In January 2012, the U.S. Food and Drug Administration approved a once-weekly form of exenatide (Bydureon) for the treatment of type 2 diabetes. Type 2 diabetes accounts for 90–95% of diagnosed cases of diabetes, and its onset is associated with older age, obesity, familial history of diabetes, gestational diabetes, impaired glucose metabolism, physical inactivity, and ethnicity (1). Diabetes is a leading cause of blindness, end-stage renal disease, and non-traumatic lower-limb amputation and is a major risk factor for coronary artery disease and stroke (2). However, tight glycemic control is associated with fewer microvascular complications involving the eyes, kidneys, and nerves and may reduce macrovascular complications such as myocardial infarction (3). Evidence from clinical trials suggests that once-weekly exenatide (EQW) further improves glucose control compared to twice-daily exenatide and basal insulin (BI) and is associated with a lower occurrence of hypoglycemia compared to BI (4–6). EQW does not require dose titration like other glucagon-like peptide 1 (GLP-1) receptor agonists and may have other advantages, such as preventing weight gain and improving blood pressure and lipid profiles (7,8).

Effectiveness and Tolerability of Therapy With Once-Weekly Exenatide Versus Basal Insulin Among Injectable-Naive Patients With Type 2 Diabetes in a Real-World Setting in the United States

Anita M. Loughlin, Qing Qiao, Anthony P. Nunes, Stephen M. Ezzy, Laura Yochum, C. Robin Clifford, Robert V. Gately, David D. Dore, and John D. Seeger

ABSTRACT

A propensity-matched cohort study compared injectable-naive patients with type 2 diabetes initiating exenatide once weekly (EQW) or basal insulin (BI), from 2012 through 2015, within a U.S. electronic health record database. A1C and weight were obtained as observed or multiply imputed values at baseline and quarterly for 1 year (Q1–Q4). Hypoglycemia and gastrointestinal symptoms were identified using diagnostic codes and clinical notes. EQW (n = 2,008) and BI (n = 4,016) cohorts were comparable at baseline (mean A1C and weight: EQW, 8.3% and 107.5 kg, respectively; BI, 8.5% and 107.9 kg, respectively). A1C declined in Q2: –0.69 and –0.50 percentage points for EQW and BI, respectively, with little further change in year 1. The EQW cohort lost 0.9 kg in Q1 and 1.9 kg by the end of the year; no weight change was observed in the BI cohort. Among EQW and BI cohorts, 25.9% and 14.3% achieved both glycemic control and weight loss, respectively. In the EQW and BI cohorts, the incidence of hypoglycemia per 1,000 person-years was 52.5 and 65.7, respectively. The incidence of nausea was greater among EQW relative to BI initiators (relative rate 1.18). EQW offers an advantage compared to BI in achieving glycemic control and weight loss and a lower incidence of hypoglycemia, but is associated with greater risk of gastrointestinal symptoms.
used in customary clinical practice. The expectation of the study was that the results would inform the extent to which the benefits of EQW observed in randomized trials translate to clinically meaningful benefits in customary care for patients with type 2 diabetes. This study protocol was approved by privacy and institutional review boards affiliated with Optum and was conducted in a manner consistent with the guidelines for good pharmacoepidemiology practices (9).

Methods

Data Source
The study population was drawn from Optum’s electronic health records (EHR) database. The EHR integrates records from many medical groups and hospitals in the United States to form a broad, de-identified patient-level database of health care encounters in ordinary clinical practice and is a geographically diverse representation of >25,000 physicians and 25 million patients. The EHR captures diagnoses, procedures, medications (prescribed and administered), clinical measures (biometric and laboratory values), and clinical notes (i.e., physician, pathology, and radiology) that have been recorded at the time of care.

Study Design and Population
We identified injectable-naive type 2 diabetes patients who initiated either EQW or BI from January 2012 to January 2015, with follow-up through March 2015. Initiators of EQW or BI (insulin glargine or insulin detemir) were identified in the EHR using National Drug Codes. Eligible patients were required to be at least 18 years of age on the date of EQW or BI initiation (index date); receive care documented in the EHR, specifically, at least one outpatient provider visit in the 6 months before and including the index date (baseline period); and have at least one diagnosis of type 2 diabetes (International Classification of Diseases, Ninth Revision, Clinical Modification [ICD-9-CM], diagnostic codes 250.x0 or 250.x2) during the baseline period. Patients with a prior diagnosis of type 1 diabetes, gestational diabetes, or evidence of an injectable antidiabetic treatment (GLP-1 receptor agonist or any insulin) during the baseline period were excluded from the study population.

Matching
Propensity score matching was implemented to achieve balance between EQW and BI initiators with respect to a large number of characteristics (10–12). Propensity scores were estimated using a logistic regression model that incorporated potential predictors of therapy as the independent variables and initiation of EQW versus BI as the dependent variable. The potential predictors of therapy included in the propensity score model were demographics, calendar year of EQW or BI initiation, health care utilization variables, a priori–specified confounding and stratification variables (age-group, race, A1C, estimated glomerular filtration rate [eGFR], and hypoglycemia), and empirically identified covariates ascertained from the 100 most prevalent diagnoses, medications, and procedures among EQW initiators identified during the baseline period. Clinical observations (i.e., body weight, BMI, systolic blood pressure [SBP], and diastolic blood pressure [DBP]) and laboratory values (i.e., A1C, serum creatinine, urine albumin/creatinine ratio, total cholesterol, HDL cholesterol, LDL cholesterol, and triglycerides) were selected from the EHR. For these measures, the last available value occurring in the baseline period was selected to represent status at initiation of therapy. If no value was observed during the baseline period, the value was multiply imputed (five imputations) using baseline covariates, follow-up values as available, and the presence or absence of clinical outcomes (e.g., microvascular disease, cardiovascular disease, and hospitalization) using Fully Conditional Specification (FCS) methods (13). eGFR was calculated based on serum creatinine, sex, and race variables using the Chronic Kidney Disease Epidemiology Collaboration equation (14). Hypoglycemia was identified using an algorithm developed by Optum that incorporated both diagnostic codes and natural language processing (NLP) from clinical notes (15,16).

Clinically important variables were identified using univariate C-statistics and were forced into the propensity score model. Other covariates were allowed to enter the model using a stepwise selection based on a univariate P value for entry (P <0.2) and a multivariate P value for remaining in the model (P <0.3). Each EQW initiator was matched to up to two BI initiators using a greedy matching algorithm. Once an EQW initiator was matched with two BI initiators, the members of the matched set were removed from subsequent matching (17,18). Covariates included in the propensity score model were balanced across cohorts, and outcome rates observed among EQW and BI initiators were directly compared.

Outcome Definitions
Change in A1C, body weight, blood pressure, and lipids (total cholesterol, HDL cholesterol, LDL cholesterol, and triglycerides) from baseline were the outcomes measuring treatment effectiveness. These outcomes were summarized in standard intervals over the first year after EQW or BI initiation. A1C and body weight were summarized quarterly (3-month intervals), and blood pressure and lipid profiles were summarized semi-annually (6-month intervals). The interval value was taken as the mean of values occurring within an interval. If no value was observed in the interval, the value was multiply imputed (five imputations) using the FCS method (13). Parameter estimates and associated variance (SEs) were determined within imputed data sets and pooled (averaged) into a single set of statistics (SAS PROC MIANALYZE;
SAS/STAT 13.1 [SAS Institute, Cary, N.C.]) that reflect the uncertainty in parameter estimates within and between all imputations (19).

The occurrences of hypoglycemia and gastrointestinal symptoms (nausea, vomiting, diarrhea, or constipation) and change in renal function from baseline were measures of treatment tolerability. Hypoglycemia and gastrointestinal symptoms were identified by using both ICD-9-CM diagnostic codes within structured fields and NLP clinical notes (16). The ICD-9-CM diagnostic codes used to identify hypoglycemia were based on a modified algorithm described by Ginde et al. (20). Gastrointestinal symptoms were identified using ICD-9-CM diagnostic codes 536.2, persistent vomiting; 787.01, nausea and vomiting; 787.02, nausea alone; 787.03, vomiting alone; 787.91, diarrhea; 564.5, functional diarrhea; and 564.0x, constipation. NLP identifies sentiment terms (denial, affirmation) of the event in the clinical notes that allows a determination of whether the provider denied or affirmed the occurrence of an event. Events identified using both ICD-9-CM diagnostic codes and NLP on the same day in an outpatient setting or within 7 days during a continuous inpatient stay were counted as a single event.

Renal function was evaluated using eGFR summarized in standard quarterly intervals over the first year after initiation of EQW or BI treatment. Again, the interval value was taken as the mean of values occurring within an interval or was multiply imputed if no value was available. Pooled estimates of effect were calculated.

**Analysis Plan**

Each patient was followed from the index date until the earliest occurrence of a new event (counted separately for each event), disenrollment from the EHR system, or end of the study follow-up period (31 March 2015). All follow-up time was attributed to the therapy initiated (EQW or BI) on the index date. The number of patients observed and person-time of observation were used to calculate the proportion and rates of outcome occurrence, respectively.

Changes in A1C, body weight, blood pressure, and lipids were calculated as the absolute difference between the measurements taken in the baseline period and in each standard follow-up interval. Distributions of changes across each measure were summarized with the mean, mean of absolute differences, or frequency of measures that were collapsed into a categorical metric. For each measurement, the estimate and its 95% CI are presented. Comparing EQW and BI initiators, non-overlapping 95% CIs indicated a significant difference that was unlikely to be explained by chance.

The frequency and proportion of hypoglycemia and gastrointestinal symptom events among EQW and BI initiators were tabulated during follow-up. We calculated event incidence rates (and 95% CIs) using person-time censored at the first event during follow-up. Cohorts were compared using relative rate (RR) estimates and their 95% CIs. RR estimates with 95% CIs not including the value 1 indicated significant differences in event incidence rates between EQW and BI initiators that are unlikely to be explained by chance.

**Results**

Between 1 January 2012 and 31 January 2015, we identified 2,075 injectable-naive EQW initiators and 73,610 injectable-naive BI initiators. The analytic cohorts included 2,008 EQW initiators who were each matched to two BI initiators (n = 4,016). The cohorts had similar baseline characteristics (Table 1), and each cohort was followed for an average of 1.5 person-years. Baseline A1C values were similar in EQW (mean 8.29, 95% CI 8.22–8.36) and BI (mean 8.49, 95% CI 8.41–8.56), and the EQW cohort had greater absolute declines in A1C across all four quarters. Within the first 3 months, the absolute decline in A1C was 0.47

| TABLE 1. Comparison of Baseline Characteristics Between Propensity Score–Matched Cohorts of Injectable-Naive EQW (n = 2,008) and BI (n = 4,016) Initiators |
|-----------------|-----------------|
| **Age-group, years** | EQW, n (%) | BI, n (%) |
| ≤34 | 65 (3.2) | 136 (3.4) |
| 35–44 | 215 (10.7) | 433 (10.8) |
| 45–54 | 540 (26.9) | 1,079 (26.9) |
| 55–64 | 693 (34.5) | 1,416 (35.3) |
| 65–74 | 421 (21.0) | 815 (20.3) |
| ≥75 | 74 (3.7) | 137 (3.4) |
| **Sex** | | |
| Male | 1,003 (50.0) | 1,979 (49.3) |
| Female | 1,005 (50.0) | 2,037 (50.7) |
| **Race/ethnicity** | | |
| White | 1,630 (81.2) | 3,277 (81.6) |
| Black/African American | 151 (7.5) | 303 (7.5) |
| Hispanic | 96 (4.8) | 220 (5.5) |
| Asian | 38 (1.9) | 62 (1.5) |
| Multiple races | 31 (1.5) | 41 (1.0) |
| Unknown race | 62 (3.1) | 113 (2.8) |
percentage points (95% CI –0.54 to –0.41) among EQW initiators and 0.31 percentage points (95% CI –0.38 to –0.24) among BI initiators (Figure 1A). By the last quarter, these absolute declines increased to 0.60 percentage points (95% CI –0.69 to –0.51) among EQW initiators compared to 0.43 percentage points (95% CI –0.50 to –0.36) among BI initiators. Simultaneously, EQW initiators lost weight, an average of 1.9 kg (95% CI 1.5–2.3) by the end of the first year, while BI initiators did not have any appreciable weight change during this time (Figure 1A). Compared to BI initiators and within each quarter, a greater percentage of EQW initiators achieved the goal of A1C ≤7% and a greater percentage of EQW initiators lost weight (Figure 1B). In every quarter, >20% of EQW initiators achieved both A1C ≤7% and weight loss compared to <15% of BI initiators. The highest proportion of patients achieving both goals occurred in the second quarter, when 25.9% (95% CI 22.1–29.8%) of EQW initiators had both A1C ≤7% and weight loss compared to 14.3% (95% CI 11.3–17.3%) of BI initiators.

In the first 6 months after the initiation, on average, EQW initiators experienced improvement in both SBP and DBP, while BI initiators had a slight increase in SBP and similar level of improvement in DBP (Figure 2A). In the second half of the year, both EQW and BI initiators had modest increases in SBP; yet the 95% CI around the percent change in SBP for EQW initiators included 0, indicating no change from baseline. Both cohorts showed a decline in DBP during the second half of the year (Figure 2A); the CIs for these estimates overlapped.

In the first year of follow-up, both cohorts showed improvement in their lipid profiles with declines in total cholesterol, LDL cholesterol, and triglycerides and increases in HDL cholesterol. The improvements were similar between cohorts, with the exception of the first 6 months of

**FIGURE 1.** Effectiveness of EQW compared to BI in reducing A1C and body weight. A) Absolute difference in A1C (%) and weight (kg) measured quarterly (Q1–Q4) from baseline. B) Proportion of cohorts achieving glycemic control and/or had any weight loss.
follow-up, when the percent decline in total cholesterol and LDL cholesterol was greater among EQW initiators than BI initiators (total cholesterol: 4.3% [95% CI 3.4–5.2%] versus 3.0% [2.5–3.6%]; LDL cholesterol: 4.5% [3.6–5.4%] versus 3.0% [2.4–3.5%]) (Figure 2B).

Overall, EQW initiators had a 20% lower incidence of hypoglycemia than BI initiators (RR 0.80, 95% CI 0.66–0.97) and a 32% lower incidence of hypoglycemia among patients with no evidence of hypoglycemia during baseline (RR 0.68, 95% CI 0.54–0.86) (Table 2). More than 90% of both cohorts did not have hypoglycemia during follow-up (EQW 92.6%, BI 90.8%). Of the 149 (7.4%) EQW initiators and 368 (9.2%) BI initiators who had hypoglycemia, the majority had only a single event (78 [52.3%] and 211 [57.3%], respectively). Only 3.5% of EQW initiators and 3.9% of BI initiators had multiple hypoglycemia events during follow-up (data not shown).

EQW initiators were 1.18 times (95% CI 1.06–1.31) more likely to experience gastrointestinal symptoms than BI initiators (Table 2). Of the four symptoms examined, EQW initiators experienced increased rates of nausea (RR 1.17, 95% CI 1.01–1.34) compared to BI initiators and elevated but not statistically different rates of vomiting and diarrhea (Table 2). Taken together, 340 (16.9%) of EQW initiators and 590 (14.7%) of BI initiators experienced at least one episode of nausea and/or vomiting. Whereas most patients in both cohorts had only a single episode (165 [48.5%] EQW initiators and 334 [56.6%] BI initiators), EQW initiators were slightly more likely to have multiple nausea and vomiting episodes (data not shown).

Baseline and last-quarter eGFRs were similar in both groups; among EQW initiators, the mean baseline eGFR was 85.7 mL/min/1.73 m² (95% CI 84.7–86.7) and mean eGFR in the fourth quarter (Q4) was 85.4 mL/min/1.73 m² (84.0–86.8).

**FIGURE 2.** Effect of EQW on blood pressure and lipids compared to BI. **A)** Change in SBP and DBP measured semiannually (S1, S2) from baseline. **B)** Change in lipid profiles and blood pressure measured semiannually (S1, S2) from baseline. S1, semiannual period 1 (0–6 months); S2, semiannual period 2 (>6–12 months).
Likewise, among BI initiators, the mean baseline eGFR was 85.7
mL/min/1.73 m² (83.0–85.0) vs. 86.5 mL/min/1.73 m² (84.9–86.0). Simi-
larly, the baseline and last-quarter urine albumin/creatinine ratios had
little change and were not differ-
ent across treatment groups (EQW, mean baseline: 40.2 mg/g [95% CI
36.0–44.3] and mean Q4: 36.9 mg/g [32.4–41.4]; BI, mean baseline: 46.9
mg/g [42.3–49.6] and mean Q4: 45.5 mg/g [40.8–48.2]).

**Discussion**

Relative to BI, our study demonstrates that EQW is associated with
lower risk of hypoglycemia, greater weight loss, and improved glycemic control.

| Event | Group | Cohort | n | Number With at Least One Event (%) | Incidence per 1,000 Person-Years* (95% CI) | RR (95% CI) |
|-------|-------|--------|---|-------------------------------------|--------------------------------------------|-------------|
| Hypoglycemia | All | EQW | 2,008 | 149 (7.4) | 52.5 (44.4–61.6) | 0.80 (0.66–0.97) |
| | | BI | 4,016 | 368 (9.2) | 65.7 (59.1–72.7) | Reference |
| | No prior hypoglycemia | EQW | 1,917 | 97 (5.1) | 34.9 (28.3–42.5) | 0.68 (0.54–0.86) |
| | | BI | 3,841 | 279 (7.3) | 51.1 (45.3–57.5) | Reference |
| GI symptoms | Nausea | EQW | 2,008 | 301 (15.0) | 114.0 (101.5–127.7) | 1.17 (1.01–1.34) |
| | | BI | 4,016 | 532 (13.3) | 97.9 (89.7–106.5) | Reference |
| | Vomiting | EQW | 2,008 | 194 (9.7) | 70.0 (60.5–80.6) | 1.13 (0.95–1.35) |
| | | BI | 4,016 | 349 (8.7) | 61.8 (55.5–68.7) | Reference |
| | Constipation | EQW | 2,008 | 149 (7.4) | 52.9 (44.7–62.1) | 1.00 (0.83–1.22) |
| | | BI | 4,016 | 299 (7.5) | 52.6 (46.8–58.9) | Reference |
| | Diarrhea | EQW | 2,008 | 263 (13.1) | 97.8 (86.3–110.3) | 1.15 (0.99–1.34) |
| | | BI | 4,016 | 464 (11.6) | 84.7 (77.2–92.7) | Reference |
| | Nausea and vomiting | EQW | 2,008 | 340 (16.9) | 130.9 (117.4–145.6) | 1.20 (1.05–1.37) |
| | | BI | 4,016 | 590 (14.7) | 109.5 (100.8–118.7) | Reference |
| | Diarrhea and constipation | EQW | 2,008 | 365 (18.2) | 142.0 (127.8–157.4) | 1.14 (1.00–1.30) |
| | | BI | 4,016 | 656 (16.3) | 124.5 (115.2–134.5) | Reference |
| | Any GI symptoms | EQW | 2,008 | 534 (26.6) | 225.5 (206.8–245.5) | 1.18 (1.06–1.31) |
| | | BI | 4,016 | 946 (23.6) | 191.0 (179.1–203.6) | Reference |

*Incidence rate per 1,000 person-years, with person-time censored at time of first event. GI, gastrointestinal.
glargine users, respectively. Although the average baseline A1C values were similar in the trial (8.3%) and in our study cohorts (8.3% EQW and 8.5% BI), the decline seen in the trial population was greater than the absolute declines seen in the first year of this cohort study (−0.60% and −0.43%, respectively). Compared to our cohort population, at 84 weeks post-trial initiation, a greater proportion of both EQW (44.6%) and insulin glargine (36.8%) users achieved the end point target of A1C <7.0%. In our cohort study, by the second quarter, 38.7% of EQW initiators and 28.4% of BI initiators achieved A1C ≤7%, yet the proportion meeting this goal declined in our cohorts by the end of the first year, to 29.1% and 21.5%, respectively.

The weight loss experienced by EQW users in the DURATION-3 extension study and in our observational cohort study was similar. In the trial population, EQW users lost 2.1 kg of weight in 84 weeks compared to 1.9 kg by the end of the first year in our cohort study. However, among trial participants, insulin glargine users gained 2.4 kg of weight by 84 weeks, whereas in our cohort study, BI initiators did not gain a significant amount of weight (0.18 kg only). Diamant et al. (22) showed that the benefits of glucose control and weight loss among EQW users relative to BI users were sustained up to 3 years after treatment initiation in the DURATION-3 trial.

Both studies indicate that hypoglycemia occurred less often among EQW versus BI users, yet the detection of hypoglycemia in trial participants by 84 weeks was much greater than in our 1.5 years of follow-up time. Specifically, among trial participants, 24% of EQW users and 54% of insulin glargine users experienced mild hypoglycemia, yet in the cohort study accounting for all hypoglycemia events in the EHR regardless of severity, we found that only 7.4% of EQW initiators and 9.2% of BI initiators experienced any hypoglycemia in 1 year of follow-up. Participants in clinical trials have been educated on the signs, symptoms, and confirmation of hypoglycemia and are asked to keep a record of all events regardless of severity. Therefore, although clinical notes in the EHR may capture more hypoglycemia mentions, including mild and moderate events that do not require third-party assistance, the passive capture of these events in the EHR is not comparable to the active recording of these events in a clinical trial. Our algorithm enumerates hypoglycemia from both structured fields and clinical notes, yet the events recorded in the EHR likely underestimate the actual event rate (23,24). Similarly, nausea occurred more frequently among EQW users (12%) compared to insulin glargine users (6%) within 84 weeks of follow-up, compared to 15% vs. 13% among EQW initiators and BI initiators, respectively, in our cohort study.

Another 6-month trial comparing EQW to a different BI, insulin detemir, had comparable results to the cohort study we conducted. In this trial, 44.1% of EQW and 11.4% of insulin detemir users achieved glycemic control, and EQW users lost 2.7 kg of weight compared to a 0.8-kg increase in weight among insulin detemir users. Gastrointestinal symptoms occurred more frequently in EQW users compared to insulin detemir users, with no major hypoglycemia in either group (6). In addition, a study that examined the pooled data from 12 clinical trials showed that EQW users had reductions in A1C and weight and improvements in SBP, total cholesterol, and LDL cholesterol that paralleled the findings in our cohort study (25).

The real-world benefits of EQW relative to BI may be attenuated compared to benefits measured in clinical trials because, in customary clinical care, EQW is used by a broader range of patients. For example, only patients with type 2 diabetes with suboptimum glycemic control (A1C >7%) were eligible for the DURATION-3 trial, whereas our cohort study included all patients with type 2 diabetes initiating either EQW or BI therapy, including 425 (21.2%) EQW initiators and 789 (19.6%) BI initiators with A1C ≤7% at initiation of therapy. Another indication of population differences is that, in the clinical trials, EQW and BI are adjunctive therapy to a first-line treatment; yet in our cohort study, approximately one-quarter of the patients initiated either EQW or BI as first-line therapy. When stratified by baseline A1C (Table 3), patients with an A1C >7% had little change (slight increases) in A1C by the end of the first year, and in contrast, patients with A1C >9% had the greatest declines in A1C (i.e., −1.45 percentage points among EQW initiators and −1.35 percentage points among BI initiators). The proportion of patients achieving glycemic control varied by strata as well, yet in all strata, it was greater among EQW initiators than BI initiators by the end of the first year.

Variation in weight gain is associated with differences in the titration of BI. Although the data on BI dosing available in the EHR data are limited, it is likely that titration of BI in routine care differs from that in the clinical trial, and these differences might be partially responsible for the lower weight gain among BI initiators that we observed relative to the randomized trial. Additionally, clinical trial patients are educated to recognize and actively report adverse events, whereas our detection of hypoglycemia and gastrointestinal symptoms in the EHR relies on both the recording of events requiring medical attention and on the passive reporting of symptoms by patients and the capture of reported symptoms by providers in the EHR. Although we used an algorithm that identified events that were recorded both in structured fields, as well as reports of events in clinical notes, the detection of these events is likely to underrepresent all events and overrep-
resent more serious events requiring clinical attention.

This study was based on an analysis of EHR data. Although EHR data are valuable for examination of clinical health care outcomes and treatment patterns, all EHR databases have certain inherent limitations because the data are collected for the purpose of clinical patient management, not research. First, these data represent the intent of the prescriber through the written prescription for a medication and do not indicate that a medication was filled, consumed, or taken as prescribed. Clinical variables are missing for some individuals because of variation in care practices and potentially other factors. When these data are missing in systemic ways, care must be taken in selecting the study population, and often analytic methods to account for the missing data are needed. Additionally, health care encounters with medical providers who do not contract with Optum’s EHR would not be observed.

To facilitate the uses of EHR data for the assessment of measures of efficacy and tolerability, a multiple imputation method was implemented to estimate values within standard intervals of follow-up. Multiple imputation is founded on the assumption that unobserved variables are missing at random (i.e., missingness is random after conditioning on observed covariates). This assumption is more broadly applicable than the assumption that missingness is completely at random (i.e., missingness is independent from any covariate, observed or unobserved), which would mean the missingness could generally be ignored in analysis. Although multiple imputation reduces the potential for bias, it is possible that patients with observed values are systematically different from patients with unobserved values in both measured and unmeasured ways.

Despite the limitations, and consistent with the findings of clinical trials, this real-world observational cohort study has shown that relative to BI, EQW offers a clinical advantage with respect to the likelihood of achieving both glycemic control and weight loss, along with lower risk of hypoglycemia, and that these benefits are balanced against a modest increase in gastrointestinal symptoms. Further observation is required to determine whether these measures of effectiveness persist beyond 1 year.

### Duality of Interest

This project was carried out under a research contract between Optum Epidemiology and AstraZeneca. All authors are employees of Optum except for Q.Q., who is an employee of AstraZeneca. No other potential conflicts of interest relevant to this article were reported.

### Author Contributions

A.M.L. contributed to the study’s concept, design, analytic plan, and conduct, as well as wrote the manuscript, contributed to the discussion, and reviewed and edited the manuscript. Q.Q. and D.D.D. contributed to the study concept design and discussion and reviewed and edited the manuscript. A.P.N. and J.D.S. contributed to the study conduct and analytic plan, as well as to the discussion, and reviewed and edited the manuscript. S.M.E., L.Y., C.R.C., and R.V.G. completed data analytics and statistical analyses for the study and reviewed and edited the manuscript. A.M.L 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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| A1C Strata at Baseline | Treatment Group | Baseline A1C, % (95% CI) | Absolute Change in A1C % by End of Year 1, Difference (95% CI) | A1C ≤7% by End of Year 1, % (95% CI) |
|-----------------------|-----------------|--------------------------|---------------------------------------------------------------|-----------------------------------|
| ≤7%                   | EQW             | 6.48 (6.43–6.52)         | 0.11 (–0.02 to 0.24)                                          | 57.2 (50.6–63.7)                  |
|                       | BI              | 6.48 (6.44–6.52)         | 0.40 (0.30–0.49)                                              | 47.5 (42.4–52.6)                  |
| 7.1–9%                | EQW             | 7.96 (7.91–8.02)         | –0.39 (–0.50 to –0.27)                                        | 27.1 (20.9–33.3)                  |
|                       | BI              | 8.06 (7.98–8.13)         | –0.21 (–0.32 to –0.10)                                        | 19.7 (15.6–23.8)                  |
| >9%                   | EQW             | 10.17 (10.06–10.29)      | –1.48 (–1.70 to –1.26)                                        | 12.1 (3.8–20.4)                   |
|                       | BI              | 10.36 (10.24–10.49)      | –1.35 (–1.49 to –1.21)                                        | 8.3 (2.9–13.7)                    |
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