

Efficacy and Safety of Exenatide Once Weekly Versus Metformin, Pioglitazone, and Sitagliptin Used as Monotherapy in Drug-Naive Patients With Type 2 Diabetes (DURATION-4)

A 26-week double-blind study

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OBJECTIVE—To test the safety and efficacy of exenatide once weekly (EQW) compared with metformin (MET), pioglitazone (PIO), and sitagliptin (SITA) over 26 weeks, in suboptimally treated (diet and exercise) drug-naive patients with type 2 diabetes.

RESEARCH DESIGN AND METHODS—Patients were randomized to subcutaneous (SC) EQW 2.0 mg + oral placebo ($n = 248$), MET 2,000 mg/day + SC placebo ($n = 246$), PIO 45 mg/day + SC placebo ($n = 163$), or SITA 100 mg/day + SC placebo ($n = 163$) for 26 weeks. MET and PIO therapies were increased to maximum-tolerated dosages. Injections with EQW or placebo were administered weekly, while oral medication or placebo was administered daily.

RESULTS—Baseline characteristics were as follows: 59% men, 67% Caucasian, mean age 54 years, HbA_{1c} 8.5%, fasting serum glucose 9.9 mmol/L, body weight 87.0 kg, and diabetes duration 2.7 years. HbA_{1c} reductions (%) at 26 weeks (least-squares means) with EQW versus MET, PIO, and SITA were -1.53 vs. -1.48 ($P = 0.620$), -1.63 ($P = 0.328$), and -1.15 ($P < 0.001$), respectively. Weight changes (kg) were -2.0 vs. -2.0 ($P = 0.892$), $+1.5$ ($P < 0.001$), and -0.8 ($P < 0.001$), respectively. Common adverse events were as follows: EQW, nausea (11.3%) and diarrhea (10.9%); MET, diarrhea (12.6%) and headache (12.2%); PIO, nasopharyngitis (8.6%) and headache (8.0%); and SIT, nasopharyngitis (9.8%) and headache (9.2%). Minor (confirmed) hypoglycemia was rarely reported. No major hypoglycemia occurred.

CONCLUSIONS—EQW was noninferior to MET but not PIO and superior to SITA with regard to HbA_{1c} reduction at 26 weeks. Of the agents studied, EQW and MET provided similar improvements in glycemic control along with the benefit of weight reduction and no increased risk of hypoglycemia.

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The 2009 consensus algorithm from the American Diabetes Association (ADA)/European Association for the Study of Diabetes (EASD) recommends lifestyle changes and metformin (MET) as the initial (tier one, well-validated) treatment at diagnosis of type 2 diabetes (1). Common adjunctive treatments not associated with an increased risk of hypoglycemia when used as monotherapy include the thiazolidinedione, pioglitazone (PIO), the dipeptidyl peptidase-4 inhibitor, sitagliptin (SITA), and the glucagon-like peptide-1 receptor agonist exenatide twice daily (BID) (2–5). PIO and exenatide BID are included in the second tier (less well-validated) of preferred agents in the ADA/EASD algorithm. SITA is not indentified, but may be an appropriate choice for selected patients (1). These agents, commonly used only in MET-intolerant patients as monotherapy, have unique risks, benefits, and mechanisms.

Effective and safe monotherapy treatment options for patients unable to tolerate MET are limited. In the United States, exenatide BID is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes. A new formulation of exenatide (exenatide once weekly [EQW]) has been shown to result in greater improvements in glycemic control, with no increased risk of hypoglycemia and similar weight reduction compared with exenatide BID (6,7). This randomized trial (Diabetes Therapy Utilization: Researching Changes in A1C, Weight and Other Factors Through Intervention with Exenatide Once-Weekly [DURATION-4]) directly compared the safety and efficacy of EQW monotherapy versus MET, PIO, and SITA monotherapy in patients with type 2 diabetes who were suboptimally treated with diet and exercise but naive to antihyperglycemic drugs.

RESEARCH DESIGN AND METHODS

Outcomes

The aim of this study was to assess the efficacy of EQW compared with MET, PIO, and SITA, as measured by change in HbA_{1c} after 26 weeks. Secondary and exploratory measures included the proportion of patients achieving HbA_{1c} <7.0 and ≤6.5%, changes in fasting serum glucose, seven-point self-monitoring of blood glucose (SMBG), weight, serum lipids, homeostasis model assessment of pancreatic β-cell function (HOMA-B) and insulin sensitivity (HOMA-S), and safety and tolerability. Patient-reported outcomes were collected, including Impact of Weight on Quality of Life Questionnaire-Lite (IWQOL-Lite), Binge Eating Scale (BES), the Diabetes Treatment Satisfaction Questionnaire (DTSQ), and EuroQol-5 dimensions (EQ-5D).

Safety end points were adverse events, clinical laboratory assessments, vital signs, hypoglycemia, and antibodies to exenatide. Treatment-emergent adverse events were defined as those occurring or worsening after the first dose of study drug. Minor hypoglycemia was defined as signs or symptoms associated with blood glucose <3.0 mmol/L (either self-treated or resolved independently). Major hypoglycemia was classified as symptoms resulting in loss of consciousness or seizure that showed prompt recovery after administration of glucose, or documented blood glucose <3.0 mmol/L that required the assistance of another person because of severe impairment in consciousness or behavior. A subset, defined as symptoms of hypoglycemia, was not confirmed by blood glucose measurement.

Sample size determination

The protocol specified that 822 patients be enrolled, with at least 740 patients (10% dropout before first HbA_{1c} collection) available for primary analysis. A sample of 740 patients (222 EQW and MET, 148 PIO and SITA) would provide ~90% power to detect true differences in HbA_{1c} change of 0.4% (EQW vs. MET), 0.5% (EQW vs. PIO), and 0.5% (EQW vs. SITA), respectively (two-sided *t* test significance of 0.05 and common SD of 1.2%) (6). A predefined noninferiority margin of 0.3% and sample size of 444 patients would provide 74% power to test the noninferiority of EQW versus MET, and a sample size of 370 would provide 65% power to test the noninferiority of EQW versus PIO (and SITA).

Patients

A total of 820 patients in 22 countries participated between November 2008 and June 2010. Adults with type 2 diabetes met the following inclusion criteria: HbA_{1c} 7.1–11.0%, BMI 23–45 kg/m², and history of stable weight. Patients were excluded if treated with any antihyperglycemic drug for >7 days within 3 months of screening. Antihypertensive and lipid-lowering medication changes were only made if medically required.

Study design

Randomization was determined by computer-generated random sequence using an interactive voice response system. Treatment assignments were stratified by country. MET and PIO dosages were increased in weekly increments up to target doses of 2,000 and 45 mg/day, respectively. MET could be increased up to 2,500 mg/day based on glycemic control. Standard diet and exercise counseling was provided in each treatment group. Following 26 weeks, patients stopped study treatment and were allowed to follow diabetes regimens deemed appropriate by the investigator, with the exception of exenatide BID. Patients returned to the study sites 10 weeks after study end for collection of additional safety data.

Statistical analysis

Data were reported for randomized patients who received at least one dose of the study drug (intent-to-treat population). To control family-wise error within 0.05, the Bonferroni-Hommel gate-keeping procedure was used to test hypotheses. Three noninferiority hypotheses (EQW is inferior to MET, PIO, and SITA) were tested first using the Bonferroni test (noninferiority margin 0.3%, Bonferroni-adjusted significance of 0.0167). If any null hypothesis was rejected (i.e., noninferiority was established), the corresponding superiority hypothesis was tested using the Hommel test (8) and decision matrix algorithm (9). The nominal significance level based on Hommel adjustment was between 0.0167 and 0.05 depending on the noninferiority hypotheses rejected.

The primary end point was tested using a maximum likelihood-based mixed-model repeated-measures (MMRM) ANCOVA with change in HbA_{1c} as the dependent variable; treatment, baseline HbA_{1c}, country, week of visit, and treatment by week interaction as fixed effects; patient and error as random effects; and an unstructured variance/covariance matrix.

All scheduled postbaseline measurements were included, with no imputation of missing data. Least-squares (LS) estimates and CIs of the treatment differences between EQW and the three oral comparators were presented. The differences were based on the estimate at 26 weeks of EQW minus the estimate for each comparator at 26 weeks. SEs were also presented. Secondary end points were tested using similar MMRM analyses. Analyses of patient-reported outcomes were performed without adjustment for multiple statistical testing.

The original primary analysis excluded unscheduled postbaseline observations for unexpected early discontinuations; therefore, a modified analysis was completed, including all postbaseline observations. This modified MMRM analysis was performed after database lock when it was determined that the original analysis excluded patients who discontinued before week 8. All statistical analyses were performed using SAS Version 9.1 (SAS Institute, Cary, NC).

RESULTS

Patients

Of 820 intent-to-treat patients, 696 (84.9%) completed the 26-week treatment period and 736 (89.8%) returned for 10-week safety follow-up (Fig. 1). Patient characteristics at baseline were similar among the treatment groups (Supplementary Table 1). By week 12, 87% of patients taking MET and 75% taking PIO had been titrated to or above target doses for each agent (PIO 45 mg/day, MET 2,000 mg/day, respectively). At week 16–26, patients were on stable doses: PIO (≥45 mg/day) 88% and MET (≥2,000 mg/day) 76%.

Glycemic control and weight

Mean baseline HbA_{1c} values ranged from 8.4 to 8.6% across treatment groups. Figure 2A presents the time course of HbA_{1c} change from modified MMRM analysis (intent-to-treat sample; all post-baseline observations included). This modified analysis demonstrated LS mean (SE) reductions in HbA_{1c} at 26 weeks of −1.53% (0.07%) with EQW; −1.48% (0.07%) with MET (*P* = 0.620 vs. EQW; 98.3% CI was −0.26 to 0.17); −1.63% (0.08%) with PIO (*P* = 0.328 vs. EQW; 98.3% CI was −0.15 to 0.35); and −1.15% (0.08%) with SITA (*P* < 0.001 vs. EQW; 98.3% CI was −0.62 to −0.13).

The LS mean (SE) HbA_{1c} at end point was 6.94 (0.07), 6.99 (0.07), 6.84 (0.08), and 7.32 (0.08) for EQW, MET, PIO, and

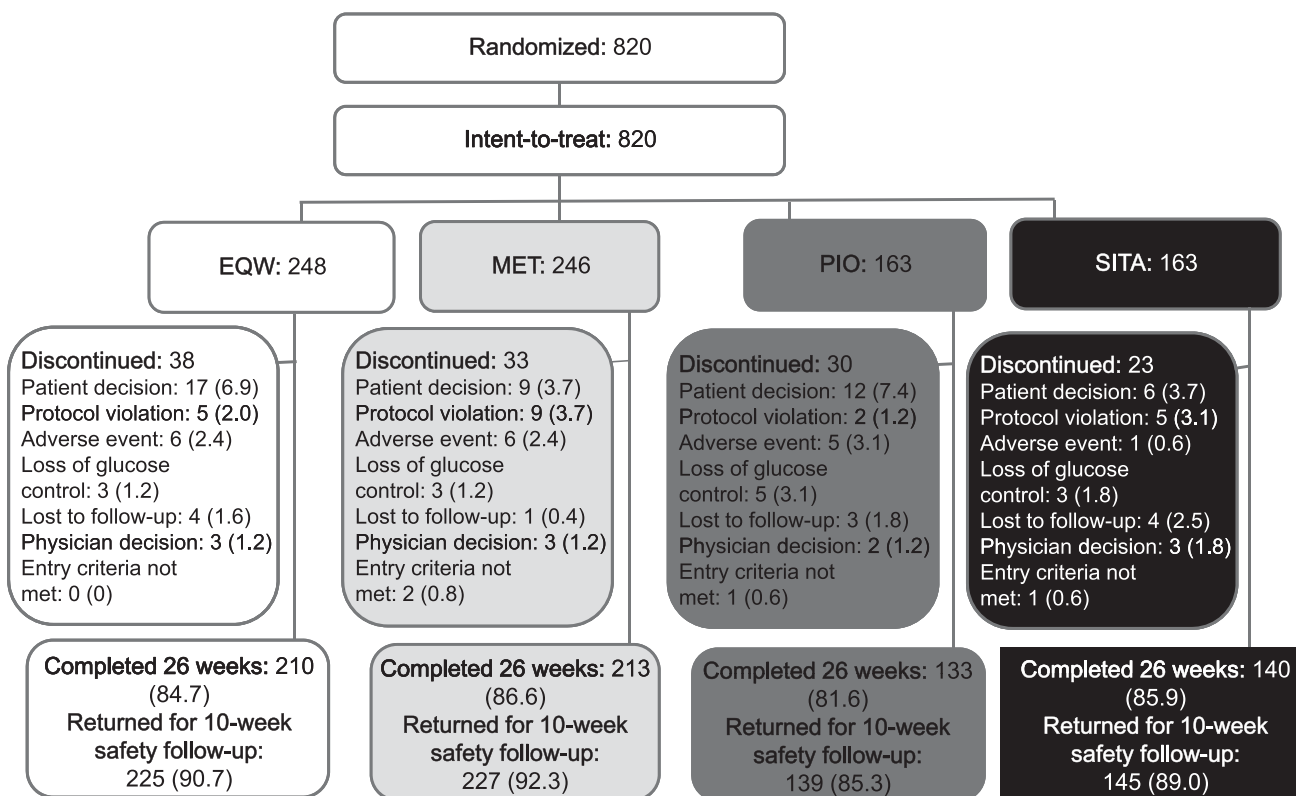


Figure 1—Disposition of all randomized patients. Data are presented as n or n (%) of patients.

SITA, respectively. The original primary analysis, which excluded post-baseline observations from patients who discontinued before week 8, showed LS mean (SE) reductions in HbA_{1c} of -1.56% (0.07%) with EQW; -1.52% (0.06%) with MET ($P = 0.609$ vs. EQW; 98.3% CI was -0.26 to 0.17); -1.73% (0.08%) with PIO ($P = 0.107$ vs. EQW; 98.3% CI was -0.08 to 0.41); and -1.17% (0.08%) with SITA ($P < 0.001$ vs. EQW; 98.3% CI was -0.63 to -0.16). Findings from original and modified primary analyses were consistent and demonstrated that EQW was noninferior to MET and SITA, but did not reach the noninferiority measure with PIO. Subsequent hypothesis testing concluded that EQW was superior to SITA, but not to MET.

Similar percentages of EQW-, MET-, and PIO-treated patients reached a target HbA_{1c} $<7.0\%$ (Fig. 2B). Significantly more patients treated with EQW versus SITA ($P < 0.001$) achieved HbA_{1c} $<7.0\%$ after 26 weeks. Moreover, significantly more patients treated with EQW achieved HbA_{1c} $\leq 6.5\%$ after 26 weeks, versus MET- and SITA-treated patients ($P = 0.004$ and $P < 0.001$, respectively).

LS mean baseline fasting serum glucose values ranged from 9.7 to 9.9 mmol/L across treatment groups. Reductions in

fasting serum glucose at 16 and 26 weeks were significantly greater in patients treated with EQW versus SITA (both $P < 0.001$). LS mean (SE) reductions in fasting serum glucose at 26 weeks were -2.3 mmol/L (0.1 mmol/L) in patients treated with EQW; -2.0 mmol/L (0.1 mmol/L) with MET ($P = 0.155$ vs. EQW); -2.6 mmol/L (0.2 mmol/L) with PIO ($P = 0.153$ vs. EQW); and -1.1 mmol/L (0.2 mmol/L) with SITA ($P < 0.001$ vs. EQW).

Mean seven-point SMBG profiles showed similar reductions in blood glucose from baseline to 26 weeks in EQW, MET, and PIO treatment groups (Supplementary Figs. 1A–C). There were no significant differences between EQW versus MET or PIO treatment groups with regard to changes from baseline for any of the seven time points or for daily mean SMBG; however, EQW was associated with greater mean reductions at all time points compared with SITA. Mean reductions in SMBG postmeal excursions after 26 weeks were similar among all treatment groups.

LS mean baseline weight values ranged from 85.9 to 88.6 kg. Weight decreased with EQW, MET, and SITA treatment, but increased with PIO treatment (Fig. 2C). Weight changes were

significantly different between EQW versus PIO and SITA starting at 4 and 8 weeks, respectively, and continued through 26 weeks (all $P \leq 0.003$). At 26 weeks, LS mean (SE) body weight changes were -2.0 kg (0.2 kg) with EQW; -2.0 kg (0.2 kg) with MET ($P = 0.892$ vs. EQW); $+1.5$ kg (0.3 kg) with PIO ($P < 0.001$ vs. EQW); and -0.8 kg (0.3 kg) with SITA ($P < 0.001$ vs. EQW). The percentage of patients with reductions in both body weight and HbA_{1c} was similar for EQW and MET; percentages were comparably lower with PIO and SITA (Supplementary Figs. 2A–D).

Pancreatic β -cell function and insulin sensitivity

β -Cell function, as measured by geometric mean HOMA-B (C-peptide), at baseline ranged from 51.0 to 54.4%. Mean (SE) HOMA-B (ratio of end point [last observation carried forward] to baseline) was significantly (all $P < 0.001$) improved in patients treated with EQW [$+1.8$ (0.06)] compared with MET [$+1.4$ (0.04)], PIO [$+1.3$ (0.05)], and SITA [$+1.3$ (0.04)]. Insulin sensitivity, as measured by geometric mean HOMA-S (C-peptide), at baseline ranged from 36.4 to 39.5%. Mean (SE) HOMA-S (ratio of end point [last observation carried forward] to baseline) was

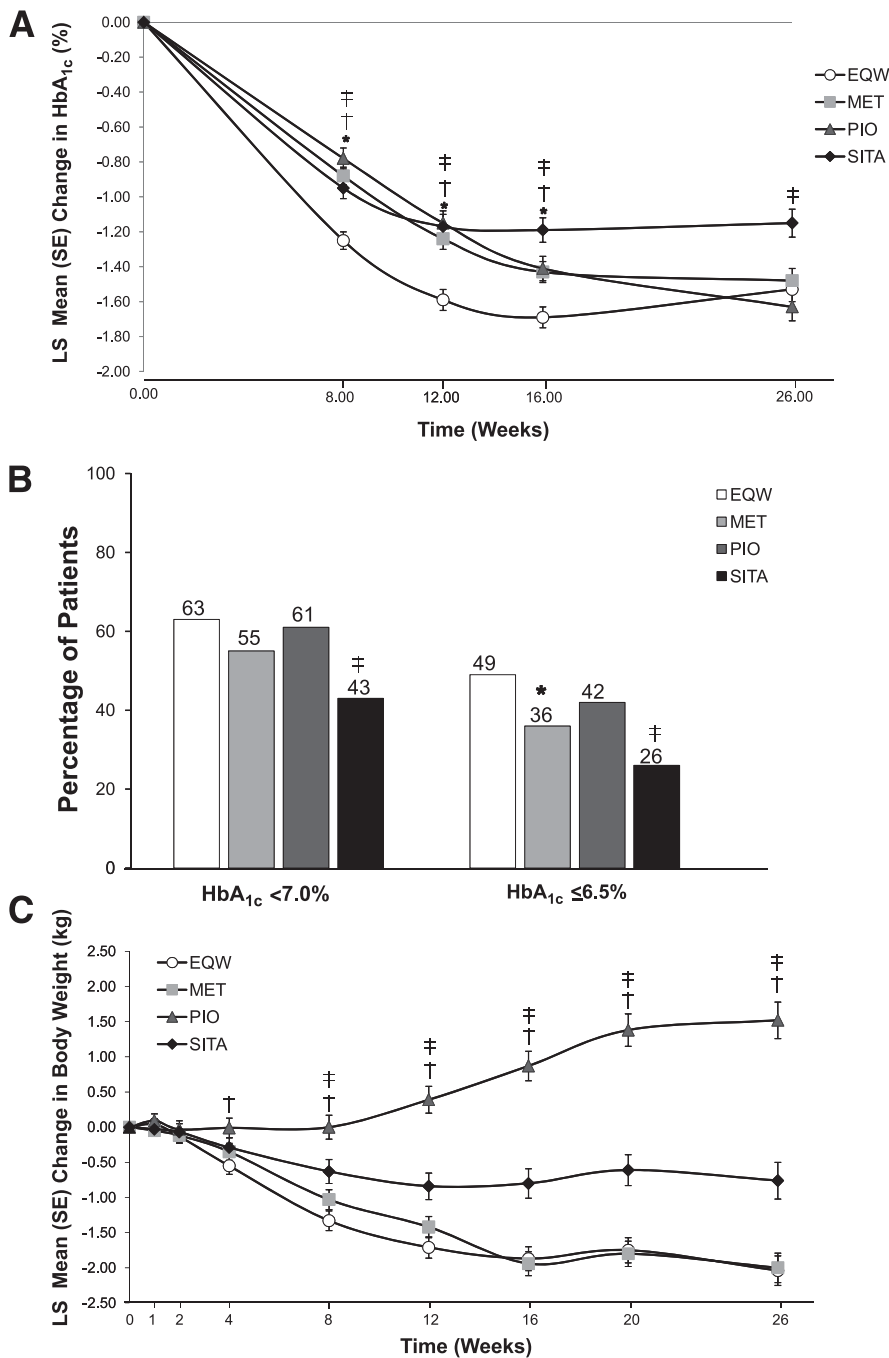


Figure 2—A: Changes in HbA_{1c} over 26 weeks. *Significant difference between MET and EQW (all $P \leq 0.002$). †Significant difference between PIO and EQW (all $P \leq 0.003$). ‡Significant difference between SITA and EQW (all $P < 0.001$). B: Percentages of patients achieving HbA_{1c} <7.0%, and $\leq 6.5\%$ at end point (last observation carried forward). *Significant difference between MET and EQW ($P = 0.004$). ‡Significant difference between SITA and EQW (all $P < 0.001$). C: Changes in weight over 26 weeks. †Significant difference between PIO and EQW (all $P \leq 0.003$). ‡Significant difference between SITA and EQW (all $P \leq 0.002$).

significantly (both $P < 0.001$) improved in patients treated with MET [+1.3 (0.04)] and PIO [+1.5 (0.06)] compared with EQW [+1.0 (0.03)]; change with EQW was similar to SITA [+1.0 (0.04), $P = 0.329$].

Safety and tolerability

Serious adverse events were reported in 1.6% (4/248), 5.3% (13/246), 5.5% (9/163), and 1.8% (3/163) of EQW-, MET-, PIO-, and SITA-treated patients, respectively,

during the treatment period. No serious adverse event was reported by more than one patient. One death, due to gastric adenocarcinoma, was reported during the 10-week follow-up in a patient receiving MET and was not considered by the investigator to be related to the study drug. One MET-treated patient experienced an adverse event of injection site nodule, considered serious for other medically significant reasons (i.e., psychological). The event was of mild severity and resolved without treatment.

Treatment-emergent adverse events reported by $\geq 5\%$ of patients in any group during the treatment period are shown in Table 1. All patients received injection, either with active EQW or placebo microsphere injection. Injection site nodules were more commonly reported with active EQW and placebo injection administered in the MET arm compared with placebo injection administered in the PIO and SITA arms. Nausea, the most common treatment-emergent adverse event with EQW, occurred in 11.3% of patients in this group. One EQW-treated patient withdrew because of nausea. Vomiting was reported in <5% of patients in all treatment groups, with incidences of 4.8% (12/248), 3.3% (8/246), 3.1% (5/163), and 1.8% (3/163) in EQW-, MET-, PIO-, and SITA-treated patients, respectively. Most treatment-emergent adverse events had resolved by the end of the 10-week follow-up period (Supplementary Table 2).

No patient had a major hypoglycemic episode during the treatment period of the study. The incidence of hypoglycemia unconfirmed by glucose measurement was low in all treatment groups: 5.2% (13/248), 4.1% (10/246), 3.7% (6/163), and 3.1% (5/163) of EQW-, MET-, PIO-, and SITA-treated patients, respectively. Minor (confirmed) hypoglycemia was limited to a small group of EQW-treated patients (5/248, 2.0%).

No clinically significant changes in fasting serum lipids were observed during the treatment period. LS mean (SE) systolic blood pressure reductions of -1.3 mmHg (0.8 mmHg), -1.7 mmHg (1.0 mmHg), and -1.8 mmHg (1.0 mmHg) were observed with EQW, PIO, and SITA treatment, respectively. Additionally, a reduction in diastolic blood pressure of -2.5 mmHg (0.6 mmHg) was observed with PIO treatment. Mean (SD) heart rate (bpm) increases were observed in the EQW [+1.5 (10.0)], MET [+0.3 (9.5)], and SITA [+0.5 (9.7)] groups; mean heart rate decreased in the PIO group [-1.7 (8.7)].

Table 1—Treatment-emergent adverse events reported in $\geq 5\%$ of patients in any treatment group

	EQW	MET	PIO	SITA
<i>n</i>	248	246	163	163
Headache	20 (8.1)	30 (12.2)	13 (8.0)	15 (9.2)
Diarrhea	27 (10.9)	31 (12.6)	6 (3.7)	9 (5.5)
Injection site nodule	26 (10.5)	25 (10.2)	6 (3.7)	11 (6.7)
Nasopharyngitis	19 (7.7)	11 (4.5)	14 (8.6)	16 (9.8)
Nausea	28 (11.3)	17 (6.9)	7 (4.3)	6 (3.7)
Dyspepsia	18 (7.3)	8 (3.3)	8 (4.9)	3 (1.8)
Constipation	21 (8.5)	8 (3.3)	3 (1.8)	4 (2.5)
Back pain	6 (2.4)	14 (5.7)	7 (4.3)	5 (3.1)
Arthralgia	13 (5.2)	3 (1.2)	5 (3.1)	3 (1.8)
Hypertension	3 (1.2)	3 (1.2)	12 (7.4)	3 (1.8)
Peripheral edema	0 (0)	1 (0.4)	12 (7.4)	1 (0.6)

Data are *n* (%) of intent-to-treat population.

No clinically significant changes in mean amylase, lipase, or calcitonin were observed during the treatment period. One SITA-treated patient with elevated lipase at screening experienced moderate chronic pancreatitis after 8 days of treatment and discontinued from study treatment.

Lower-titer ($<1/125$) and higher-titer ($\geq 1/625$) antibodies to exenatide at end point were observed in 43.1% (107/248) and 11.3% (28/248) of EQW-treated patients, respectively. Mean HbA_{1c} was reduced irrespective of antibody status: negative (-1.33%), positive lower (-1.51%), and positive higher (-1.02%) (Supplementary Table 3). Events with higher incidence in antibody-positive patients included injection site-related events (i.e., injection site erythema, injection site extravasation, injection site hematoma, injection site nodule, injection site pruritus, and injection site reaction). Injection site nodules are expected with microsphere injection and were not reported as an adverse event unless accompanied by symptoms such as pain, erythema, or pruritus.

Patients in all treatment groups had mean improvements from baseline in perceived treatment satisfaction, weight-related quality of life, and binge-eating behavior (Supplementary Tables 4–9). All treatments with the exception of PIO were associated with significant mean improvements in health status. Significant improvements in weight-related quality of life, binge-eating behavior, and health status were reported for patients treated with EQW compared with PIO.

CONCLUSIONS—Head-to-head comparative studies are needed to better inform

treatment decisions for type 2 diabetes (1), a disease for which there are numerous treatment options. This study evaluated the efficacy and safety of EQW monotherapy, in comparison with MET, PIO, and SITA monotherapy, in drug-naïve patients with type 2 diabetes. Treatment with EQW, MET, and PIO all resulted in improvements in glycemic control, achieving mean HbA_{1c} concentrations at 26 weeks of $<7\%$. EQW demonstrated superiority to SITA and noninferiority to MET but not to PIO with regard to HbA_{1c} reduction at 26 weeks. The lack of noninferiority of EQW monotherapy compared with PIO monotherapy was unexpected based on DURATION-2 study results, where EQW was superior to PIO on a background of MET (10), and the fact that the HbA_{1c} reduction with PIO was greater than that reported in other PIO studies with a similar baseline HbA_{1c} (2,3,11–14). Several disparate factors could have contributed to the incongruent outcomes, including differences in background therapy and mean duration of type 2 diabetes.

SITA treatment led to comparatively lesser glycemic improvement than the other agents, which supports the contention that the increase in plasma glucagon-like peptide-1 associated with dipeptidyl peptidase-4 inhibition is not as effective as pharmacological concentrations achieved with receptor agonism (15,16). The similar effects obtained with EQW monotherapy and MET monotherapy in terms of HbA_{1c} and body weight reductions support the appropriateness of considering MET as the first-line antihyperglycemic agent in type 2 diabetes. For example, the ADA/EASD recommends MET as a first-line agent; other antihyperglycemic agents

are added in stepwise fashion with disease progression after MET failure (1). Findings from DURATION-4 demonstrate that both EQW and PIO offer similar improvements in glycemia as MET, with one key difference between these agents being the effect on body weight. Thus, health care practitioners have more treatment choices for drug-naïve patients.

Clinicians are advised to consider multiple factors when treating patients with type 2 diabetes. Similar to previous studies evaluating PIO as monotherapy (3,13), patients treated with PIO in the current study gained weight. EQW and MET led to similar significant reductions in body weight after 26 weeks, whereas SITA led to a lesser reduction. Although variability based on study design and patient characteristics was expected, weight reduction observed in this study with EQW was on the lower end of the range (-2.0 to -3.7 kg) observed in previous DURATION studies (6,7,10,17). Conversely, reductions observed with SITA and MET in the current study tended to be greater than results from meta-analyses and recent monotherapy trials of similar duration (5,18–20). The potential for improvements in HbA_{1c} and body weight in studies with placebo injection therapy has been noted in a previous study of exenatide therapy (21). These data show that EQW and MET provided the best profile in terms of improving glycemic control as well as reducing weight, without increased risk of hypoglycemia, particularly important for treatment of overweight or obese patients with type 2 diabetes.

The findings with respect to safety and tolerability were consistent with previous studies, including the observance of gastrointestinal adverse events in patients treated with EQW and MET, and hypertension and peripheral edema with PIO (3,5,6,10,17,20,22–24). Most notably, the safety profile of EQW in the current trial was consistent with previous DURATION studies (6,10,17), with low rates of confirmed minor hypoglycemia and few patients discontinuing treatment due to nausea (one patient) and vomiting (zero patients). Less nausea and vomiting with EQW have previously been reported in head-to-head studies versus exenatide BID. In general, hypoglycemia incidence and incidence of serious adverse events were low across all treatment groups during the current study. The small percentage (2%) of patients experiencing minor hypoglycemia with EQW monotherapy was similar to that observed with EQW

adjunct to MET in previous clinical trials (0–3%) (6,7,10,17). Most treatment-emergent adverse events in this study had resolved by the end of the 10-week safety follow-up period, with few treatment-emergent adverse events starting during the safety follow-up.

There were several limitations to this study. First, patients were enrolled based on specific criteria and were followed according to the study schedule, which may not reflect real-world use. Second, no specific compliance data were collected; however, patient-reported outcomes indicated that both oral and injectable therapies were associated with increases in treatment satisfaction and quality of life in these previously drug-naïve patients. Additionally, 26 weeks is too short a study duration to evaluate long-term glycemic control, weight loss, and β -cell preservation (25). For example, potential implications of the upward shift in HbA_{1c}, observed in the EQW group between weeks 16 and 26 (Fig. 2A), cannot be assessed further without additional data points.

In conclusion, in these patients with type 2 diabetes who were naïve to anti-hyperglycemic therapy, all four treatments resulted in improvements in HbA_{1c}, and a majority of EQW-, MET-, and PIO-treated patients achieved a target HbA_{1c} of <7.0%. This study recognizes that guidelines typically recommend MET as the first agent used, because it is inexpensive and supported by long-term data. Of the agents studied, EQW and MET provided similar improvements in glycemic control along with the benefit of weight reduction and no increased risk of hypoglycemia. There were no unexpected findings with regard to safety or tolerability. Based on these 26-week data, EQW is a once-weekly dosing option for initial therapy. Longer-term studies will be required to assess the durability of the observations in this study.

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D.R.-J., R.M.C., M.H., A.K., and J.G.G. were principal clinical investigators for this trial. M.C. was the lead statistician. A.M.W. was the project manager, performed literature searches, and drafted sections of the manuscript. M.K.B. was involved in the study design and protocol development. All coauthors contributed to the interpretation of data, critically revised the manuscript for important intellectual content, and approved the version to be published. M.K.B. is the designated guarantor for this publication.

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