DURATION-5: Exenatide Once Weekly Resulted in Greater Improvements in Glycemic Control Compared with Exenatide Twice Daily in Patients with Type 2 Diabetes

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Context: We wanted to understand the effects of once-weekly vs. twice-daily glucagon-like peptide-1 receptor agonism for treatment of patients with type 2 diabetes.

Objective: The objective of the study was to compare effects of exenatide once weekly (ExQW) and exenatide twice daily (ExBID) on glycemic control, body weight, and safety.

Design: This was a 24-wk, randomized, open-label, comparator-controlled study.

Setting: The study was conducted at 43 sites in the United States.

Patients: The study population was 252 intent-to-treat patients with type 2 diabetes [baseline (mean ± SD): glycosylated hemoglobin (HbA1c) 8.4 ± 1.2%, fasting plasma glucose 171 ± 47 mg/dl, weight 96 ± 20 kg] that were drug naïve (19%) or previously treated with one (47%) or multiple (35%) oral antidiabetic medications.

Interventions: Interventions included ExQW 2 mg for 24 wk or ExBID 5 μg for 4 wk followed by ExBID 10 μg for 20 wk.

Main Outcome Measure: The change in HbA1c from baseline to wk 24 was measured.

Results: At 24 wk, ExQW produced significantly greater changes from baseline (least squares mean ± SE) vs. ExBID in HbA1c (−1.6 ± 0.1% vs. −0.9 ± 0.1%; P < 0.0001) and fasting plasma glucose (−35 ± 5 mg/dl vs. −12 ± 5 mg/dl; P = 0.0008). Similar reductions in mean body weight from baseline to wk 24 were observed in both groups (−2.3 ± 0.4 kg and −1.4 ± 0.4 kg). Both treatments were generally well tolerated. Transient and predominantly mild to moderate nausea, the most frequent adverse event, was less common with ExQW (14%) than with ExBID (35%). Injection-site reactions were infrequent, but more common with ExQW. No major hypoglycemia occurred.

Conclusions: Continuous glucagon-like peptide-1 receptor agonism with ExQW resulted in superior glycemic control, with less nausea, compared with ExBID in patients with type 2 diabetes. Both groups lost weight. (J Clin Endocrinol Metab 96: 1301–1310, 2011)
Type 2 diabetes mellitus is a complex disorder characterized by defects in the secretion and action of multiple glucoregulatory hormones, resulting in hyperglycemia. Achieving glycemic control and reduction of glycosylated hemoglobin (HbA1c) has been shown to reduce the risk of long-term microvascular and possibly macrovascular complications of diabetes (1). However, optimal treatment of diabetes must address both glycemic control and such comorbidities as obesity, hypertension, and dyslipidemia (2, 3). Although several therapies are currently approved for the treatment of type 2 diabetes, there remains a need for treatments with demonstrated effects on both hyperglycemia and associated comorbidities, with minimal risk of hypoglycemia and weight gain.

The American Diabetes Association/European Association for the Study of Diabetes treatment algorithm published in 2009 cites glucagon-like peptide-1 (GLP-1) receptor agonists as a less-validated but potential add-on therapy for the treatment of type 2 diabetes if glycemic control is not achieved after lifestyle intervention and metformin therapy (4). In addition, the 2009 consensus algorithm created by the American Association of Clinical Endocrinologists (AACE)/American College of Endocrinology (ACE) for the treatment of type 2 diabetes supports combination therapy for patients who require advanced treatment. Although metformin is recommended for monotherapy and as a component of combination antidiabetes therapies, GLP-1 receptor agonists are positioned as preferred secondary agents because of their efficacy and overall safety profile, notably glucose-dependent stimulation of insulin secretion and the resultant low risk of hypoglycemia, ability to produce weight loss, and postprandial glucose-lowering characteristics (5).

An incretin hormone secreted from the gut in response to food ingestion, GLP-1 has been demonstrated to play a key role in pancreatic β-cell stimulation, insulin secretion, regulation of gastric emptying and satiety, and suppression of inappropriate glucagon secretion (6–8). GLP-1 infusion over 24 h has been demonstrated to normalize blood glucose and both basal and stimulated β-cell function (9), demonstrating the potential role of continuous GLP-1 receptor agonism in improving glycemic control in type 2 diabetes (10).

Exenatide administered twice daily (ExBID), a well-characterized GLP-1 receptor agonist approved for use as an adjunct to diet and exercise, has been shown to promote glycemic control in patients with type 2 diabetes and produce weight loss; in addition, exenatide has been reported to improve cardiovascular risk factors, such as blood pressure and lipid profiles (11). Exenatide, like GLP-1, acts to enhance glucose-dependent insulin secretion by the pancreatic β-cell, suppress inappropriately elevated glucagon secretion, reduce food intake, and slow gastric emptying (12–14).

An extended-release formulation of exenatide administered once weekly (ExQW), currently under review by regulatory authorities, provides steady-state concentrations of exenatide in the range shown to elicit effects on glycemic control within approximately 6–10 wk of initiating therapy (15, 16). As in the case of ExBID, ExQW has been demonstrated to improve glycemic control and reduce body weight (15, 16). The continuous GLP-1 receptor agonism achieved with ExQW has the potential to provide improved glycemic control with additional benefits of weight loss, blood pressure reduction, and improvement in lipid profiles. In addition, once-weekly administration has been reported to reduce patient burden by providing patients with a weekly dosing regimen (17).

Diabetes Therapy Utilization: Researching Changes in HbA1C, Weight, and Other Factors Through Intervention with Exenatide Once Weekly (DURATION)-5 was a randomized, open-label trial comparing the safety and efficacy of ExQW and ExBID, both provided in their (intended) commercial forms, over 24 wk in patients with type 2 diabetes treated with diet and exercise alone or in combination with a single or multiple oral antidiabetic agents.

Patients and Methods

Patients

Randomized patients (n = 254) were at least 18 yr of age and diagnosed with type 2 diabetes, otherwise healthy, and treated for at least 2 months with diet and exercise alone or with a stable, maximally effective regimen of metformin, sulfonylurea (SU), thiazolidinedione, or a combination of these medications. Additional entry criteria included an HbA1c of 7.1–11.0%, fasting plasma glucose (FPG) concentration less than 280 mg/dl (15.5 mmol/liter), and a body mass index of 25–45 kg/m². Patients were to refrain from changes to oral antidiabetic, lipid-lowering, and antihypertensive medications during the study, unless instructed otherwise by the investigator. Use of concomitant weight-loss agents was not allowed; no supplementary lifestyle modification program was applied.

A common clinical protocol was approved for each site by the appropriate institutional review board, and all patients provided written informed consent before participation. The study was conducted in accordance with the principles described in the Declaration of Helsinki (1946) up to and including the Seoul revision (2008) (18).

Study design

This study was a randomized, comparator-controlled, open-label evaluation of the efficacy, safety, and tolerability of ExQW (intended commercial material) compared with ExBID. Patients were randomized 1:1 to treatment with ExBID or ExQW, with randomization performed centrally via an interactive voice or
web response system. Randomization was stratified according to concomitant SU use at screening and baseline HbA1c stratum (<9.0% or ≥ 9.0%). Patients randomized to ExQW received sc 2-mg doses once weekly for 24 wk. Patients randomized to ExBID received 5 µg sc twice daily (BID) for 4 wk followed by 10 µg sc BID for 20 wk, consistent with recommended dosing for ExBID (19). Patients self-administered study medication after training by study site personnel. Sponsor personnel remained blinded to HbA1c and FPG data throughout treatment.

Study end points

The study was designed to compare the effects of ExQW and ExBID on the primary end point of change in HbA1c from baseline to wk 24. Secondary end points included body weight, FPG, proportion of subjects achieving HbA1c targets of less than 7% and 6.5% or less at wk 24, proportion of patients achieving FPG target of 126 mg/dl (7.0 mmol/liter) or less at wk 24, systolic blood pressure (SBP) and diastolic blood pressure, fasting lipid concentrations, safety, and tolerability.

Laboratory values

Blood tests, including HbA1c, were performed by Quintiles Laboratories (Smyrna, GA) using standard methods. HbA1c was measured by HPLC. Plasma concentrations of antibodies to exenatide were measured using a validated ELISA (20). Antibody titers were determined by serial 1:5 dilutions after minimal dilution of 1:25, with the titer expressed as the reciprocal of the highest dilution of sample that tested positive. Antibody to exenatide titers less than 625 were classified as low and titers of 625 or greater were classified as higher.

Statistical analysis

A sample size of approximately 250 patients (ratio of 1:1) was estimated to provide 90% power to demonstrate that ExQW was noninferior to ExBID by a 0.4% difference in the HbA1c change from baseline to wk 24, using a one-sided, two-sample t test with a significance level of 0.025 and assuming a greater (0.1%) reduction in HbA1c by ExQW compared with ExBID, a 15% withdrawal rate, and a common SD of 1.1%. Hypotheses for demonstration of both superiority and noninferiority were prespecified in the protocol. Noninferiority of ExQW to ExBID was demonstrated if the upper limit of the two-sided 95% confidence interval (CI) for the difference between treatments fell beneath 0.4%; superiority was demonstrated if the CI was below zero (21). Other tests were conducted two sided at a significance level of 0.05. Multiplicity from tests of treatment differences for the proportion of patients achieving the targets of HbA1c less than 7.0% and FPG 126 mg/dl (7.0 mmol/liter) or less at wk 24, and the change in FPG from baseline to wk 24 were adjusted using the Hochberg procedure (22) to control the overall type I error rate at a 5% level.

The changes in HbA1c and FPG between treatments were compared using general linear models, including factors for treatment group, baseline HbA1c stratum, and concomitant SU use at screening. The proportions of patients achieving HbA1c and FPG targets were compared between treatments using a Cochran-Mantel-Haenszel test, adjusted by the factors of baseline HbA1c stratum and concomitant SU use at screening. Differences in the changes in other parameters from baseline to wk 24 were assessed using general linear models, including factors for treatment group, concomitant SU use at screening, baseline HbA1c stratum, and baseline values of the parameter. The triglyceride data were analyzed after natural logarithmic transformation.

The intent-to-treat (ITT) population (n = 252) consisted of all randomized patients receiving at least one dose of randomized study medication. The evaluable population (n = 204) consisted of all ITT patients completing study procedures through at least wk 20 in compliance with the protocol and receiving adequate study medication exposure. With the exception of safety and subgroup analyses, performed for the ITT population only, all analyses were performed for both the ITT and evaluable populations. Missing postbaseline efficacy data were imputed using the last observation carried forward (LOCF) approach. As a sensitivity analysis, the change in HbA1c was evaluated using all observed postbaseline data (without imputation) in a mixed-effects model repeated-measure analysis (change in HbA1c as dependent variable; treatment, week, treatment by week interaction, concomitant SU use at screening, and baseline HbA1c stratum as fixed effects; subject as random effect). Efficacy data on mean changes from baseline were expressed as least squares (LS) means. The statistical analyses were performed using SAS version 9.2 (SAS Institute, Cary, NC).

Treatment-emergent adverse events were defined as adverse events that occurred or worsened after the first injection of study medication. Hypoglycemic episodes were classified as major or minor. Major hypoglycemia was defined as events that resulted in loss of consciousness, seizure, coma, or other change in mental status consistent with neuroglycopenia, in which symptoms resolved after administration of intramuscular glucagon or iv glucose. Hypoglycemia requiring assistance because of severe impairment in consciousness or behavior accompanied by a blood glycemic event was defined as severe hypoglycemia.
glucose concentration less than 54 mg/dl (3.0 mmol/liter) before treatment was also classified as major. Minor hypoglycemia was defined as events with symptoms consistent with hypoglycemia accompanied by a blood glucose concentration less than 54 mg/dl (3.0 mmol/liter) before treatment.

Results

Patient disposition and baseline characteristics

Of 252 patients in the ITT population, a total of 81% completed the study (Fig. 1). With the exception of withdrawal of consent (six patients, ExQW; 10 patients, ExBID), reasons for withdrawal were similar between treatment groups. Demographic and baseline characteristics were generally evenly distributed among treatment groups (Table 1). Background antidiabetic therapy regimens encompassed the range of treatments commonly observed in patients with type 2 diabetes, beginning at initial diagnosis (diet and exercise modification) through long-term management (combination therapy) but before initiation of insulin therapy.

| TABLE 1. Demographic and baseline characteristics by treatment for the ITT population |
|---------------------------------|-----------------|-----------------|
|                                 | ExBID (n = 123) | ExQW (n = 129)  |
| Gender, n (%)                   |                 |                 |
| Male                            | 68 (55)         | 77 (60)         |
| Age at consent (yr)             |                 |                 |
| Mean ± sd                       | 55 ± 10         | 56 ± 11         |
| Minimum, maximum                | 23, 79          | 23, 83          |
| Race/ethnicity, n (%)           |                 |                 |
| Caucasian                       | 68 (55)         | 81 (63)         |
| Black                           | 9 (7)           | 6 (5)           |
| Asian                           | 5 (4)           | 5 (4)           |
| Hispanic                        | 41 (33)         | 37 (29)         |
| Mean ± sd weight (kg)           | 94.3 ± 18.9     | 97.0 ± 20.7     |
| Mean ± sd BMI (kg/m²)           | 33.0 ± 5.3      | 33.6 ± 5.5      |
| Mean ± sd HbA1c (%)             | 8.4 ± 1.2       | 8.5 ± 1.1       |
| HbA1c stratum, n                | 122             | 128             |
| <9.0%, n (%)                    | 88 (72)         | 90 (70)         |
| ≥9.0%, n (%)                    | 34 (28)         | 38 (30)         |
| Mean ± sd FPG (mg/dl)           | 168 ± 47        | 173 ± 47        |
| Mean ± sd duration of diabetes at screening (yr) | 7 ± 5 | 7 ± 5 |
| Diabetes management method at screening, n (%) |                 |                 |
| Alone or in combination Metformin | 87 (71)         | 103 (80)        |
| Sulfonylurea                    | 34 (28)         | 40 (31)         |
| Thiazolidinedione               | 12 (10)         | 22 (17)         |
| Category Diet and Exercise      | 26 (21)         | 21 (16)         |
| Single oral antidiabetic therapy | 62 (50)         | 56 (43)         |
| Combination oral antidiabetic therapy | 35 (28) | 52 (40) |

Percentages may not add to 100% due to rounding. FPG conversion factor (milligrams per deciliter to millimoles per liter) is 0.0555. BMI, Body mass index.

Duration of diabetes ranged from less than 1 yr to 24 yr in ExQW patients and from less than 1 yr to 25 yr in ExBID patients.

Glycemic control parameters and body weight

Patients treated with ExQW demonstrated an improvement in HbA1c by wk 4 of treatment, with a significantly greater improvement compared with ExBID observed from wk 8 through wk 24 (Fig. 2A). At wk 24, the LS mean ± se change in HbA1c from baseline was -1.6 ± 0.1% in ExQW and -0.9 ± 0.1% in ExBID patients (ITT; P < 0.0001), resulting in a treatment difference of -0.7% (-0.9, -0.4). LS mean ± se changes from baseline to wk 24 in the evaluable population were identical with those in the ITT population. Mixed-effects model repeated-measure sensitivity analysis provided similar results (-1.5 ± 0.1% in ExQW patients and -0.8 ± 0.1% in ExBID patients, P < 0.0001). At wk 24, the mean ± se HbA1c was 7.1 ± 0.1% for ExQW and 7.7 ± 0.1% for ExBID patients in the ITT population. Compared with ExBID, a significantly greater number of ExQW patients achieved the HbA1c targets of less than 7.0% (adjusted P < 0.0001) and 6.5% or less (P < 0.0001) at wk 24 (Fig. 2B). In the subgroup of patients with baseline HbA1c less than 9% (n = 178), LS mean reductions in HbA1c from baseline to wk 24 were -1.2% and -0.5% in the ExQW and ExBID groups, respectively (treatment difference P < 0.001). Larger decreases in HbA1c were achieved in patients with baseline HbA1c of 9% or greater (n = 72), in which a -1.9% LS mean reduction in HbA1c was observed with ExQW compared with a -1.3% reduction with ExBID. Significant decreases in FPG were evident at wk 4 in both groups, with ExQW producing a significantly greater change in FPG from baseline to wk 24 [-35 ± 5 mg/dl (-1.9 ± 0.3 mmol/liter)] than ExBID [-12 ± 5 mg/dl (-0.7 ± 0.3 mmol/liter); treatment difference adjusted P = 0.0008; Fig. 2C]. The proportion of patients achieving FPG of 126 mg/dl (7.0 mmol/liter) or less at wk 24 was greater for ExQW (50.4%) compared with ExBID (30.9%; treatment difference adjusted P = 0.0008).

Similar to previous results with ExBID and ExQW (16, 19), antibody status had no overall predictable effect on the change in HbA1c (Fig. 2D). The HbA1c changes in ExQW patients with low treatment-emergent antibody to exenatide titers (<625; n = 51) and antibody-negative patients (n = 44) at the last visit on or before wk 24 were similar; ExQW patients with higher treatment-emergent antibody to exenatide titers (≥625) (n = 28), exhibited a variable HbA1c change, from -4.1% to +2.4%. ExBID patients remaining antibody negative (n = 57) had a similar mean change in HbA1c compared with ExBID patients with low antibody to...
exenatide titer (n = 45). The ExBID patients with higher antibody to exenatide titer (n = 9) had HbA1c changes ranging from −2.2% to +0.6%.

In both treatment groups, progressive reductions in mean body weight were observed through 24 wk [Fig. 2E; between group difference: −0.95 kg (−1.9, 0.01)]. By wk 24, approximately 77% of ExQW and 63% of ExBID patients experienced weight loss, whereas 71% of ExQW and 51% of ExBID patients experienced both a reduction in HbA1c and weight loss (Fig. 2F).

A consistently positive effect of ExQW therapy on the mean change in HbA1c from baseline to wk 24 was observed, regardless of background antidiabetic therapy (Fig. 3). Reductions in HbA1c, the proportion of patients achieving HbA1c targets, and reductions in body weight observed across diabetes management methods were consistent with results observed in the overall ITT population.

Changes in cardiovascular risk factors

Significant reductions in SBP from baseline to wk 24 were observed in ExQW patients [LS mean change (95% CI) −2.9 (−5.2, −0.7) mm Hg]; nonsignificant changes in SBP were also observed in ExBID patients [−1.2 (−3.5, 1.2) mm Hg; Table 2]. No significant change in diastolic blood pressure was observed in either treatment arm. Larger improvements in SBP [ExQW: −7.9 (−11.3, −4.5) mm Hg and ExBID: −7.7 (−11.3, −4.0) mm Hg] were observed in patients with elevated baseline SBP (≥ 130 mm Hg; Table 2). Significant reductions in mean fasting total cholesterol and low-density lipoprotein cholesterol were observed with ExQW; no significant changes in mean lipid parameters were observed with ExBID. Relatively few subjects (−5%) adjusted antihypertensive or lipid-lowering medication regimens during the study.

Safety and tolerability

Nausea, the adverse event reported with the highest frequency in both ExQW (14%) and ExBID (35%) patients (Table 3), occurred at lower incidence in patients treated with ExQW, consistent with previously reported data (16). In both groups, the majority of nausea was transient and mild to moderate in intensity, and the incidence decreased over time. No ExQW patients experienced severe nausea. Two ExBID subjects experienced severe nausea. Injection-site related adverse events were more common in ExQW patients (13%) compared with ExBID patients (10%) and included events of localized erythema, pruritus, rash, and urticaria; however, all injection-site related events were mild to moderate in intensity. One ExQW patient withdrew due to mild injection-site pruritus.

There were no events of major hypoglycemia. Minor hypoglycemia occurred only among subjects using a concom-
Withdrawals due to adverse events were infrequent, occurring in six patients in each group (5%); the only events occurring in more than one patient were nausea (two, ExBID) and vomiting (two, ExBID). No ExQW patient withdrew due to nausea or vomiting. Seven patients (three, ExQW and four, ExBID) were withdrawn due to loss of glucose control (as determined by the investigator) during the study. The incidence of serious adverse events was low, including three ExQW (2%) and five ExBID (4%) patients. One ExBID patient experienced a fatal myocardial infarction. One ExQW patient with a history of dyslipidemia was hospitalized and withdrew due to a diagnosis of pancreatitis. Abdominal computerized tomography scan demonstrated no acute inflammatory abnormality and the pancreas, adrenal glands, spleen, and gallbladder were normal. The event resolved in 3 d, whereas the subject was still receiving study medication.

Pancreatic-amylase (p-amylase) or lipase concentrations were above the upper limit of the normal range in 5 and 14% of subjects, respectively, before treatment. During the course of the study, there was substantial variability in pancreatic-amylase and lipase concentrations. The incidence of adverse events, including gastrointestinal symptoms, was similar between subjects with normal and abnormal postbaseline amylase and lipase measured at any postbaseline time point.

A statistically significant increase in heart rate was observed [LS mean change (95% CI) from baseline of +4.1 (2.5, 5.6) beats per minute [bpm] in ExQW and +2.1 (0.4, 3.7) bpm in ExBID], which was not associated with cardiovascular or arrhythmia-related adverse events. Approximately 73% ExQW and 51% ExBID patients were positive for treatment-emergent antibodies to exenatide at any time point during the study. There was no apparent association of antibody status on the overall incidence of adverse events.

There were no events of thyroid neoplasms reported during the study. No change in mean calcitonin concentrations, a marker of thyroid C cell hyperplasia and medullary carcinoma, was observed in either treatment group.

**Discussion**

The results of this study reinforce the results of a 30-wk, randomized, open-label study (DURATION-1), in which the
continuous GLP-1 receptor agonism achieved with ExQW therapy demonstrated superiority to ExBID in reducing HbA1c in patients with type 2 diabetes (16). Although mean improvements in HbA1c were greater in the DURATION-1 study, the magnitude of the difference between ExQW and ExBID was greater in the current study and the reductions in HbA1c observed in the current 24-wk study are consistent with those observed in two 26-wk studies of ExQW

[DURATION-2 and DURATION-3 (23, 24)] and in previous studies of ExBID (25–28).

In some rodent models, long-acting GLP-1 receptor agonists have been demonstrated to activate thyroid C cells, resulting in calcitonin secretion (29). In the current study, continuous exenatide exposure via ExQW treatment did not affect mean calcitonin concentrations over 24 wk. This result is consistent with observations in primate models and in patients with type 2 diabetes treated for 2 yr with the GLP-1 receptor agonist liraglutide (29).

Fewer gastrointestinal adverse events were observed with ExQW therapy compared with ExBID. These results are consistent with the results of DURATION-1 and with observations that a gradual increase in plasma exenatide concentrations may decrease the incidence of gastrointestinal adverse events (16, 30). Treatment with ExQW has been shown to generate steady-state plasma exenatide concentrations within approximately 6–10 wk (15, 16). In the current study, improvements in glycemic control were observed with ExQW as early as the first postbaseline measurement (4 wk after first dose) and in a time frame comparable with that of ExBID, suggesting that the gradual rise in plasma exenatide concentrations, although enhancing tolerability, does not substantially delay improvements in glycemic control.
In the 2009 AACE/ACE consensus algorithm for the treatment of type 2 diabetes, ExBID was suggested as a secondary agent in combination with metformin for dual and triple therapy based on the overall clinical profile of exenatide (5). Exenatide was also cited as a potential add-on therapy in the 2009 American Diabetes Association/European Association for the Study of Diabetes algorithm (4). Although ExBID has a greater effect on post-prandial glucose concentrations compared with ExQW (16), the once-weekly formulation still produces greater reductions in HbA1c and fasting hyperglycemia compared with ExBID, with a lower risk of gastrointestinal adverse events. These three benefits demonstrate the value of ExQW within the class of GLP-1 receptor agonists.

It should be noted that dipeptidyl-peptidase-4 inhibitors (sitagliptin or saxagliptin) were also cited as potential secondary agents in the 2009 AACE/ACE algorithm for dual or triple therapy, given their low risk of hypoglycemia, safety, and efficacy (5). However, sitagliptin has been shown to have a smaller impact on postprandial glucose excursions compared with ExBID (31), and ExQW (23) demonstrated superior reduction in HbA1c and significantly greater weight loss over 26 wk compared with sitagliptin.

Additional GLP-1 receptor agonists approved or in development for the treatment of type 2 diabetes include liraglutide and taspoglutide, respectively. The 1.8-mg dose of liraglutide, a GLP-1 analog with two amino acid substitutions (32) that is administered once daily, has been reported to improve HbA1c by $-1.0\%$ to $-1.5\%$ over 26- or 52-wk treatment periods (33–37). Once-weekly administration of 5–20 mg taspoglutide over 8 wk has been reported to improve HbA1c by $-1.0\%$ to $-1.2\%$ over 8 wk (38). Studies directly comparing the safety and efficacy of ExQW, liraglutide, and taspoglutide are warranted.

Consistent with previous results with ExQW and liraglutide (24, 35), ExQW was associated with a modest elevation in heart rate. Although such increases in heart rate might indicate risk of cardiovascular events, no associated cardiovascular events were noted in the current study, and previous clinical trials have shown that ExQW treatment was associated with improvements in blood pressure and fasting lipids (18, 23, 24). Furthermore, retrospective analyses have suggested that patients treated with the ExBID were less likely to have cardiovascular events or cardiovascular-related hospitalizations than non-exenatide-treated patients (39, 40).

The open-label design of the study represents an important limitation that may have influenced patient expectations or behaviors. Patient withdrawal rates were higher among ExBID patients compared with ExQW patients; however, the identical HbA1c reductions observed in both the ITT and the evaluable populations suggest this difference in withdrawal rates did not impact study outcomes. Continuous GLP-1 receptor agonism with ExQW resulted in superior glycemic control, with less nausea, compared with ExBID in patients with type 2 diabetes. Similar weight loss was observed in both groups, with no difference in the risk of hypoglycemia.

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