Efficacy and safety of exenatide once-weekly vs exenatide twice-daily in Asian patients with type 2 diabetes mellitus

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ABSTRACT

Aims/Introduction: To compare safety and efficacy of the extended-release formulation exenatide once weekly (EQW) vs exenatide twice daily (EBID) for 26 weeks in type 2 diabetes patients from China, India, Japan, South Korea and Taiwan.

Materials and Methods: A randomized, comparator-controlled, open-label study included 681 patients with type 2 diabetes inadequately controlled (hemoglobin A1c [HbA_{1c}] ≥ 7 and $\leq 11\%$) with oral antihyperglycemic medications (OAMs). Patients added 2 mg EQW or 10 µg EBID to current OAMs. Safety was re-evaluated 10 weeks after last treatment.

Results: EQW was superior to EBID on HbA_{1c} measures at week 26 (Least-squares mean treatment difference: −0.31% [95% confidence interval −0.49, −0.14%]). More EQW-treated patients achieved target HbA_{1c} $\leq 7.0\%$ ($P = 0.003$), $\leq 6.5\%$ ($P < 0.001$), or $\leq 6.0\%$ ($P = 0.003$). Fasting serum glucose reductions were greater among EQW-treated patients ($P < 0.001$). Blood glucose profiles improved in both treatment groups ($P < 0.001$). Weight loss occurred with both treatments, but was greater with EBID. Adverse events ($\geq 10\%$, either group) were nausea, injection-site induration, dyslipidemia and vomiting. Injection-site induration was more frequent with EQW, whereas nausea, vomiting and hypoglycemia were less frequent. One episode each of major hypoglycemia (EBID) and pancreatitis (EQW) were reported.

Conclusion: In this population, EQW and EBID showed efficacious glucose and weight control; safety and tolerability were consistent with observations in non-Asian patients. This trial was registered with ClinicalTrials.gov (no. NCT00917267). (J Diabetes Invest, doi: 10.1111/j.2040-1124.2012.00238.x, 2013)

KEY WORDS: Asian, Exenatide, Type 2 diabetes

INTRODUCTION

Diabetes is an increasingly prevalent chronic condition in Asia. India, China and Japan are ranked among the top 10 countries with the highest estimated number of patients with diabetes[1]. Although less likely than Western populations to be overweight or obese[2,3], Asian populations have a greater tendency for more visceral fat and less muscle mass[4,5], characteristics that increase the risk for insulin resistance and diabetes at a lower body mass index (BMI). Rising insulin resistance is met with inadequate β-cell response among Asian adults with relatively low bodyweight and BMI[6,7], including those with normal glucose tolerance[8]. These factors help to explain the substantial prevalence of diabetes in Asia despite low obesity rates.

First-line treatment for type 2 diabetes generally includes oral antihyperglycemic medications (OAMs). Metformin (MET) is typically recommended – largely due to the benefits observed in overweight patients[9,10] – although sulfonylureas (SUs) are the most commonly prescribed OAMs in Asia, and thiazolidinediones (TZD) are also used[11,12]. Higher use of SUs might be due, in part, to the metabolic attributes and low BMI of Asians, relative to non-Asians, with diabetes. Despite treatment with OAMs, patients eventually experience increasingly inadequate glycemic control as the duration of diabetes increases[13–15], and must transition to more advanced therapy to maintain glycemic targets[9,10].

Exenatide, a glucagon-like peptide-1 (GLP-1) receptor agonist indicated for treatment of type 2 diabetes in adults not achieving adequate glycemic control on maximally tolerated doses of OAMs, has multiple glucoregulatory effects, including enhanced glucose-dependent insulin secretion, suppression of inappropriately elevated postprandial glucagon secretion and slowing of gastric emptying[16–18]. The exenatide twice-daily

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(EBID) formulation has been shown to improve glycemic control, as well as other metabolic measures, with a similar safety profile[19–25] when used adjunctively with MET and/or a SU in Asian[19–21] and non-Asian patients with type 2 diabetes[22–25].

An extended-release formulation of exenatide (EQW), developed as a once-weekly injection, has also been shown to improve glycemic control and other metabolic measures, without increasing the risk of clinically significant hypoglycemia[26–30].

The present study assessed whether EQW 2-mg given once weekly is non-inferior to EBID 10-μg given twice daily with regard to glycemic control and safety after 26 weeks of treatment in Asian patients with type 2 diabetes.

MATERIALS AND METHODS

Participants, Materials and Methods

Patients were male and female, aged ≥ 20 years and had inadequate glycemic control (hemoglobin A1c [HbA_{1c}] ≥ 7 and $\leq 11\%$) while treated with a stable dose of OAMs (i.e. MET, SU, TZD, MET plus SU, MET plus TZD, or SU plus TZD) for at least 3 months before screening. Before study entry, patients were required to have a stable bodyweight, and BMI ≥ 21 and ≤ 35 kg/m^2. Female patients were not pregnant. Patients were excluded if they had other clinically significant medical conditions or had taken excluded medications within 90 days of screening, or had ≥ 2 episodes of severe hypoglycemia within 6 months of screening.

Patients from 49 sites in China, India, Japan, South Korea and Taiwan participated (August 2009 to September 2010). The clinical protocol was approved by an ethical review board at each study site and was in accordance with the ethical principles described in the Declaration of Helsinki. Before study start, informed consent was obtained from each patient in compliance with the International Conference on Harmonization Guideline on Good Clinical Practice.

This randomized, open-label, multicenter, comparator-controlled, two-arm study was designed to evaluate glucose control and safety in patients with type 2 diabetes after 26 weeks of treatment with EQW vs EBID. In the 2-week screening period, patients were screened for eligibility and discontinued from alpha glucosidase inhibitors or meglitinide derivatives. Patients were stratified by country and OAM treatment (±SU), and randomized by computer-generated random sequence to add either EQW or EBID to current therapy. EBID patients subcutaneously injected 5 μg twice-daily for the first 4 weeks, followed by EBID 10 μg twice-daily for the remaining 22 weeks, while EQW patients injected 2 mg once-weekly for 26 weeks. All patients continued the same doses of MET or TZD (SU dosages were decreased to the country-specific minimum for the duration of the study). A follow-up visit occurred approximately 10 weeks after the last study treatment visit.

If hypoglycemia occurred, SU treatment could be discontinued, but not restarted. Protocol-required reasons for study withdrawal included need for treatment with another antidiabetes agent, MET or TZD dosage change for >14 days, insulin use for >7 days, evidence of pancreatitis, a serious adverse event (SAE) or abnormal laboratory value that warranted withdrawal.

Study Outcome Measures

The primary outcome measure was the difference between EQW 2 mg and EBID 10 μg in change in HbA_{1c} from baseline to week 26. Secondary outcome measures included the proportion of patients achieving $HbA_{1c} \leq 7$, ≤ 6.5 and $\leq 6.0\%$; fasting serum glucose (FSG); 6-point self-monitoring blood glucose (SMBG; before and after morning, midday, and evening meals); change in bodyweight; fasting serum lipids; and homeostasis model assessment of β-cell function (HOMA-B) and insulin sensitivity (HOMA-S). Incidence of hypoglycemic events, and changes in laboratory values and vital signs were also measured. Treatment-emergent adverse events (TEAEs) were assessed at each visit, regardless of relationship to study drug.

Statistical Analysis

Analyses were carried out using SAS version 9.1 (SAS Institute, Cary, NC, USA). In the primary analysis, if non-inferiority was achieved, a test for superiority was carried out. A sample size of approximately 306 patients per treatment arm was estimated to provide 98% power to detect a true difference of 0.4% in change in HbA_{1c} from baseline ($\alpha = 0.05$; two-sided t-test). All analyses were carried out using the intent-to-treat (ITT) population, defined as patients who took at least one dose of study drug. HbA_{1c} values are shown as National Glycohemoglobin Standardization Program values. The primary efficacy outcome was analyzed by maximum likelihood-based, mixed-model repeated measures (MMRM) analysis of covariance (ANCOVA) with treatment, baseline HbA_{1c}, country, OAM stratum at screening, week of visit and treatment-by-week interaction as fixed effects, and with patient and error as random effects. Least-squares means (LSMs) of the treatment difference and 95% confidence intervals (CI) estimated the magnitude of treatment difference. The LSMs difference estimated the magnitude of treatment effect. Non-inferiority of EQW was concluded if the upper limit of the 95% CI for the treatment difference was <0.4%. Superiority was concluded if the upper limit of the 95% CI was <0.

The proportion of patients achieving $HbA_{1c} \leq 7$, ≤ 6.5 and $\leq 6.0\%$ at week 26 was compared between treatment groups using a Cochran–Mantel–Haenszel test that controlled for country and SU use. The remaining treatment group comparisons were made using a MMRM ANCOVA model similar to that described earlier; the baseline values of the dependent variable were covariates. Triglyceride, HOMA-B and HOMA-S values were logarithmically transformed for the analysis of treatment group differences.

Clinical laboratory evaluations and incidences of TEAEs, SAEs and hypoglycemic episodes were summarized at baseline, end-point and each visit. Treatment-emergent adverse events were defined as those that occurred after the patient had

received the first dose of exenatide. Minor hypoglycemia was defined as signs or symptoms of hypoglycemia with a concurrent blood glucose concentration of 54 mg/dL that either resolved on its own or with self-treatment. Major hypoglycemia was defined as any episode with symptoms of hypoglycemia that resulted in loss of consciousness or seizure, which showed prompt recovery in response to administration of glucagon or glucose, or a documented blood glucose concentration of 54 mg/dL that required assistance from another person because of severe impairment in consciousness or behavior.

RESULTS

Participant Disposition
A total of 681 patients were randomized; three patients discontinued before receiving study medication. A total of 678 (EQW = 340; EBID = 338) patients received at least one dose of exenatide (ITT population; Figure 1). On completion of treatment, 267 (78.5%) patients in the EQW group and 278 (82.2%) patients in the EBID group entered the 10-week follow-up period; 516 (94.7%) patients completed follow up (EQW = 258; EBID = 258).

Baseline Demographics and Clinical Characteristics
On average, patients were aged 55–56 years, had a history of diabetes >7 years and HbA_{1c} of 8.7% (Figure 1). Most patients (EQW = 77.6%; EBID = 79.0%) were taking SU alone or in combina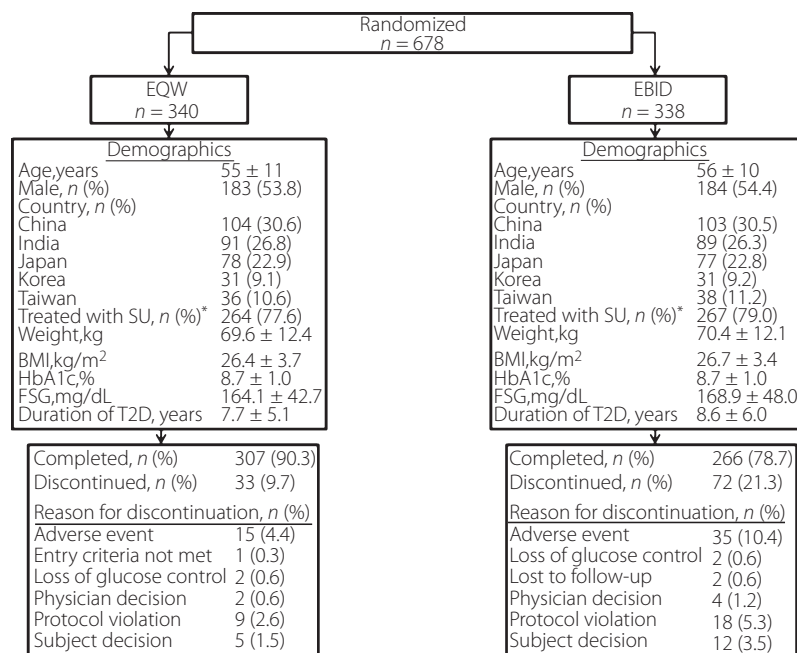tion with another OAM. Baseline weight (EQW = 69.6 kg; EBID = 70.4 kg) and BMI (EQW = 26.4 kg/m^2; EBID = 26.7 kg/m^2) were similar between groups.

Changes in Glycemic Control
At end-point, EQW was superior to EBID in reducing HbA_{1c}, with a −0.31% LSM treatment difference (95% CI −0.49%, −0.14%). HbA_{1c} change from baseline was significantly greater with EQW vs EBID at the 26-week end-point (LSM ± standard error, −1.43 ± 0.07% vs −1.12 ± 0.07%, $P < 0.001$; Figure 2a). Improvements in HbA_{1c} were observed with both treatments at each visit; EQW treatment resulted in significantly lower LSM HbA_{1c} compared with EBID at week 12 (7.28 ± 0.05% vs 7.56 ± 0.05%, $P < 0.001$), week 20 (7.15 ± 0.06% vs 7.51 ± 0.06%, $P < 0.001$) and week 26 (7.26 ± 0.07% vs 7.57 ± 0.07%, $P < 0.001$; Figure 2b).

A higher proportion of EQW patients achieved HbA_{1c} targets of ≤ 7.0% ($P = 0.003$), ≤ 6.5% ($P < 0.001$) or ≤ 6.0% compared with EBID patients ($P = 0.003$; Figure 2c). Each analysis included only patients whose baseline HbA_{1c} was above the specified target.

More improvement in HbA_{1c} was observed in patients receiving EQW compared with those receiving EBID among patients with HbA_{1c} ≥ 9% at baseline (LSM treatment difference: −0.29%; 95% CI −0.54, −0.03; $P = 0.027$). Similarly, more improvement in HbA_{1c} was observed in patients receiving EQW compared with those receiving EBID among patients with HbA_{1c} <9% at baseline (−0.31%; [95% CI −0.51, −0.11; $P = 0.002$).

Figure 1 | Patient disposition and baseline characteristics. Data are mean ± standard deviation, unless otherwise noted. BMI, body mass index; EBID, exenatide twice daily; EQW, exenatide once-weekly; FSG, fasting serum glucose; HbA_{1c}, hemoglobin A1c; MET, metformin; SU, sulfonylurea; T2D, type 2 diabetes; TZD, thiazolidinedione.
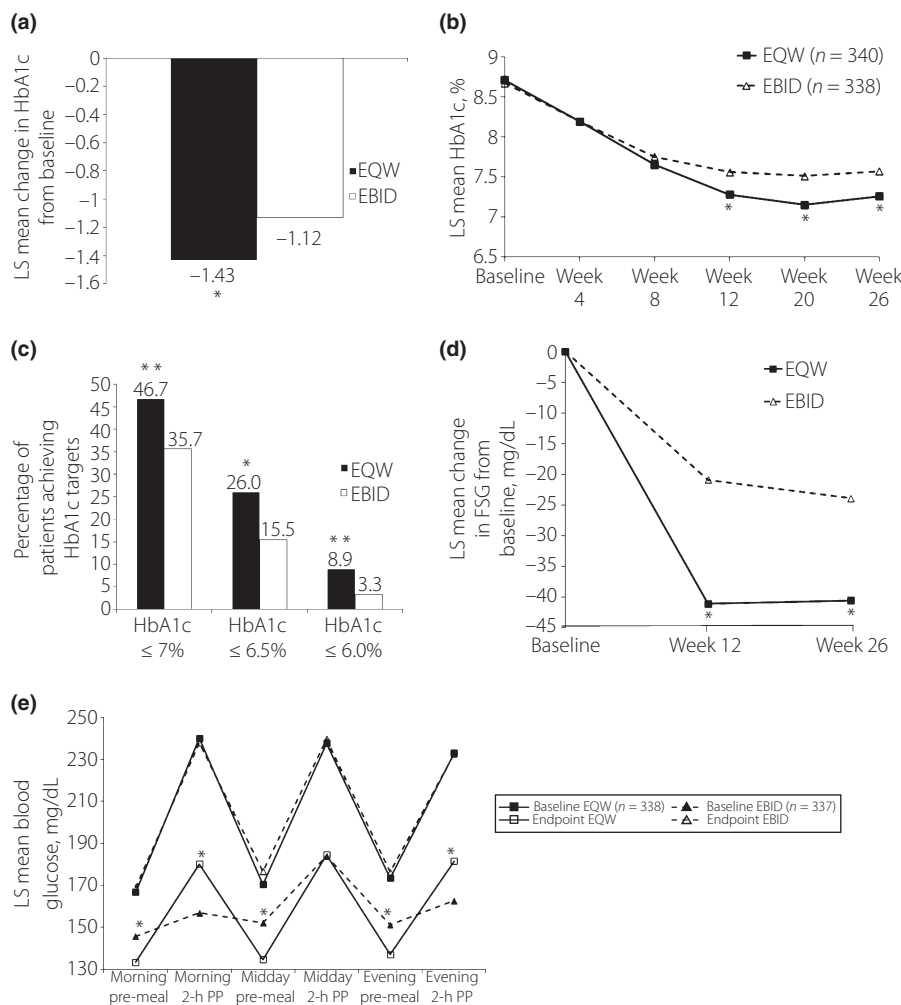
Figure 2 | Glycemic parameters in patients treated with oral antihyperglycemic medications plus exenatide once-weekly (EQW) or exenatide twice daily (EBID). (a) Change in hemoglobin A1c (HbA$_{1c}$) from baseline at week 26. *$P < 0.001$, EQW vs EBID. (b) HbA$_{1c}$ values over the course of the study. *$P < 0.001$, EQW vs EBID. (c) Percentage of patients reaching target HbA$_{1c}$ at week 26. *$P = 0.003$; **$P < 0.001$, EQW vs EBID. (d) Change in fasting serum glucose (FSG) from baseline at week 26. (e) Changes from baseline to end-point on 6-point self-monitoring blood glucose profiles. *$P < 0.001$, EQW vs EBID. LS, least squares; PP, postprandial.

Baseline FSG concentrations were similar between groups (Figure 1). Significant decreases from baseline were observed in both groups at week 26 (EQW = -40.57 ± 2.36 mg/dL; EBID = -23.90 ± 2.45 mg/dL, $P < 0.001$; Figure 2d). These reductions were significantly greater in patients treated with EQW compared with EBID at week 12 (-20.21 ± 2.85 mg/dL, $P < 0.001$) and week 26 (-16.67 ± 2.97 mg/dL, $P < 0.001$).

The 6-point SMBG profile of both treatment groups significantly improved from baseline on all measures at each time point ($P < 0.001$ for all measures, both groups; Figure 2e). At the 26-week end-point, the EQW group had a significantly greater reduction from baseline than the EBID group at morning premeal (-36 ± 2 mg/dL vs -25 ± 2 mg/dL, $P < 0.001$), midday premeal (-39 ± 3 mg/dL vs -24 ± 3 mg/dL, $P < 0.001$) and evening premeal (-40 ± 2 mg/dL vs -28 ± 3 mg/dL,

$P < 0.001$). Significantly greater reductions in postprandial blood glucose concentrations were observed in the EBID group compared with the EQW group, 2-h post-morning meal (-87 ± 3 mg/dL vs -63 ± 3 mg/dL, $P < 0.001$) and 2-h post-evening meal (-75 ± 3 mg/dL vs -55 ± 3 mg/dL, $P < 0.001$). Both groups had similar reductions in postprandial blood glucose concentrations at 2-h post-midday meal (EQW = -58 ± 3 mg/dL vs EBID = -60 ± 3 mg/dL, $P = 0.548$).

Bodyweight Changes and Bodyweight vs HbA$_{1c}$

Significant decreases from baseline in weight were observed with both treatments at each visit (Figure 3a). At the 26-week end-point, the EBID group had a significantly greater LSM weight loss (-2.45 ± 0.16 kg) compared with the EQW group (-1.63 ± 0.16 kg, $P < 0.001$). The distribution of patients,
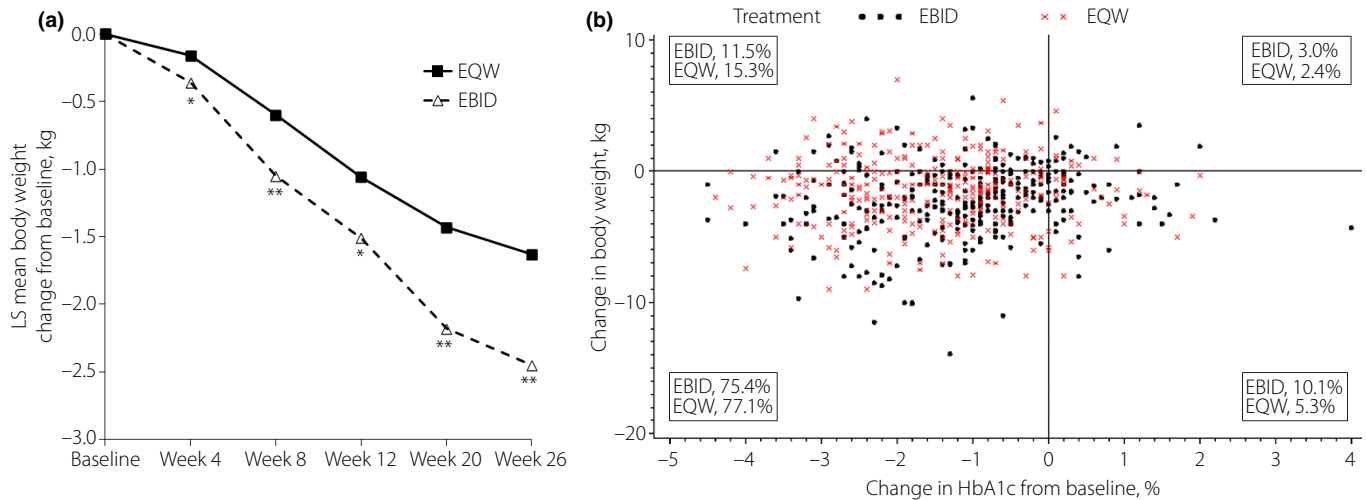
Figure 3 | (a) Effects of exenatide once-weekly (EQW) or exenatide twice daily (EBID) on bodyweight over the 26-week treatment period. *$P < 0.05$; *$P < 0.001$, EQW vs EBID. (b) Scatterplot of change in hemoglobin A1c (HbA$_{1c}$) vs change in bodyweight from baseline to week 26. LS, least squares.

based on changes in both HbA$_{1c}$ and bodyweight, is shown in Figure 3b. Significant reductions in HbA$_{1c}$ were observed with both treatments, independent of concomitant weight loss. Patients with baseline BMI $\geq$ 25 kg/m^2 experienced greater mean weight decrease (EQW = −1.75 kg; EBID = −2.33 kg) than patients with BMI < 25 kg/m^2 (EQW = −1.26 kg; EBID = −1.95 kg). At end-point, weight decrease was greater with EBID compared with EQW for both BMI groups.

Cardiovascular and Metabolic Measures

All fasting serum lipid values were similar between groups at end-point (Table 1). Significant reductions from baseline were observed for total cholesterol and low-density lipoprotein cholesterol with EQW and EBID. No notable changes from baseline were observed for high-density lipoprotein cholesterol or triglycerides with either treatment.

Changes from baseline to end-point for high-sensitivity C-reactive protein (hsCRP), waist-to-hip ratio, urinary albumin-to-creatinine ratio and blood pressure were similar between groups, with both treatment groups showing decreases in systolic and diastolic blood pressure. Mean heart rate increased in the EQW group compared with the EBID group at end-point; no other cardiovascular measures differed between the two groups.

Pancreatic β-Cell Function and Insulin Sensitivity

At end-point, the EQW group had significantly increased β-cell function, as measured by the ratio of end-point to baseline HOMA-B (1.59 ± 0.06), compared with EBID (1.21 ± 0.05, $P < 0.001$). The EBID group had a significant increase in insulin sensitivity, as measured by HOMA-S (1.18 ± 0.04), compared with the EQW group (1.08 ± 0.03, $P = 0.026$).

Safety and Tolerability

Gastrointestinal events were the most frequently reported TEAEs, and included nausea, vomiting and diarrhea (Table 2). Nausea and vomiting were highest from week 4 to week 8 for both treatment groups, and decreased in frequency as the study progressed. Most events were mild or moderate in intensity; however, one EQW-treated patient had a SAE of acute gastritis, which resolved when treated with injectable anti-emetics. The EQW group reported higher incidences of injection-site reactions, including injection-site induration, injection-site pruritus and injection-site nodule ($n = 74$; 21.8%) compared with the EBID group ($n = 11$; 3.3%). At end-point, 112 of 266 patients (42.1%) in the EQW group and 121 of 276 patients (43.8%) in the EBID group had TEAEs that continued into the 10-week follow-up period. The TEAEs that were still ongoing in $\geq 2\%$ of patients in either treatment group by the end of the 10-week follow-up period were dyslipidemia, microalbuminuria, diabetic nephropathy, hyperchlorhydria, injection-site nodule, hyperlipidemia, hyperlipasemia and hypertension. The most frequent SAE overall by system organ class was for infections and infestations (EBID: 2 [0.6%], EQW: 3 [0.9%]). There was not a predominant (>1.0%) SAE by preferred term in either group. The following SAEs were reported: EBID (acute myocardial infarction, aortic aneurysm, tendon rupture, ankle fracture, acute pyelonephritis, vitreous hemorrhage, transient global amnesia, ileus, rotator cuff syndrome, pneumonia) and EQW (cerebral infarction, fall, lower limb fracture, vaginal hemorrhage, acute pancreatitis, increased blood calcitonin, bronchopneumonia, diabetic ketoacidosis, gastritis, cerebral artery occlusion, chronic sinusitis, coronary artery disease, pneumonia haemophilus, small intestine hemorrhage, atrial tachycardia, diplegia). No deaths were reported.

Table 1 | Cardiovascular and metabolic outcomes

	EQW (n = 340)		EBID (n = 338)		P-value for treatment comparison
	Baseline	Change from baseline	Baseline	Change from baseline	
Total cholesterol (mg/dL)	182.08 (2.11)	−9.41 (1.96)‡	183.97 (2.12)	−8.10 (2.04)‡	0.609
HDL (mg/dL)	48.83 (0.68)	−0.11 (0.41)	48.69 (0.69)	−0.48 (0.43)	0.476
LDL (mg/dL)	102.65 (1.84)	−7.30 (1.48)‡	104.67 (1.83)	−8.13 (1.53)‡	0.653
Triglycerides (mg/dL)†	136.95 (4.00)	0.97 (0.02)	136.57 (3.77)	0.97 (0.03)	0.807
Heart rate (b.p.m.)	76.48 (0.52)	3.03 (0.53)‡	76.86 (0.52)	0.77 (0.56)	0.001
Systolic blood pressure (mmHg)	131.09 (0.84)	−5.41 (0.82)‡	131.59 (0.84)	−5.38 (0.86)‡	0.974
Diastolic blood pressure (mmHg)	78.80 (0.51)	−1.62 (0.52)§	79.51 (0.51)	−2.26 (0.55)‡	0.349
hsCRP (mg/dL)†	0.13 (0.01)	0.85 (0.06)	0.13 (0.01)	0.78 (0.05)	0.368
Urinary albumin-to-creatinine ratio†	0.02 (0.00)	0.78 (0.05)	0.02 (0.00)	0.72 (0.05)	0.370
Waist-to-hip ratio	0.93 (0.00)	0.00 (0.00)	0.94 (0.00)	0.00 (0.00)	0.364

Data are presented as least-squares (LS) mean (standard error) unless otherwise noted. †Geometric mean is presented at baseline and the geometric LS mean (standard error) ratio of week 26 to baseline is presented as change from baseline. ‡$P < 0.001$, difference from baseline; §$P = 0.002$, difference from baseline. b.p.m., Beats per minute; HDL, high density lipoprotein; hsCRP, high-sensitivity C-reactive protein; LDL, low density lipoprotein.

More EBID-treated patients (10.4%) discontinued as a result of TEAEs than in the EQW group (4.4%). In EBID-treated patients, 12 (3.6%) and 6 (1.8%) discontinued because of nausea and vomiting, respectively, whereas no patients discontinued EQW because of nausea and 1 (0.3%) discontinued because of vomiting. The TEAEs most often cited as reasons for discontinuation with EQW were rash and injection-site nodule. For each of these events, two patients (0.6%) discontinued.

In each group, similar proportions of both antibody-positive and antibody-negative patients reported one or more TEAE in each group, and both antibody-positive and antibody-negative patients showed a significant decrease in HbA$_{1c}$ from baseline to end-point (Table 3). The majority of patients in both groups were taking a concomitant SU (Figure 1). Among patients

taking a SU, fewer in the EQW group experienced minor hypoglycemia relative to the EBID group (6.8% vs 12.0%, $P = 0.053$). The incidence of minor hypoglycemia was similar in EQW- vs EBID-treated patients who were not taking a SU (1.3% vs 1.4%). Symptoms of hypoglycemia were reported by fewer patients who were taking a SU in the EQW group, compared with the EBID group (19.7% vs 26.2%, $P = 0.080$). Of patients not taking a SU, 5.3% in the EQW group and 11.3% in the EBID group reported symptoms of hypoglycemia ($P = 0.234$). One EBID-treated patient taking a concomitant SU experienced an event of major hypoglycemia, which resolved when treated with i.v. glucose. The patient recovered promptly and completed the study without discontinuing the study drug.

Table 2 | Overview of treatment-emergent adverse events

	26-Week treatment period	
	EQW (n = 340)	EBID (n = 338)
≥ 1 SAE, n (%)	13 (3.8)	9 (2.7)
TEAEs, n (%) [in ≥ 5% patients]	229 (67.4)	250 (74.0)
Injection site reactions*	74 (21.8)	11 (3.3)
Nausea	37 (10.9)	89 (26.3)
Dyslipidemia	34 (10.0)	33 (9.8)
Diarrhea	33 (9.7)	28 (8.3)
Vomiting	28 (8.2)	41 (12.1)
Constipation	20 (5.9)	24 (7.1)
Microalbuminuria	15 (4.4)	18 (5.3)
Decreased appetite	16 (4.7)	32 (9.5)

*Injection-site reactions include induration, pruritus and nodule. EBID, exenatide twice daily; EQW, exenatide once weekly; SAE, serious adverse event; TEAEs, treatment-emergent adverse events.

Table 3 | Change in hemoglobin A1c and adverse event reporting by anti-exenatide antibody status

	Anti-exenatide antibody status	
	Negative	Positive
EQW		
n	130	206
≥ 1 TEAE, n (%)	86 (66.2)	142 (68.9)
Change in HbA$_{1c}$	−1.67 ± 0.10*	−1.28 ± 0.09*
EBID		
n	226	107
≥ 1 TEAE, n (%)	170 (75.2)	77 (72.0)
Change in HbA$_{1c}$	−1.15 ± 0.09*	−1.15 ± 0.11*

Data are presented as least-squares mean (SE) unless otherwise noted. *$P < 0.001$, difference from baseline. EBID, exenatide twice daily; EQW, exenatide once weekly; HbA$_{1c}$, hemoglobin A1c; TEAE, treatment-emergent adverse event.

Mean total amylase and lipase concentrations increased slightly, but remained within normal limits for both treatment groups. One patient who entered the study with elevated pancreatic enzyme concentrations and who was randomized to EQW treatment had further persistent increases in enzyme concentrations. A computed tomography scan was carried out, which showed the pancreas to be diffuse and mildly enlarged; acute pancreatitis was diagnosed based on this finding. The patient remained asymptomatic, except for increased enzyme concentrations, and was discontinued from the study. The patient was not hospitalized, and the event resolved without treatment.

Mean calcitonin concentrations remained within the normal range for both study arms. One EQW-treated patient had increased calcitonin (18.3–26.1 pg/mL, normal range 0–18.2 pg/mL). A high-resolution ultrasound scan of the thyroid was carried out and a small (<2 mm) clinically non-significant thyroid nodule was identified, for which no treatment was required.

DISCUSSION

The present study supports the general conclusions from previous studies that compared EQW and EBID, and in which continuous GLP-1 receptor stimulation achieved with EQW therapy showed superiority to EBID in reducing HbA_{1c} and other measures of metabolic control[29,30]. Over 26 weeks of treatment, EQW improved HbA_{1c} to a greater degree than EBID, and a higher proportion of patients achieved target $HbA_{1c} \leq 7$ and $\leq 6.5\%$, and reduced FSG. Morning, midday and evening premeal glucose levels were reduced during treatment with EQW compared with EBID, whereas morning and evening 2-h PPG levels were reduced with EBID compared with EQW treatment. Greater reductions in glucose in EQW-treated vs EBID-treated patients might be partly due to continuous exposure to exenatide with EQW, resulting in a greater reduction in FSG. The greater postprandial effects observed with EBID are also consistent with the observations of Drucker et al.[29] and might be due to different effects of EQW and EBID on gastric emptying[30]. Previous studies of EQW therapy in Japanese[28] and non-Asian patients[26,27,29,31,32], and EBID therapy in Asian[19–21] and non-Asian[22–25] patients have shown analogous improvements on similar glycemia measures. Insulin sensitivity, as measured by HOMA-S, was also improved with EBID relative to EQW. Conversely, the long-acting EQW formulation was associated with improved β-cell function, based on HOMA-B.

In the present study, both the EQW and EBID formulations resulted in consistent gradual weight loss, which was notable, as various OAMs used concomitantly in the study (e.g. SUs and TZDs) have been shown to cause weight gain[33]. In non-Asian populations, weight loss observed with exenatide has been similar with EQW and EBID formulations[29,31]. Among Japanese adults, bodyweight reduction with EQW[28] (−0.8 kg) and EBID[20,21] (−1.3 to −1.5 kg) have not been as great. This result might be partly attributed to the comparative leanness of Asian

patients with type 2 diabetes. However, it should be noted that SU use in the present study and the aforementioned Japanese study (approximately 70%) was much higher than in previous studies of non-Asian patients (approximately 30%) – this difference in SU use might also partly explain why bodyweight changes are less remarkable in the present study than previously reported. A small percentage of patients in each group gained weight and/or experienced increased HbA_{1c} during the present study. Because of biological variation, not all patients will respond to every diabetes treatment. Additionally, factors such as patient compliance with therapy, diet, exercise, illness due to other conditions and other factors might influence individual patient responses.

Minor hypoglycemia occurred primarily in patients using a concomitant SU, and the incidence was higher among EBID-treated than EQW-treated patients. Overall, these data were consistent with clinical trials comparing EQW and EBID in non-Asian patients[29,31]. Previous studies of EBID in predominantly non-Asian patients have shown an increased incidence of hypoglycemia when SUs are used concomitantly, which might be a product of increased susceptibility to hypoglycemia in SU-treated patients coupled with lower ambient glycemia.[22,34]

Both treatments were generally well-tolerated; 90% of patients who took EQW and 79% of patients who took EBID completed the 26-week study. The incidences of nausea and vomiting, the most common TEAEs in EBID-treated patients, were considerably lower with EQW treatment. These results are consistent with earlier comparative studies of EQW and EBID[29,31]. It has been suggested that gradual increases in plasma exenatide concentrations decrease the occurrence of gastrointestinal TEAEs[35]. The pharmacokinetic profile of EQW, characterized by a gradual rise in plasma exenatide concentrations reaching steady state at approximately 6–10 weeks[29] is consistent with the lower incidence of nausea and vomiting for EQW compared with EBID. A higher incidence of injection-site reactions was observed with EQW treatment. It is likely that some injection-site reactions are a result of the poly (D,L-lactide-co-glycolide) technology used in the EQW formulation and not as a result of the drug itself[36]. Although exenatide has been reported to positively influence blood lipids[21], several cases of dyslipidemia were reported in the present study. These cases were most likely pre-existing conditions that were undiagnosed before study entry and the condition was subsequently detected during the study.

As previously reported in patients taking exenatide[19–29,31,37], a subset of patients in both groups developed antibodies to exenatide, but both antibody-positive and antibody-negative patients showed a significant decrease in HbA_{1c} from baseline to end-point. A 10-week follow-up visit was included in the study design and was based on the detectable levels of exenatide that exist for approximately 8 weeks after the last 2-mg dose of EQW. No safety concerns emerged during the follow-up period, and the majority of TEAEs that continued at the end of

the treatment period resolved by the end of the follow-up period.

One limitation of the present study was the open-label design. Because patients were not blinded to the treatment they were receiving, patient expectations and adherence to therapy might have biased the results. Another limitation was the relatively short study duration. Finally, the present study focused only on five Asian subgroups – there is some indication in the literature that there might be racial/ethnic differences in the treatment of type 2 diabetes; thus, there is a need for more studies to evaluate the impact of treatments by racial/ethnic groups to clarify these differences.

The present randomized comparator-controlled study, carried out among Asian patients with type 2 diabetes, found that EQW was superior to EBID with regard to overall glycemic control. Both formulations resulted in weight loss, with EBID showing greater improvement than EQW. The long-acting EQW formulation was associated with a lower incidence of hypoglycemia, nausea and vomiting, but higher incidence of injection-site reactions compared with EBID. These findings might aid clinicians as they seek treatment options when OAM therapy fails to maintain adequate glycemic control in Asian patients with type 2 diabetes.

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