Safety and Efficacy of Once-Weekly Exenatide Compared With Insulin Glargine Titrated to Target in Patients With Type 2 Diabetes Over 84 Weeks

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OBJECTIVE—We recently reported that after 26 weeks, exenatide once weekly (EQW) resulted in superior A1C reduction, reduced hypoglycemia, and progressive weight loss compared with daily insulin glargine (IG) in patients with type 2 diabetes who were taking metformin alone or with sulfonylurea. This 84-week extension study assessed the long-term safety and efficacy of EQW versus IG.

RESEARCH DESIGN AND METHODS—This multicenter, open-label, randomized, two-arm, parallel trial assessed change in A1C, proportions of patients achieving A1C <7.0 and $\leq 6.5\%$, body weight, incidence of hypoglycemia, and overall safety.

RESULTS—Of 415 patients who completed 26 weeks, 390 (194 EQW and 196 IG patients) entered the extension study. At 84 weeks, A1C decreased from baseline (8.3%) by -1.2% for EQW vs. -1.0% for IG ($P = 0.029$). The proportions of patients who achieved end point A1C targets <7.0 and $\leq 6.5\%$ were 44.6% for EQW patients vs. 36.8% for IG patients ($P = 0.084$) and 31.3% for EQW patients vs. 20.2% for IG patients ($P = 0.009$), respectively. Patients taking EQW lost 2.1 kg of body weight, whereas those taking IG gained 2.4 kg ($P < 0.001$). Among patients taking metformin plus sulfonylurea, the incidence of minor hypoglycemia was 24% for EQW patients vs. 54% for IG patients ($P < 0.001$); among patients taking metformin alone, it was 8% for EQW patients vs. 32% for IG patients ($P < 0.001$). Among adverse events occurring in $\geq 5\%$ of patients, diarrhea and nausea occurred more frequently ($P < 0.05$) in the EQW group than in the IG group (12 vs. 6% and 15 vs. 1%, respectively).

CONCLUSIONS—After 84 weeks, patients treated with EQW continued to experience better glycemic control with sustained overall weight loss and a lower risk of hypoglycemia than patients treated with IG.

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Type 2 diabetes is characterized by progressive β-cell failure in the presence of insulin resistance. Glucagon-like peptide-1 (GLP-1) and its receptor agonists (GLP-1RAs) have the potential to counteract many metabolic defects of the type 2 diabetes phenotype. Indeed, GLP-1RAs, such as exenatide, have been shown to lower blood glucose by slowing gastric emptying, stimulating meal-related insulin secretion, and reducing glucagon secretion, thus improving pancreatic islet-cell function. Also, GLP-1RAs have been demonstrated to induce satiety, reduce food intake, and decrease body weight, the latter resulting in improved insulin sensitivity (1).

A previous study showed that 3-year exposure to the twice-daily formulation of the GLP-1RA exenatide resulted in sustained improvements in A1C and body weight (2). Likewise, long-term (52 weeks) treatment with the once-weekly formulation of exenatide (EQW) led to sustained improvements in glycemic control, in the presence of body weight reduction and low hypoglycemia event rates in patients with type 2 diabetes (3).

Previously, we showed that 26 weeks of EQW compared with insulin glargine (IG) in patients with type 2 diabetes who failed on oral blood glucose–lowering agents led to significant improvements in A1C compared with IG (4). Therefore, the objective of the current extension study was to assess, in a controlled setting, the long-term safety and efficacy of EQW versus IG by keeping patients in their originally assigned randomization arms for up to 84 weeks of therapy. This is the longest controlled clinical trial of EQW yet reported.

RESEARCH DESIGN AND METHODS

—This was a preplanned interim analysis (at 84 weeks) of an open-ended, controlled extension (expected to last at least 2.5 years) of a previously reported 26-week, phase 3, multicenter, open-label, randomized, two-arm, parallel, comparator-controlled trial in patients with type 2 diabetes failing to maintain sufficient glycemic control using metformin alone or in combination with sulfonylurea (4).

A detailed description of the research design and methods was previously reported (4). Patients were randomly assigned to add EQW (2 mg) or once-daily IG (10 IU/day, using the Initiate Insulin by Aggressive Titration and Education [INITIATE] dosing algorithm [5]) to their existing blood

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glucose–lowering regimens. Up to 48 weeks, investigators were required to keep patients on the metformin dose at which they entered the study. Investigators could decrease or stop sulfonylurea therapy if hypoglycemia was a concern and could subsequently return patients to a sulfonylurea dose as high as the dose used at baseline. After 48 weeks of treatment, investigators were allowed to increase the dose of the patients' current oral blood glucose–lowering medication or add other blood glucose–lowering medications to their treatment regimen, if needed. However, it is important to note that, for a clear interpretation of the long-term effect of the study treatments, data collected after any treatment regimen changes at 48 weeks or after (other than IG titration) were excluded from the analyses.

This study was conducted in accordance with the ethics principles stated in the Declaration of Helsinki, as revised in 2000 (6). The protocol was approved by an ethics review board at every study site, and all participants gave written informed consent.

The key efficacy measure was change in A1C from baseline to study treatment end point. End point was defined as the last nonmissing postbaseline measurement prior to any change to treatment regimen after week 48. Secondary measures included the following: time to failure to maintain glycemic control (defined as the time from randomization to the first visit after week 18 when A1C was ≥7.0%); proportions of patients achieving A1C <7.0 and ≤6.5%; change in body weight; fasting serum glucose; self-monitored blood glucose; and fasting serum lipids. Exploratory measures included urinary albumin-to-creatinine ratio, high-sensitivity C-reactive protein, homeostasis model assessment of β-cell function (using fasting blood glucose and fasting C-peptide concentrations), and waist and hip circumference. We also evaluated A1C by anti-exenatide antibody titer, as previously described (7). Antibody status was classified in two ways, either two-level status (positive or negative) or three-level status (positive-low [antibody titers <1/625], positive-high [antibody titers ≥1/625], or negative).

Safety measures included adverse events (AEs), clinical laboratory assessments, vital signs, and hypoglycemia. An episode of hypoglycemia was categorized as major if the patient had a documented blood glucose <3.0 mmol/L, necessitating the assistance of another person because of severe impairment in consciousness or behavior, or if the episode resulted in loss of consciousness or seizure that was promptly reversed upon administration of glucose.

Statistical analyses

All analyses were conducted using SAS (version 9.1). Analysis for the key efficacy measure was performed for the intention-to-treat (ITT) analysis set, which was defined as the group of patients who were randomly assigned to treatment and exposed to one or more doses of the study drug. The study was powered to detect A1C difference as described previously (4). We used a maximum likelihood–based, mixed-model, repeated-measures ANCOVA, with treatment, baseline A1C, country, oral blood glucose–lowering treatment stratum (use of sulfonylurea or metformin only), week of visit, and treatment-by-week interaction as fixed effects and patient and error as random effects.

Secondary analyses for the key efficacy measure were performed on the ITT analysis set. The proportions of patients achieving A1C <7.0% (for patients with baseline A1C ≥7.0%) and ≤6.5% (for patients with baseline A1C >6.5%) at 84 weeks were summarized using frequencies and percentages by treatment group. Treatment group difference was assessed using a Cochran-Mantel-Haenszel test, adjusting for country and background oral blood glucose–lowering medication. In addition, change in A1C from baseline to the last-observation-carried-forward end point by 84-week anti-exenatide antibody status (two-level and three-level) was performed using ANCOVA. Time to failure to maintain glycemic control was defined as the time from randomization to the first visit after week 18 where A1C was ≥7.0%. The log-rank test was used to compare the time-to-failure distributions of the two treatment groups.

Analyses for other secondary measures used a mixed-model repeated-measures procedure similar to that used for the primary efficacy measure and were conducted on the ITT analysis set. All treatment difference tests were conducted at a two-sided significance level of 0.05, unless specified otherwise. Categorical variables, other than the A1C target analyses, were compared using the Fisher exact test.

Hypoglycemia events were summarized by treatment, oral blood glucose–lowering therapy, and classification (major, minor, symptomatic, or nocturnal).

Post hoc (and postrandomization) assessments were conducted to establish whether treatment effects on A1C and weight were consistent among subgroups on the basis of study completion status (ITT population or 84-week completers) and oral blood glucose–lowering medication use (metformin alone). All data are presented as least squares means ± SE, unless otherwise noted.

RESULTS

Patient disposition and baseline characteristics

Figure 1 shows patient flow through the study and reasons for discontinuation. Demographic and baseline characteristics were comparable between treatment groups for the ITT population, as well as for the 84-week completer subgroup (Supplementary Table 1). Likewise, baseline characteristics were comparable between the ITT population and subgroups analyzed (84-week completers [Supplementary Table 1] and patients requiring a change in their treatment after 48 weeks [data not shown]). Over the course of the study, the metformin least squares mean ± SE dose was 1,985 ± 7.7 mg for the EQW group and 2,058 ± 7.8 mg for the IG group. The sulfonylurea dose was reduced from baseline for 19 of 70 (27%) patients taking EQW and 20 of 66 (30%) patients taking IG. The IG dose increased from 10 ± 0.1 IU/day at baseline to 31 ± 2.1 IU/day at 26 weeks and was continuously titrated over the duration of the study to 35 ± 1.9 IU/day at 84 weeks. Between 48 and 84 weeks, the number of patients [*n* (%)] who had changes made to their study treatment was as follows: current oral blood glucose–lowering medication dose increased [EQW: 12 (5%); IG: 4 (2%)], additional oral blood glucose–lowering medication added [EQW: 4 (2%); IG: 3 (1%)], and insulin added [EQW: 1 (0.4%); IG: 3 (1%)]. For the purpose of the analyses, the observations after any treatment change were set to missing and handled by the mixed models for repeated measures (MMRM) model. Thus, any data collected after these treatment changes were made were excluded from the analyses.

Glycemic control

In the ITT population, the end point A1C was 7.1 ± 0.1% for patients taking EQW and 7.3 ± 0.1% for patients taking IG (P = 0.029) (Fig. 2*A*). Likewise, in the subgroup of patients completing 84 weeks of treatment, end point A1C values were

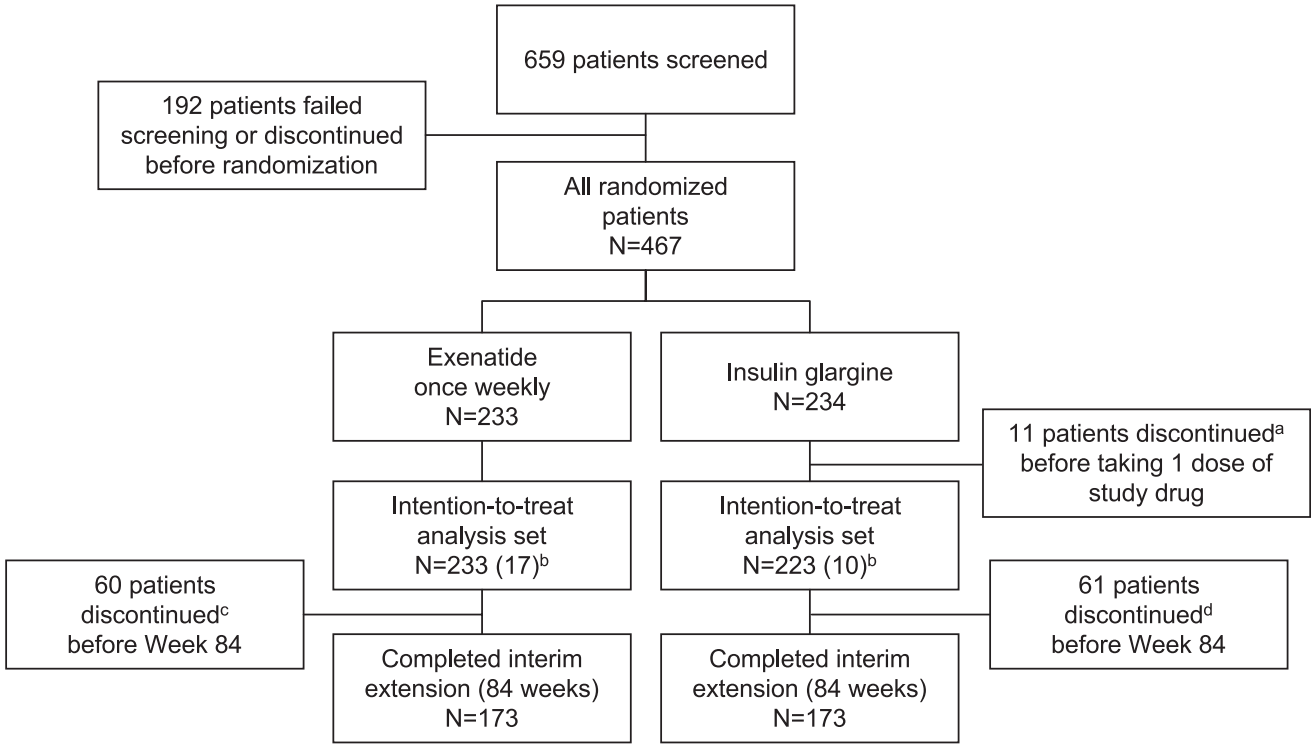

Figure 1—*Patient flow through study. A number of patients were screened, randomly assigned, and participated in the study. Reasons for discontinuation are provided in the following footnotes.* [a]*Discontinued as a result of subject decision. Although these patients were not included in the ITT analysis set, they are counted in the number of patients who discontinued before week 84.* [b]*Number of patients who required a change in their study treatment at or after week 48. These patients were included in the ITT analysis set, using their last observation before treatment change carried forward.* [c]*Reasons for discontinuation: AEs* (n = *16), subject decision* (n = *14), protocol violation* (n = *12), completed 26-week core treatment period and chose not to continue in open-ended extension period* (n = *9), entry criteria not met* (n = *3), physician decision* (n = *3), lost to follow-up* (n = *2), and sponsor decision* (n = *1).* [d]*Reasons for discontinuation: subject decision* (n = *30), completed 26-week core treatment period and chose not to continue in open-ended extension period* (n = *14), protocol violation* (n = *7), AEs* (n = *4), physician decision* (n = *2), lost to follow-up (2), and entry criteria not met* (n = *2).*

7.0 ± 0.1% for the EQW group and 7.2 ± 0.1% for the IG group ($P = 0.011$) (Fig. 2*B*).

In the ITT population, the change in A1C from baseline to end point was significantly greater for patients in the EQW group (−1.2 ± 0.1%) compared with those in the IG group (−1.0 ± 0.1%) (treatment difference −0.18 ± 0.08% [95% CI −0.33 to −0.02]; $P = 0.029$). This finding was similar in the subgroup of patients who completed 84 weeks (−0.20 ± 0.08% [−0.35 to −0.05]; $P = 0.011$). The proportion of patients with A1C <7.0% at 84 weeks was not significantly different between treatment groups (EQW: 44.6%, IG: 36.8%; $P = 0.084$). However, the proportion of patients with A1C ≤6.5% was significantly greater for the EQW group than the IG group (31.3 vs. 20.2%; $P = 0.009$). Supplementary Fig. 1 shows the cumulative distribution of A1C values at baseline and at 84 weeks. Within each treatment group, baseline characteristics (diabetes duration, age, A1C, weight, lipids, and sex) were analyzed for the subgroup of patients with an A1C that decreased between 26 and 84 weeks versus the subgroup whose A1C increased during the same period. No differences in baseline characteristics were found between the subgroups for either of the treatment groups. The mean (median) ± SE time to failure to maintain glycemic control was significantly longer for patients taking EQW than for patients taking IG [57.1 (72) ± 1.9 weeks vs. 47.0 (26) ± 1.9 weeks; $P = 0.0007$]. These results were consistent when the EQW group was broken down by antibody titer status (positive or negative). Antibody titer status did not show a significant interaction with time to failure.

Within the EQW treatment group, mean A1C was reduced regardless of whether patients tested positive for anti-exenatide antibodies ($P < 0.05$ for baseline–to–end point comparison for each anti-exenatide antibody status level). The small group of 24 patients (10%) who exhibited higher titer antibodies had a smaller reduction in A1C (−0.44 ± 0.21%) than either the group of 78 (33%) patients who tested positive-low (−1.20 ± 0.12%) (mean difference −0.77 ± 0.24% [95% CI −1.23 to −0.30]) or the group of 123 (53%) patients who tested negative (−1.25 ± 0.11%) (−0.82 ± 0.23% [−1.27 to −0.36]). The group of patients who tested positive-low had similar A1C lowering as those who tested negative.

All glucose measurements were collected by protocol at specific time points (last at 48 weeks). Both treatments were associated with significant ($P < 0.0001$) reductions in laboratory-assessed fasting serum glucose; change from baseline was greater in the IG group than in the EQW group (2.97 ± 0.16 mmol/L vs. 2.36 ± 0.16 mmol/L; $P = 0.003$). Both treatments were associated with significant ($P < 0.001$) reductions in self-monitored blood glucose values from baseline through 48 weeks for all eight time points measured (Supplementary Fig. 2).

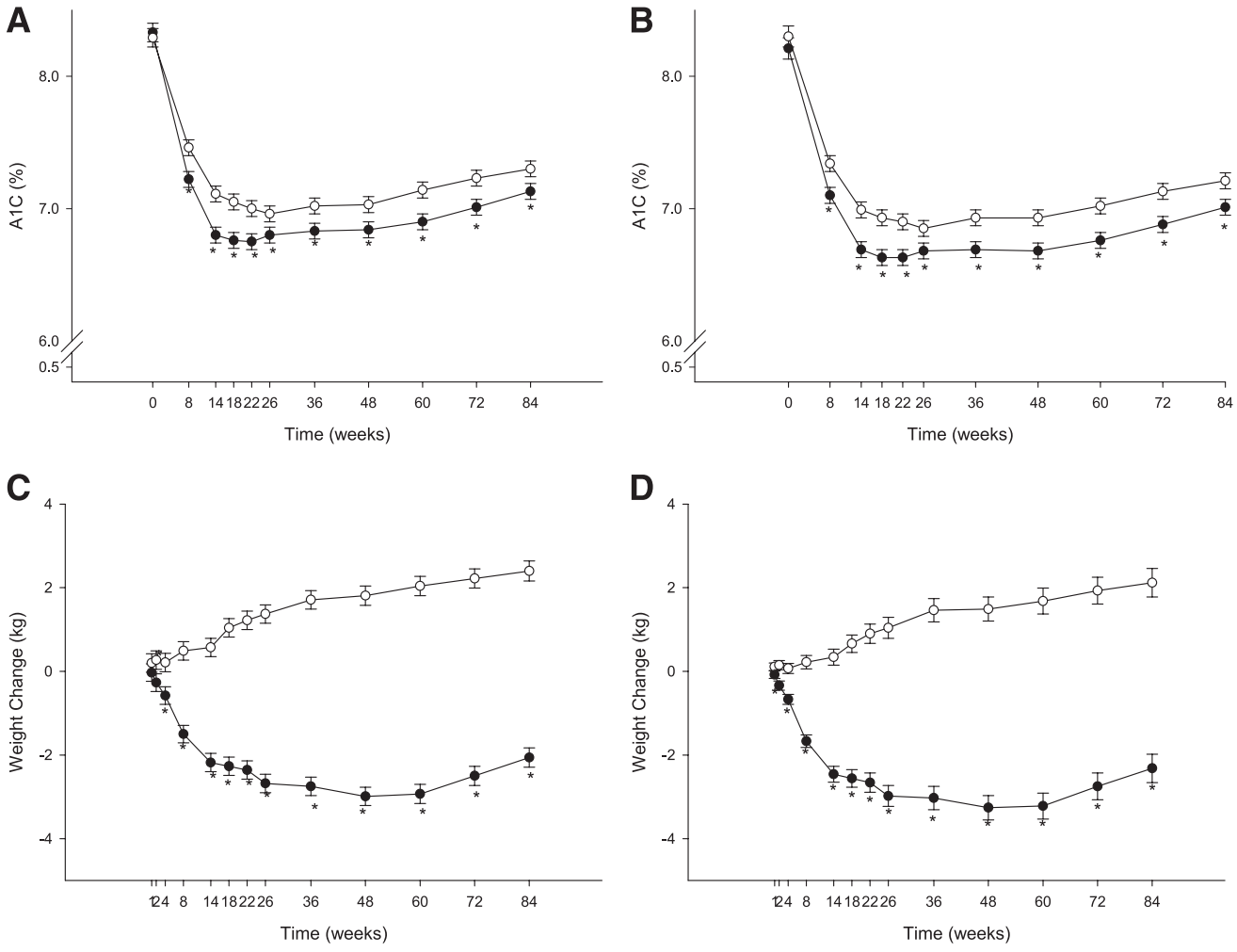

Figure 2—*Effects of EQW vs. IG on A1C and body weight over 84 weeks of therapy.* A: *A1C values over time for the ITT population.* B: *A1C values over time for the 84-week completer population.* C: *Body weight change over time for the ITT population.* D: *Body weight change over time for the 84-week completer population.* ●, *EQW;* ○, *IG.* *P < *0.05.*

Effects on body weight

Treatment with EQW resulted in significant weight loss as opposed to weight gain with IG. In the ITT population, the change in body weight from baseline to end point was −2.1 ± 0.2 kg for the EQW group and +2.4 ± 0.2 kg for the IG group, with a treatment difference (EQW minus IG) of −4.5 ± 0.3 kg (95% CI −5.0 to −3.9; $P < 0.001$) (Fig. 2*C*). In the 84-week completer population, the change in body weight from baseline to end point was −2.3 ± 0.3 kg for the EQW group and +2.1 ± 0.3 kg for the IG group, with a treatment difference of −4.4 ± 0.5 kg (−5.4 to −3.5; $P < 0.001$) (Fig. 2*D*). Within the EQW group, there was not a significant difference in the amount of weight lost in the subgroup of patients who reported nausea at 84 weeks ($n = 36$; −3.2 ± 0.7 kg) compared with those who did not ($n = 197$; −1.7 ± 0.4 kg) ($P = 0.062$). For the subgroup of patients on metformin only, the change in body weight from baseline to end point was −2.5 ± 0.3 kg for patients taking EQW and +2.2 ± 0.3 kg for patients taking IG (treatment difference: −4.7 ± 0.4 kg [−5.4 to −4.0]; $P < 0.001$).

An analysis of associations between A1C change and body weight change for individual patients following 84 weeks of treatment is shown in Supplementary Fig. 3. A reduction in A1C paired with a reduction in body weight was observed for 60% of patients taking EQW vs. 25% of patients taking IG ($P < 0.001$). By contrast, 27% of patients taking EQW vs. 61% of patients taking IG experienced a reduction in A1C paired with an increase in body weight ($P < 0.001$).

Changes in cardiometabolic parameters

Supplementary Table 2 shows baseline–to–end point changes in cardiometabolic parameters and β-cell function. Greater reductions were observed for the EQW group compared with the IG group for waist and hip circumference and systolic blood pressure. Heart rate was increased in the EQW group. Homeostasis model assessment of β-cell function values improved to a greater extent in the EQW group than the IG group.

Safety

The incidence of AEs occurring between baseline and 84 weeks is shown in Table 1. No deaths occurred through 84 weeks of treatment in either treatment arm. Five patients experienced six serious AEs considered by the study investigator to be related to study drug, procedure, or device (EQW: edematous pancreatitis, rectal polyp, cholelithiasis, B-cell lymphoma, and leukemia; IG: esophageal carcinoma). The patients with edematous pancreatitis

Table 1—*Overview of AEs*

	EQW	IG
N	233	223
Patients with one or more AEs	183 (78.5)	164 (73.5)
AEs occurring in ≥5% of the ITT population		
Nasopharyngitis	48 (21)	51 (23)
Headache	30 (13)	19 (8)
Diarrhea	28 (12)	13 (6)*
Nausea	34 (15)	3 (1)*
Influenza	17 (7)	13 (6)
Back pain	15 (6)	11 (5)
Arthralgia	14 (6)	10 (4)
Patients with one or more serious AEs	22 (9)	23 (10)
Discontinuations as a result of an AE	16 (7)	4 (2)

Data are *n* (%). *$P < 0.05$ for comparison between treatment groups.

and esophageal carcinoma discontinued the study. The case of edematous pancreatitis occurred in the first 26 weeks and was described previously (4). Two other patients, one from each treatment group, discontinued from the study because of serious AEs considered unrelated to the study drug (EQW: cerebrovascular accident; IG: Cushing's syndrome). Most patients in the EQW group who reported treatment-emergent AEs that typically are associated with GLP-1RAs (nausea and diarrhea) did so in the first 26 weeks of the study (nausea incidence 12.9%, diarrhea incidence 8.6% over 26 weeks). An additional 2.1% of patients reported nausea, and an additional 3.4% of patients reported diarrhea after 26 weeks of treatment. The proportion of patients reporting one or more AEs did not differ between the group of patients testing negative for anti-exenatide antibodies (73 of 98 [74.5%]) and the group testing positive for antibodies (88 of 128 [68.8%]).

The overall incidence of hypoglycemia was assessed separately for the two subgroups of patients on metformin alone or metformin plus sulfonylurea (Table 2). Overall, hypoglycemia was less frequent in patients taking EQW than in patients taking IG (4). No major hypoglycemia (defined as a hypoglycemic episode in which the patient had a documented blood glucose <3.0 mmol/L and lost consciousness or required the assistance of another person because of severe impairment in consciousness or behavior) was reported between weeks 26 and 84.

CONCLUSIONS—This open-label, controlled, long-term extension study in patients with type 2 diabetes on metformin or metformin plus sulfonylurea demonstrated that the previously observed significant improvements in glycemic control and metabolic factors after 26 weeks of treatment with EQW or with IG were sustained through 84 weeks. Treatment with EQW reduced A1C and postprandial glucose to a statistically greater extent than IG titrated to target. In addition, a greater proportion of patients taking EQW achieved an A1C ≤6.5% compared with those taking IG, and there was a similar treatment-associated trend for the proportion of patients who achieved an A1C <7%. The time to failure to maintain glycemic control was longer for patients taking EQW than for patients taking IG, even though a higher number of patients taking EQW (17 EQW vs. 10 IG patients) eventually required a change to their treatment to maintain good metabolic control (i.e., the need to intensify treatment occurred later for patients taking EQW). Among patients taking EQW, A1C was reduced to a similar degree in those testing negative for anti-exenatide antibodies compared with those who had positive low titers. Furthermore, the incidence of high positive antibody titers was low (~10%), but the mean A1C reduction was smaller in this group. In addition, EQW treatment was associated with significant weight reduction (as opposed to weight gain with IG) from baseline through 84 weeks and fewer hypoglycemic episodes than IG treatment.

These results should be interpreted cautiously, given the study limitations that have been previously described in detail (4). Although well controlled, study limitations include the open-label nature of the design and the fact that the study population was predominately Caucasian. It should be noted that ~30% of patients in both groups required a reduction from baseline in their sulfonylurea dose. Although a reduction in sulfonylurea dose may reduce the risk of hypoglycemia, such a change in sulfonylurea dose may be associated with a negative impact on glucose control. In addition, the possibility for bias introduced through patient self-selection for continuation into the extension study exists. However, the results for A1C and weight changes in the ITT population were similar to those observed in the 84-week completer cohort, arguing against confounding of interpretation of study results as a result of self-selection bias.

Notable strengths of the study are the use of optimized IG as the comparator throughout the 84-week treatment period (basal insulin is the standard next step in treatment for patients with type 2 diabetes not responding to oral blood glucose–lowering medications) (8), the use of the insulin titration schedule from the

Table 2—*Overall hypoglycemia incidence at 84 weeks*

Hypoglycemia category	EQW	IG	*P*
Patients on metformin alone			
Minor*	13 (8)	51 (32)	<0.001
Symptomatic†	19 (12)	63 (40)	<0.001
Nocturnal‡	7 (4)	27 (17)	<0.001
Patients on metformin plus sulfonylurea			
Minor*	17 (24)	36 (54)	<0.001
Symptomatic†	25 (36)	37 (56)	0.025
Nocturnal‡	9 (13)	31 (47)	<0.001

Data are *n* (%). *Defined as any time a patient felt that he or she had a sign or symptom of hypoglycemia that was associated with concurrent blood glucose <3.0 mmol/L and that was either self-treated by the patient or resolved independently. †Included any episode in which the patient reported signs or symptoms of hypoglycemia with or without a confirmed blood glucose measurement. ‡Defined as any hypoglycemic episode occurring after bedtime and before breakfast.

INITIATE trial (5), and the continuation of patients in their originally assigned randomization arm, eliminating the possibility of any carryover effects from changing therapies. As described previously (4), during the first 26 weeks of IG treatment, patients were instructed to titrate their insulin dosage to achieve a target fasting glucose of 4.0–5.5 mmol/L, as outlined by Yki-Järvinen et al. (5). This same titration schedule was used between 26 and 84 weeks, with an overall increase in the mean daily insulin dose from 31 IU at week 26 to 35 IU at this interim analysis. The A1C improvement observed in the IG group in our study was comparable with that observed in other trials of IG, despite a lower final insulin dose in our study (5,9,10).

Although mean end point A1C values remained significantly lower than baseline for both treatment groups, an upward drift in A1C was observed beginning at ~26 weeks of treatment, consistent with the progressive nature of type 2 diabetes (11). The investigators were instructed to follow the same dosing/titration algorithm after 26 weeks as they did in the first 26 weeks, but such titration apparently was insufficient to prevent the slight rise in A1C to 7.3%, despite the mean daily IG dose increase of 4 IU. We analyzed individual patient response to EQW or IG treatment between 26 and 84 weeks by A1C increase versus A1C decrease and found no differences between groups in baseline characteristics that could explain why some patients lost glycemic control over time and other patients had continued improvements in glycemic control over time. An analysis of the rate of change in A1C between 26 and 84 weeks revealed a similar ($P = 0.7786$) rate of increase in each group (~0.0065% per week, which was significantly greater than zero [$P < 0.0001$]), suggesting a continuation of disease progression irrespective of study treatment.

Although body weight progressively increased over time in the IG treatment group, the mean body weight in the EQW treatment group decreased up to 48 weeks of therapy, and an overall weight loss of ~2 kg was sustained up to 84 weeks. However, it was noted in the EQW group that body weight trended upward between 48 and 84 weeks. The reason for this upward trend is not known. One possibility may be that patients did not adhere as closely to their instructed lifestyle modifications after 26 weeks, feeling that the core study period was over. However, this explanation remains speculative.

Both therapies seemed to be well tolerated over the 84 weeks of treatment. The small but statistically significant increase in heart rate with EQW treatment is of uncertain clinical importance. No adverse outcomes related to increased heart rate were observed in this study at the time of this interim analysis. In general, after 26 weeks, new cases of AEs slowed compared with the period of time between baseline and 26 weeks (4). This is noteworthy with regard to nausea and vomiting, a typical AE of exenatide therapy. Our observation is consistent with several clinical trials of exenatide twice daily, which showed decreased gastrointestinal distress over time (12–15). There were some AEs that emerged only after 26 weeks of therapy. Among the most prevalent were injection site nodule at 6% of the EQW group and bronchitis, cough, and toothache at ~5% of the IG group.

The data from this 84-week interim analysis demonstrated that treatment with EQW provided significantly better glycemic control than IG and was associated with significant weight loss through 84 weeks of treatment. These results, coupled with the significantly lower incidence of hypoglycemia observed with EQW compared with IG therapy, suggest that EQW can be a therapeutic option for patients with type 2 diabetes for whom the convenience of once-a-week dosing, weight loss, and reduction of risk for hypoglycemia are important.

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M.D., L.V.G., S.S., and B.G. participated as principal investigators for the study, contributed to the interpretation of data, and reviewed and edited the manuscript. L.M. contributed to the study design and interpretation of the data, and reviewed and edited the manuscript. H.H. conducted the statistical analyses and reviewed and edited the manuscript. J.S.-B. contributed to the interpretation of the data and wrote the manuscript. M.T. served as the lead clinical research physician for the study and in that capacity contributed to the design of the study, oversaw the conduct of the clinical trial, contributed to the interpretation of the data, and reviewed and edited the manuscript. M.D. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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