placebo, have also been observed previously in a study of exenatide BID in Japanese patients with T2D [13]. This observed neutral effect of exenatide on body weight in Japanese patients, regardless of exenatide formulation, may be due to the relative leanness of Japanese patients with T2D [13] as compared with Caucasians [14, 15, 18-21].

Body weight reductions of -3.7 to -3.8 kg have been observed with the exenatide QW 2.0 mg dose in previous studies in primarily Caucasian populations [14, 15]. However, these previously studied patients had greater baseline body mass indexes (35-36 kg/m²) than the Japanese patients who received exenatide QW 2.0 mg in the current study (26 kg/m²). Again, this observation is consistent with the hypothesis that the leanness of the Japanese could be a contributing factor to the apparent neutral effect of exenatide QW on body weight in this population.

The results of this Phase 1 study should be interpreted cautiously due to several limitations in study design. First, the sample size was modest. Also, the treatment period was only 10 weeks in duration, so the full effects of exenatide QW on glycemia and other measures may not have been fully realized. Study drug was administered by trained site personnel rather than patients themselves, which may not accurately reflect real-world use. Finally, there were no standardized diet and exercise recommendations in the current study.

These preliminary data show that exenatide QW offers the potential of 24-hour glycemic control for the treatment of Japanese patients with T2D. Data from this study support further investigation of exenatide QW in the Japanese.

Principal Investigators

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