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ORIGINAL ARTICLE

A real-world study of treatment patterns and outcomes in US managed-care patients with type 2 Diabetes initiating injectable therapies

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Aims: Examine real-world outcomes in patients with type 2 diabetes mellitus (T2DM) initiating injectable therapy as part of the Initiation of New Injectable Treatment Introduced after Anti-diabetic Therapy with Oral-only Regimens (INITIATOR) study.

Materials and methods: Linked insurance claims and medical record data were collected from 2 large US health insurers (April 1, 2010 to March 31, 2012) of T2DM adults initiating treatment with glargine (GLA) or liraglutide (LIRA). Baseline characteristics were examined and changes in 12-month follow-up outcomes were described for both treatment groups: HbA1c, weight change, hypoglycaemia, persistence, healthcare utilisation and costs.

Results: A total of 4490 patients were included (GLA, 2116; LIRA, 2374). At baseline, GLA patients had significantly higher HbA1c vs LIRA patients (9.72% vs 8.19%; $P < .001$), lower likelihood of having HbA1c < 7% (7.1% vs 23.8%; $P < .001$), lower bodyweight (100.9 kg vs 110.9 kg, $P < .001$), higher Charlson Comorbidity Index score (0.88 vs 0.63; $P < .001$), and higher diabetes-related costs ($3492 vs $2089; $P < .001$), respectively.

During 12-months of follow-up, treatment persistence was 64%, mean HbA1c reduction was −1.24% and weight change was + 1.17 among GLA patients, and was 49%, −0.51% and −2.74 kg, respectively, among LIRA patients. Diabetes-related costs increased significantly from baseline to follow-up for LIRA patients ($2089 vs $3258, $P < .001$) but not for GLA patients ($3492 vs $3550, $P = .890$).

Conclusions: There were clinically relevant baseline differences in both groups, suggesting that GLA and LIRA are prescribed for different patient groups, and highlighting that efficacy results from clinical trials do not always translate into real-world practice. Significant increases in healthcare costs were observed in the LIRA group, warranting further cost-effectiveness analysis.

KEYWORDS

basal insulin, database research, incretin therapy, observational study, type 2 diabetes

1 | INTRODUCTION

Many patients with newly diagnosed type 2 diabetes mellitus (T2DM) initially achieve glycaemic control with first-line oral therapy and lifestyle changes. However, the progressive nature of the disease will result in the need for intensification of therapy for most patients within 5 years of diagnosis.[1] Second-tier therapies recommended by the American Diabetes Association/European Association for the

Study of Diabetes (ADA/EASD) include additional classes of oral therapy or injectable therapy with a basal insulin or glucagon-like peptide 1 (GLP-1) receptor agonists.[2] The American Association of Clinical Endocrinologists/American College of Endocrinology (AACE/ACE) guidelines also suggest that GLP-1 receptor agonists could even be used as first-line therapy.[3] Individualization of therapy is key to the successful control of T2DM, yet many patients delay the initiation of beneficial therapeutic strategies because of misconceptions related to injectable therapies, and healthcare providers may still inaccurately view insulin therapy as a last resort.[4]

Fear of injections, concerns regarding hypoglycaemia, the need for lifestyle changes and a sense of failure because of a lack of understanding of T2DM's progressive nature are common barriers to therapy intensification.[4,5] Some of these barriers, particularly those related to impacts on lifestyle, have been mitigated by advances in injection devices. The use of insulin pen devices, rather than traditional vial and syringe delivery, may help address issues related to convenience, ease of use and discreet delivery.[6,7] Adherence, persistence and clinical outcomes also appear to be improved by pen use which may lead to long-term advantages in terms of reducing morbidity, attaining health plan quality goals (such as healthcare effectiveness data and information set [HEDIS] measures) and achieving cost savings.[8–13] Both the basal analogue insulin glargine (GLA, 100 U/mL) and the GLP-1 receptor agonist liraglutide (LIRA) are available for delivery using pen devices, with this being the exclusive route of delivery in the case of liraglutide.

Basal insulins and the GLP-1 receptor agonists have 2 very distinctive mechanisms of action (MOA). A basal insulin analogue activates insulin receptors. As a result, it acts like physiological insulin to increase glucose disposal and decrease hepatic glucose production. Advantages of this MOA include a near-universal response, a theoretically unlimited efficacy, and a decrease in microvascular risk. Disadvantages of basal insulins include an increased risk of hypoglycaemia, and weight gain. GLP-1 receptor agonists activate GLP-1 receptors, thereby increasing insulin secretion and satiety.[14] They also decrease glucagon secretion[15] and slow gastric emptying.[14] Advantages of the GLP-1 receptor agonists' MOA include no increased risk of hypoglycaemia, weight loss and reduction in postprandial glucose excursions.[2] Reduced cardiovascular risk has been suggested as well, with the recent LEADER trial demonstrating superior cardiovascular outcomes for liraglutide vs placebo.[16] Disadvantages include gastrointestinal side effects[17,18] and an increased heart rate.[19,20] The GLP-1 receptor agonists might be associated with an increased risk of acute pancreatitis and animal studies have reported an increase in c-cell hyperplasia and medullary thyroid tumours.[21–23] Finally, both basal insulins and GLP-1 receptor agonists are currently available only as injectable products and patients must receive self-administration training.[2]

Two randomized controlled clinical trials have investigated the efficacy of insulin glargine 100 U/mL vs liraglutide for patients with T2DM who were unable to achieve glycaemic control on previous oral therapy alone.[24,25] The Efficacy Assessment of insulin Glargine Versus LiraglutidE After Oral Agent Failure (EAGLE) trial demonstrated that similar numbers of patients initiating GLA and LIRA attained a glycated haemoglobin A1c (HbA1c) level of <7% (48.4% and 45.9%, respectively). Patients using GLA had a greater mean reduction in HbA1c and in fasting plasma glucose compared with patients using LIRA. Patients using GLA gained a mean 2.0 kg in bodyweight while patients using LIRA lost weight (−3.0 kg). Hypoglycaemia was more common among GLA users, while gastrointestinal adverse events were more commonly reported by patients using LIRA.[24] The Liraglutide Effect and Action in Diabetes-5 (LEAD-5) trial found a greater reduction in HbA1c among LIRA users compared with GLA users (−1.33% and −1.09%, respectively), with 53.1% of LIRA users and 45.8% of insulin glargine users achieving an HbA1c level of <7%. Safety outcomes were comparable to those reported in the EAGLE trial.[25]

However, it is increasingly recognized that clinical trials might not always provide sufficient information for decision-making in real-world settings, as they operate in an idealized environment and assess limited patient populations.[26] There is currently a need for more real-world studies revealing how therapies for T2DM management are best applied within the larger environment of the healthcare delivery system, in which patients are more heterogeneous, and treatment costs and access become issues for patients and clinicians.

The Initiation of New Injectable Treatment Introduced after Antidiabetic Therapy with Oral-only Regimens (INITIATOR) study aimed to investigate real-world treatment patterns and clinical outcomes among patients with T2DM who were previously treated with only oral anti-diabetes drugs (OADs) and initiated injectable therapy with GLA disposable pen or LIRA. This analysis expands on the previously published pilot data[27]; we report treatment pattern data and describe changes in observed clinical and economic outcomes within treatment groups from the full study phase of INITIATOR.

2 | MATERIALS AND METHODS

2.1 | Data sources

This study combined medical chart data with health plan medical and pharmacy claims data, including enrolment information, and linked electronic laboratory results from 2 large US commercial health insurers associated with Optum™ (OP) and HealthCore® (HC). The study protocol was developed collaboratively between the study sponsor, OP and HC. However, data collection was conducted by OP and HC independently of each other. In the current analysis, data are presented as a single combined dataset, but also stratified by data source (ie, OP and HC). Medical records were abstracted from paper, electronic medical records or hybrid type of medical records. When data were available in both the administrative claims and in medical charts, a prioritization was used for retaining the final measures presented in the study results. For laboratory results that were available from both claims and chart data sources for a given period, the results from the chart were retained for the measure. Hypoglycaemic events were captured from both claims and charts and are presented separately. Other study measures were available in only one data source as described elsewhere in the description of study methodology (see Box S1).

Institutional review board (IRB) approval was obtained to identify patients so that medical chart information could be collected. Individual patients were not identifiable during data analysis, in compliance

with the United States Health Insurance Portability and Accountability Act (HIPAA).

2.2 | Study population

Data were included for patients with T2DM aged ≥18 years who were previously on only OADs (metformin, sulfonylureas, dipeptidyl peptidase [DPP]-4 inhibitors, thiazolidinediones [TZD], meglitinides or α-glucosidase inhibitors) and who initiated either GLA disposable pen or LIRA between April 1, 2010 and March 31, 2012. T2DM was defined as having ≥ 1 inpatient/emergency department (ED) medical claim or ≥2 ambulatory medical claims (≥30 days apart) with a primary or secondary diagnosis code for T2DM according to the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) (250.x0 or 250.x2), as used in previously published claims-database studies.[28–30] The index date was the date when the initial GLA or LIRA prescription was filled. Patients were required to have continuous healthcare coverage during the 6 months before (baseline) and 1 year after initiation (follow-up). All patients were required to have ≥1 pharmacy claim for an OAD during the baseline period and no use of injectable therapy. In addition, patients were required to have an HbA1c result (either from laboratory data linked to the claims or from the medical record) during the baseline period through 15 days after the index date, as well as at least one measurement of weight at baseline. A complete list of patient inclusion and exclusion criteria can be found in the Appendix S1 and patient attrition charts in Figure S1.

2.3 | Baseline measures

Baseline demographic and clinical characteristics included age, gender, geographic region, health plan type, body mass index (BMI), weight, diabetes medication usage, duration of disease and individual comorbidities. In addition, the Charlson Comorbidity Index (CCI) score was calculated, which is the weighted sum of 19 categories of comorbidity defined using ICD-9-CM diagnoses codes, with a higher score indicating a more severe burden of comorbidity and a higher mortality risk.[31,32] Further measures that were captured at baseline, from chart and/or claims, included HbA1c levels, fasting plasma glucose (FPG) levels, blood pressure, hypoglycaemic events, healthcare resource utilization, healthcare costs and reasons for index drug initiation (see Box S1). When multiple values were available, the value closest to the index date was chosen as the baseline value.

Data on hypoglycaemia were captured from both charts and claims and reported separately. Overall hypoglycaemia was captured from claims via ICD-9-CM diagnosis codes as described by Ginde et al.[33] The specific settings (inpatient and/or ED or ambulatory [outpatient hospital visit or physician office visit]) for these hypoglycaemic events were identified and used as a proxy for severity of hypoglycaemia. Severe hypoglycaemia was defined as a hypoglycaemic event in an inpatient or ED setting. Hypoglycaemia events from chart were separately identified, but their severity was not assessed.

HbA1c values are expressed as a % of total haemoglobin (% = [0.09148 × mmol/mol value] + 2.152).[34] Healthcare resource utilization included hospitalizations and visits to the ED, ambulatory care and other outpatient visits. Resource utilization was considered diabetes-related when a claim included a primary or secondary diagnosis of diabetes (ICD-9-CM: 250.xx). Healthcare costs were the sum of health plan-paid and patient-paid amounts. Diabetes-related healthcare costs included costs from medical claims with a primary or secondary diagnosis of diabetes (ICD-9-CM: 250.xx), anti-hyperglycaemic medications and diabetes supplies such as glucose meters and test strips.

2.4 | Endpoint measures

We describe changes in observed 12-month outcome measures within each of the 2 treatment groups, including treatment persistence, HbA1c, change in HbA1c from baseline, bodyweight and BMI, change in bodyweight and BMI from baseline, hypoglycaemia, medication use (including persistence, dose and daily average consumption of insulin [DACON]), and healthcare resource utilization and costs during the follow-up period (see Box S1). When multiple HbA1c, weight or BMI values were available, values closest to the end of follow-up (index date + 359 days) were chosen. Follow-up hypoglycaemia events were captured using the same approach as the baseline.

Treatment persistence was defined as the percentage of patients remaining on therapy without discontinuation. Therapy was considered discontinued if the prescription was not refilled within the expected time of medication coverage (using the 90th percentile of observed time between first and second fills), stratified by the metric quantity supplied, during the 12-month follow-up period.[35] Persistence rates for GLA were based on claims for glargine pen as well as vial-and-syringe fills, as patients could switch their insulin delivery device without changing insulin glargine treatment regimen. Daily dose was evaluated from charts if documented and from pharmacy claims for all patients. Dose was averaged for the first and second 6 months of the follow-up period, using the dose reported in the medical chart. The daily average consumption (DACON) was estimated from pharmacy claims as the total amount of GLA (insulin units/day) or LIRA (mg/day) dispensed before the last refill of the study drug divided by the total number of days between initiation and last refill during follow-up. Information on gastrointestinal (GI) symptoms such as abdominal pain, bloating, constipation, diarrhoea, nausea, vomiting, etc. was collected from patient charts. Healthcare resource utilization and costs during the follow-up period were computed using definitions consistent with those used for the baseline period.

A simple cost-effectiveness analysis was conducted by examining population-average incremental costs per 1% HbA1c reduction, which was calculated as follows: (mean second half-year of follow-up costs – mean half-year baseline costs)/mean % reduction in HbA1c from baseline to 12-months' follow-up.

2.5 | Statistical analyses

The analysis was conducted using an intent-to-treat approach, with patients who added to or switched from their initial treatment regimen remaining in their original analysis cohort. This approach both

captures physicians' prescribing intentions and reflects real-world outcomes of therapy including the consequences of switching or adding a new therapy.

The primary analysis used one analytic data set of pooled OP and HC data. Sub-analyses on OP and HC datasets were conducted independently.

Differences in baseline characteristics were compared using Student t tests or χ^2 tests, depending on the distribution of the measure. Because of significant baseline demographic and clinical differences observed between the 2 cohorts, we examined the propensity score distributions (measuring the aggregated likelihood of initiating the study drugs).[36] In the sub-group analysis of OP data with baseline HbA1c ≥ 7%, the GLA and LIRA propensity score distributions were quite different and had poor overlap near the endpoints, suggesting significant methodological challenges in conducting traditional comparative analysis between the 2 cohorts (Figure S2). In fact, a drop of nearly 50% in sample size was seen when 1:1 greedy propensity score matching was implemented in an attempt to balance observed baseline differences between the cohorts. Analysis on HC data showed similar patterns (data not shown).

Therefore, changes in outcomes from baseline to 12-months' follow-up were assessed descriptively within each cohort, and no statistical comparisons of follow-up outcomes between the cohorts are reported. Within each cohort, HbA1c levels, patient bodyweight, hypoglycaemia rates, healthcare utilization and costs were compared between baseline and the first and second 6 months of the follow-up period using paired t-tests and McNemar tests as applicable.

3 | RESULTS

3.1 | Baseline patient characteristics

A total of 4490 patients were included in the analysis, 2747 from the OP database (GLA-OP, n = 1278; LIRA-OP, n = 1469) and 1743 from the HC database (GLA-HC, n = 838; LIRA-HC, n = 905). In total, 2116 patients initiated GLA therapy and 2374 patients initiated LIRA therapy and were included in the combined cohort (GLA and LIRA, respectively).

At baseline, significant demographic and clinical differences were observed between GLA and LIRA groups for both combined (Table 1) and individual cohorts (Tables S1 and S2). In general, GLA patients were older, were more likely to be men, and had significantly more comorbid diagnoses, as indicated by a higher CCI. When examining reasons for initiating the study drugs as documented in the medical chart, GLA and LIRA patients also differed significantly (Figure 1). Clinically, GLA patients had significantly higher HbA1c, were more likely to be receiving sulfonylurea treatment, had numerically, but not statistically significant, higher rates of hypoglycaemia and macrovascular and microvascular diseases, and incurred significantly higher diabetes-related healthcare costs ($3492 vs $2089; $P < .001$). LIRA patients, however, had significantly higher bodyweight, were more likely to be obese, and almost 1 of 4 LIRA patients had baseline HbA1c < 7.0%. In addition, for GLA patients, prescribing physicians were more likely to be primary care physicians, whereas, for LIRA patients, prescribing physicians were more likely to be endocrinologists. At baseline, GLA patients (compared with LIRA patients) more frequently had a hospitalization (7.9% vs 3.3%; $P < .001$) or ED visit (6.6% vs 3.1%; $P < .001$). Outpatient visits were comparable at baseline (94.9% vs 95.9%, $P = .089$). Diabetes-related medical costs were higher for GLA patients ($2740 vs $1319 per patient; $P < .001$), while baseline diabetes-related pharmacy costs and diabetes supply costs were comparable ($680 vs $700, $P = .359$ and $72 vs $70, $P = .448$, respectively).

3.2 | 12-Month follow-up outcomes

3.2.1 | Treatment persistence and dosing patterns

At 12-month follow-up, overall treatment persistence was 64% for GLA and 49% for LIRA patients, and the mean number of persistent days was 306.2 for GLA and 263.3 for LIRA. Similar persistence patterns were observed in the individual database cohorts for GLA and LIRA (Table S3).

As documented on charts, the average daily dose during the first and second half-year of follow-up among GLA patients was 21.6 U/day (n = 919) and 35.0 U/d (n = 854), respectively. For LIRA patients, it was 1.08 mg/d (n = 1001) and 1.49 mg/d (n = 757), respectively. Among GLA patients for whom the number of injections was documented in the chart, the majority used GLA once daily during the first (97.4%, total n = 1438) and second half-year of follow-up (90.7%, total n = 862).

Estimated from filled pharmacy claims, the mean DACON among GLA and LIRA patients was 29.2 U/d and 1.14 mg/d over the follow-up period, respectively. Similar patterns were observed in the individual database cohorts (Table S3).

3.2.2 | HbA1c

Improvements in HbA1c levels were observed at 12-month follow-up compared with baseline in both GLA and LIRA groups. Among patients with follow-up HbA1c data available (GLA, n/N = 1467/2116; LIRA, n/N = 1713/2374) the average 12-month follow-up HbA1c was 8.35% in the GLA group and 7.62% in the LIRA group (Figure 2), with similar follow-up values in the OP and HC cohorts (Figure S3A). At 12-month follow-up, with a significantly higher HbA1c at baseline, the average reduction in HbA1c for GLA patients was −1.24%, and the percentages of GLA patients achieving HbA1c target levels <7.0% and <8.0% were 24.5% and 50.4%, respectively. For LIRA patients, the average HbA1c reduction was −0.51%, and the percentages for LIRA patients were 42.2% and 68.2%. Similar HbA1c patterns were observed in the individual database cohorts for GLA and LIRA (Figure 2B, Figure S3B and Table S3).

3.2.3 | Weight/BMI

At 12-month follow-up, GLA patients with follow-up weight data available (n/N = 1613/2116) exhibited a slight weight gain (+1.17 kg, 1.2% increase from baseline) and average BMI increased by 0.39 kg/m^2. LIRA patients with follow-up weight data available (n/N = 1828/2374) lost weight (−2.74 kg, 2.5% decrease from baseline) and their average BMI decreased by 0.99 kg/m^2 in the combined cohort (Figure 3A and B). Similar patterns were observed in individual cohorts (Figure S4A and B).

TABLE 1 Baseline patient demographic and clinical characteristics (N = 4490)

Characteristic	GLA (n = 2116)	LIRA (n = 2374)	*P* value
Age in years, mean (SD)	53.2 (8.86)	52.3 (8.78)	<.001
Sex, n (%)			
Male	1222 (57.8)	1226 (51.6)	<.001
Female	894 (42.2)	1148 (48.4)	<.001
Health plan type, n (%)			
HMO	345 (16.3)	337 (14.2)	.049
POS	1060 (50.1)	1197 (50.4)	.827
PPO	551 (26.0)	644 (27.1)	.411
Other	160 (7.6)	196 (8.3)	.390
Bodyweight, kg, mean (SD)[1]	100.9 (23.4)	110.9 (24.3)	<.001
BMI, kg/m^2, mean (SD)[1,2]	34.6 (7.4)	37.9 (7.5)	<.001
BMI, n (%)[1]			
Normal/underweight (<25 kg/m^2)	120 (7.1)	24 (1.3)	<.001
Overweight (25 to <30 kg/m^2)	372 (21.9)	217 (11.5)	<.001
Severely/morbidly obese (≥30 kg/m^2)	1208 (71.0)	1654 (87.2)	<.001
HbA1c, %, mean (SD)[1]	9.72 (2.1)	8.19 (1.7)	<.001
HbA1c < 7.0%, n (%)[1]	151 (7.1)	566 (23.8)	<.001
Prescribing physician, n (%)			
Endocrinologist	397 (18.8)	612 (25.8)	<.001
Primary care physician	1472 (69.6)	1498 (63.1)	<.001
OADs, n (%)[3]			
Metformin	1680 (79.4)	1969 (82.9)	<.001
DPP-4 inhibitors	812 (38.4)	891 (37.5)	.561
Meglitinides	62 (2.9)	65 (2.7)	.699
Sulfonylureas	1289 (60.9)	1115 (47.0)	<.001
Thiazolidinediones	666 (31.5)	787 (33.2)	.231
Alpha-glucosidase inhibitors	17 (0.8)	9 (0.4)	.061
Number of OADs per patient, mean (SD)	2.14 (0.90)	2.04 (0.90)	<.001
Duration of diabetes, years, mean (SD)[4]	7.3 (7.5)	6.2 (5.5)	.010
Comorbidities, n (%)			
Myocardial infarction	46 (2.2)	31 (1.3)	.025
Congestive heart failure	74 (3.5)	55 (2.3)	.018
Renal disease	134 (6.3)	84 (3.5)	<.001
Hypoglycaemia	49 (2.3)	44 (1.9)	.278
Neuropathy	165 (7.8)	151 (6.4)	.060
Nephropathy	82 (3.9)	87 (3.7)	.711
Retinopathy	158 (7.5)	123 (5.2)	.002
CCI, mean (SD)	0.88 (1.53)	0.63 (1.17)	<.001
Total diabetes-related costs in $, mean (SD) per patient	3492 (13 902)	2089 (4399)	<.001

Abbreviations: BMI, body mass index; CCI, Charlson Comorbidity Index; DPP-4, dipeptidyl peptidase-4; GLA, glargine; HbA1c, glycated haemoglobin A1c; HMO, health maintenance organization; LIRA, liraglutide; POS, point of service; PPO, preferred provider organization; OADs, oral anti-diabetes drugs; SD, standard deviation.

[1] Between 6 months prior to and 15 days after index date.

[2] Based on n = 1335 GLA patients and n = 1501 LIRA patients.

[3] During the baseline period, ie, 6 months prior to the index date.

[4] Disease duration data was available for part of the study population (total n = 963).

3.2.4 | Hypoglycaemia

Overall claims-based hypoglycaemia rates in the first and second half-year of follow-up data were 2% to 3% for GLA. When using chart-based data to assess rates of hypoglycaemia, any type of hypoglycaemia event was reported for 16.3% of GLA patients during the 12-months' follow-up. For LIRA patients, those rates were 1% to 2% for claims-based, and 9.4% for chart-based data. Rates of claim-based inpatient/ED hypoglycaemia in both cohorts were low

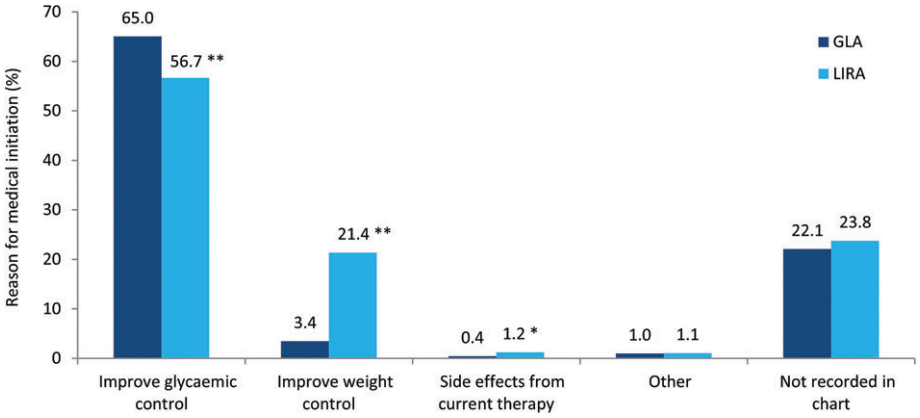

FIGURE 1 Reasons for initiating GLA or LIRA. Levels of significance: *P = .004; **P < .001. GLA, glargine; LIRA, liraglutide.

(Figure 4). Patterns were similar in the 2 individual cohorts although there was more variability in incidence of hypoglycaemia in the HC cohort (Figure S5).

3.2.5 | GI symptoms

During follow-up, 22.9% of GLA patients had at least one GI symptom documented in the chart. The most frequent symptoms were: nausea (8.3%), abdominal pain (6.4%), diarrhoea (6.3%) and vomiting (3.6%). For LIRA patients, the rate of having at least one chart-documented GI symptom was 34.5%, and corresponding rates of individual symptoms were: nausea (17.7%), abdominal pain (7.6%), diarrhoea (8.5%) and vomiting (5.8%).

3.2.6 | Healthcare utilization and costs

During follow-up, GLA and LIRA patients showed different healthcare utilization patterns as compared with baseline. While both groups used fewer concomitant OADs, for GLA patients significantly lower rates of diabetes-related hospitalizations and ED visits were observed, while for LIRA patients, there was no significant change in diabetes-related hospitalizations and ED visits from baseline (Figure 5). All-cause healthcare utilization showed similar patterns (data not shown). Compared with baseline, in both the GLA and LIRA groups, significant increases in diabetes drug and diabetes supply costs were observed at the second half-year follow-up (Figure 6A and B). However, overall, LIRA patients had a significant increase in total diabetes-related healthcare costs in the second half-year follow-up, whereas GLA patients had no significant increase (Figure 6A and B and Figure S6A-D). Total costs remained higher for GLA patients compared to LIRA patients after the first ($4436 vs $3242) and second half year of follow-up ($3550 vs $3258). The biggest contributor to increased costs in the LIRA group was pharmacy costs. All-cause healthcare costs showed similar patterns (data not shown).

For GLA patients, incremental diabetes-related total costs and drug costs per 1% HbA1c reduction per patient were $477 and $483, respectively. For LIRA patients, incremental diabetes-related total

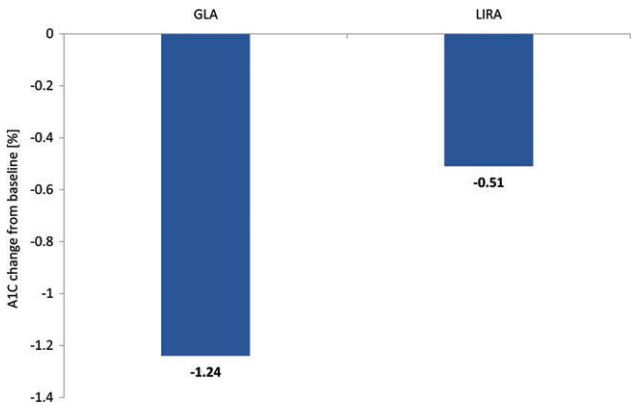

FIGURE 2 HbA1c change from baseline among patients with follow-up HbA1c data available (GLA, n = 1467; LIRA, n = 1713). GLA, glargine; HbA1c, glycated haemoglobin A1c; LIRA, liraglutide.

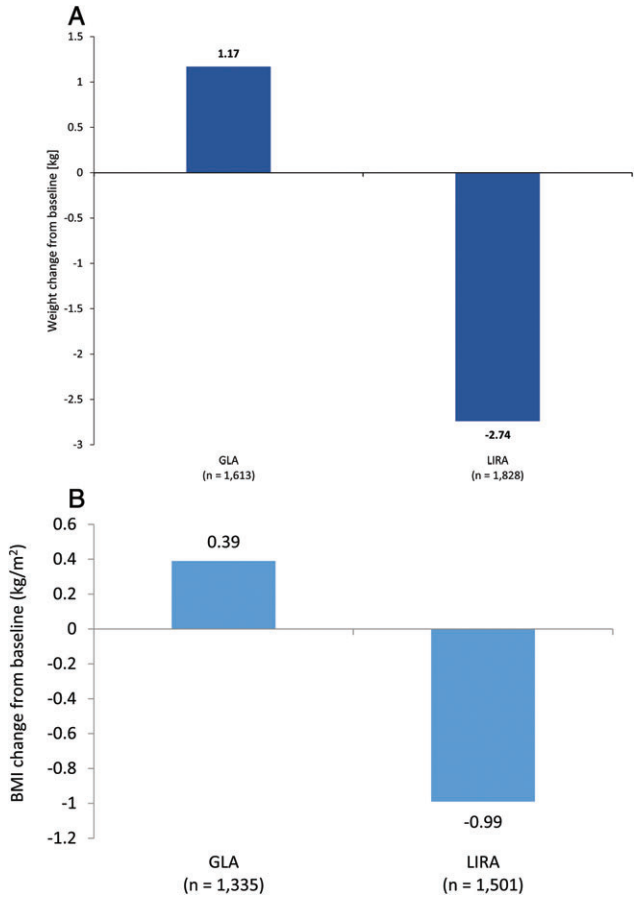

FIGURE 3 Bodyweight change from baseline to follow-up at 12-months (A) and BMI change from baseline to follow-up at 12-months (B). BMI, body mass index; GLA, glargine; LIRA, liraglutide.

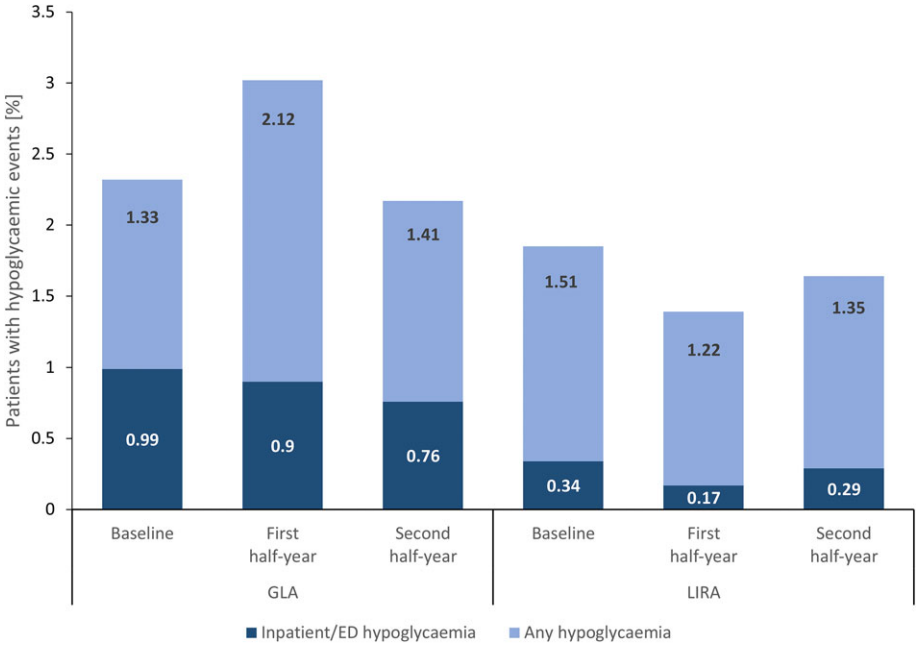

FIGURE 4 Hypoglycaemia rates at baseline, first half-year follow-up and second half-year follow-up for the combined cohort (based on claims data only). ED, emergency department; GLA, glargine; LIRA, liraglutide.

costs and drug costs per 1% HbA1c reduction per patient were $4407 and $3534, respectively (Figure 7).

4 | DISCUSSION

This large-scale real-world study revealed significant and clinically relevant differences in prescribing patterns between GLA and LIRA in patients whose T2DM was uncontrolled by OADs alone. The INITIATOR study aimed to provide a better understanding of medical practice beyond the controlled environment of randomized clinical trials, including baseline characteristics of patients starting on GLA or LIRA, the extent to which patients adhere and persist on each treatment, and the descriptive clinical and economic outcomes associated with both GLA and LIRA. Patients receiving treatment with GLA had a higher HbA1c, were treated with more OADs, had a higher Quan-modified CCI, and had a higher prevalence of renal disease and retinopathy at baseline. In contrast, patients treated with LIRA were more likely to have an HbA1c < 7% and to be obese before starting treatment.

Clinical trials have demonstrated that insulin is more effective than any other available diabetes therapy, whether used as first-line therapy, or as second-line or later in those patients with progressive hyperglycaemia.[2,37] Guidelines suggest that insulin is more likely than other options to be successful as a third-line therapy in patients with high HbA1c values (≥9%) which may in part be driving insulin prescribing patterns.[2] In line with this recommendation, patients treated with GLA had a numerically larger reduction in HbA1c than those treated with LIRA. The high prevalence of patients with a baseline HbA1c < 7% in the LIRA group, along with greater prevalence of obesity and higher mean bodyweight, suggests that treatment decisions could have been driven partially by the potential for reductions in bodyweight with GLP-1 receptor agonist treatment.[38–40] Indeed, mean follow-up weight was reduced in patients receiving LIRA in all the patient cohorts studied.

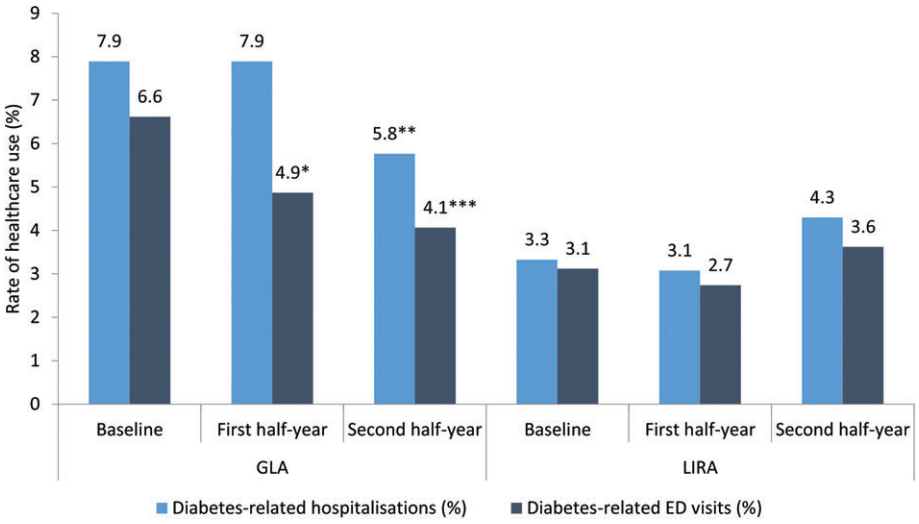

FIGURE 5 Diabetes-related hospitalization and ED visit rate at baseline and during the first and second half-years of follow-up in GLA patients and LIRA patients. Change from baseline: *P < .05; **P < .01; ***P < .001. ED, emergency department; GLA, glargine; LIRA, liraglutide.

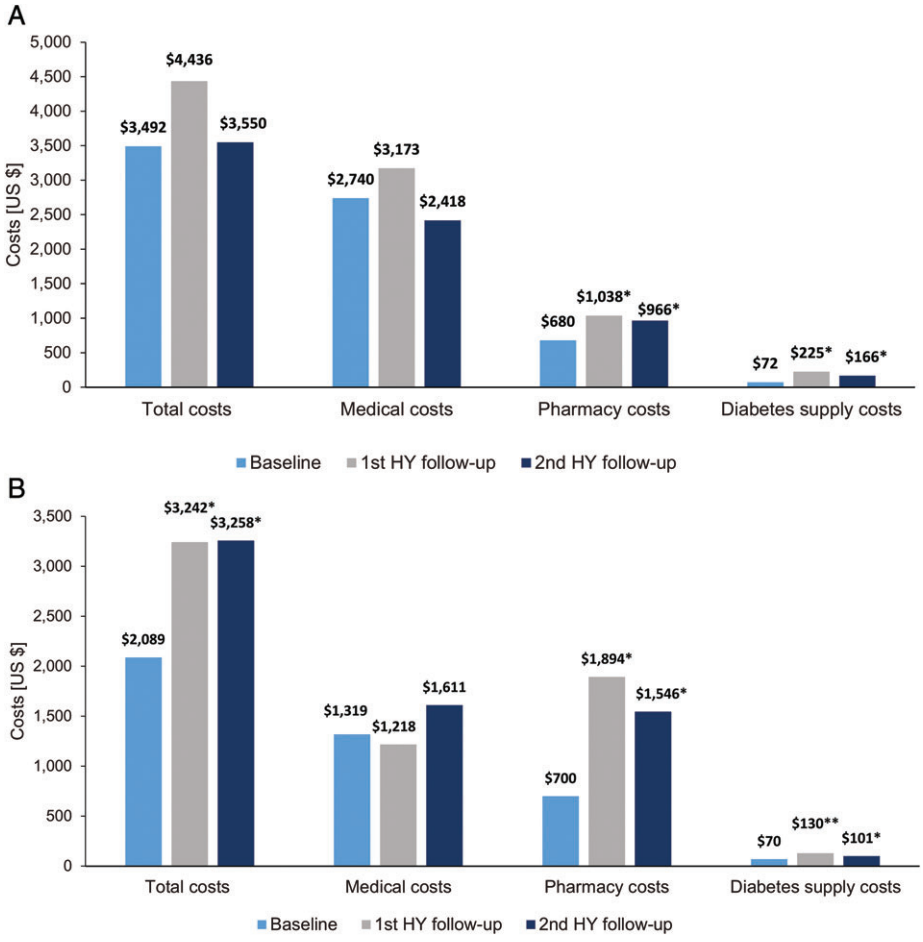

FIGURE 6 Diabetes-related healthcare costs at baseline and during the first and second half-years of follow-up in GLA patients (A) and LIRA patients (B). GLA, glargine; HY, half-year; LIRA, liraglutide. *$P < .001$ vs baseline.

Fewer patients with renal disease received LIRA and it is tempting to speculate that the safety concerns associated with the related GLP-1 receptor agonist exenatide may be affecting prescribing patterns.[41] However, a recently presented study suggests that LIRA can be used by patients with moderate renal impairment without exacerbating their condition.[42] It is notable that baseline hypoglycaemia was higher and severe hypoglycaemia was markedly higher in patients who received GLA than in those who received LIRA. The greater prevalence of sulfonylurea prescription may be related to the difference in the rate of hypoglycaemia in GLA patients.[43] Especially when considering more frequent sulfonylurea prescription rates in conjunction with the higher baseline congestive heart failure rates and chronic kidney disease rates among GLA patients, it is probable that these patients were at a higher baseline risk of hypoglycaemia even before starting injectable therapy.

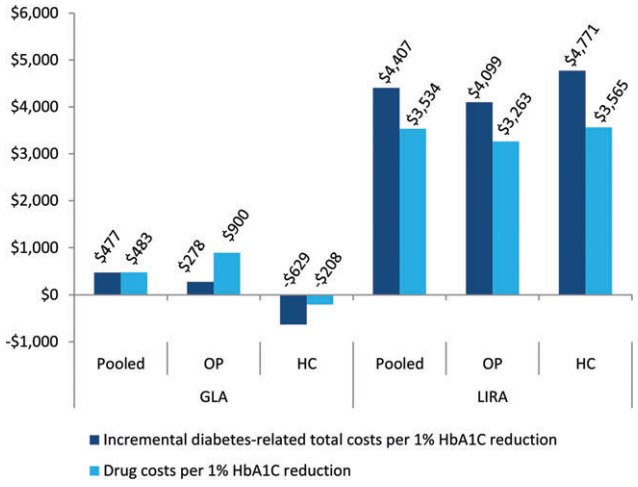

FIGURE 7 Incremental diabetes-related total costs per 1% HbA1c reduction and drug costs per 1% HbA1c reduction in GLA users and LIRA users. Outcomes are shown for the pooled analysis as well as for the separate analyses in the OP and HC databases. GLA, glargine; HbA1c, glycated haemoglobin A1c; HC, HealthCore; LIRA, liraglutide; OP, Optum.

The rate of any claims-based hypoglycaemia and severe hypoglycaemia rose in the first 6 months in the GLA group but had returned to slightly below baseline levels after the second 6-month follow-up. Hypoglycaemia levels dropped following initiation of injectable therapy in the LIRA group, remaining below baseline levels for the full follow-up period. Claims data probably significantly underestimate the rate of hypoglycaemia, especially mild or moderate hypoglycaemia, and the use of the care setting as a proxy for severity may be limited by poor specificity. However, these data suggest that initiation of injectable therapy does not result in a major increase in provider-reported hypoglycaemia, which is a significant concern for both patients and physicians initiating injectable therapy, particularly insulin.[5] Chart data on reported hypoglycaemia was obtained as well, showing higher rates for hypoglycaemia (16% in the GLA group and 9% in the LIRA group, up from 5% to 6% at baseline [data not shown]). In clinical trials comparing insulin with GLP-1 receptor agonists, the

insulin arm will invariably show an increase in patient-reported rates of hypoglycaemia. The discordance between claim-based and chart-based rates of hypoglycaemia results from differences in the methods by which rates of hypoglycaemia are ascertained. The lack of glycaemic equipoise at baseline in the 2 groups complicates the interpretation of between-group differences in hypoglycaemia. A greater between-group difference in hypoglycaemia may have been observed if the 2 patient groups had similar glycaemic control at baseline.

Overall, GLA and LIRA patients in this real-world study not only differed from each other, but also differed substantially from the patient population studied in comparative randomized clinical trials (EAGLE[24] and LEAD-5[25]), particularly regarding baseline HbA1c, weight and cardiovascular comorbidities (Table S2). Although randomized clinical trials may be considered the gold standard because of their high levels of internal validity, and are invaluable in showing therapy effects in specific patient populations, their selective populations and controlled conditions complicate the generalizability of their efficacy and safety outcomes to the broader population of patients being treated in real-world clinical practice.[44–46] Observational studies such as the INITIATOR study have less stringent inclusion and exclusion criteria and will more closely mirror real-world situations and outcomes in patients with chronic health conditions.[47] Also, patients participating in clinical studies have been shown to be more adherent to and persistent in their treatment regimens.[48] Therefore, the results from randomized clinical trials should be applied with caution to real-world practices, and complimented with the outcomes of well-designed real-world observational studies to obtain clinically relevant, long-term outcomes data.[49] The comparison between baseline profiles in real-world patients with those of patient cohorts participating in randomized clinical trials, such as LEAD-5 and EAGLE, exemplifies that data from studies with high internal validity and standard of evidence may not be generalizable to the general population, and suggests challenges when translating these data into guidelines for clinical practice.

Cost changes following initiation of injectable therapy differed between patients who received GLA or LIRA. Total diabetes-related costs did not change significantly in the GLA treatment group, although pharmacy costs did increase significantly. There was a marked 56% increase in total diabetes-related costs in the LIRA group, primarily driven by significant increases in pharmacy costs and diabetes supply costs as well as a small non-significant increase in medical costs. Total costs were higher for the GLA group than for the LIRA group at baseline and remained higher during both the first and second half-years of follow-up. A systematic review of recent cost-effectiveness studies suggests that LIRA is cost-effective when compared with a number of oral therapies as well as with the injectable GLP-1 receptor agonist exenatide. However, the authors point out a number of limitations including the exclusion of drug costs, a major driver of cost in our study, and an assumption of life-long treatment which is brought into question by the lower than 50% persistence rate found here.[50] Our data show a large disparity between GLA and LIRA in incremental costs per 1% HbA1c reduction, suggesting that LIRA treatment may not be the optimal choice where cost-effective glycaemic control is the major long-term goal of physicians, patients and insurers. In this context it should be kept in mind that LIRA patients were at baseline already at significantly lower HbA1c levels, with 24% of LIRA patients having a baseline HbA1c below 7.0%. As it is well-established that baseline HbA1c is a predictor of the magnitude of HbA1c response,[51] it is not unexpected that the LIRA group was a priori less likely to have large absolute reductions in HbA1c levels. Additionally, LIRA, with a higher maximal dose than that approved for use in T2DM, recently received FDA approval as a treatment option for chronic weight management.[52] The American Health Association/American College of Cardiology/The Obesity Society guidelines on the treatment of obesity recommend that patients who have a BMI of at least 30 kg/m^2 or a BMI of at least 27 kg/m^2 with at least one obesity-associated complication, such as T2DM, high blood pressure or high cholesterol, may consider the option of adding pharmacotherapy of FDA-approved obesity medications as an adjunct to lifestyle interventions to help achieve targeted weight loss and health goals.[53] This may have a substantial impact on pharmacy costs for use of LIRA, because of a possible influx of obese patients with diabetes with HbA1c levels < 7%. Long-term longitudinal data will be required before more solid evidence-based judgements can be made on the cost-effectiveness of LIRA.

This large study used claims data complemented with medical record data to examine prescribing practices, reflecting real-world outcomes outside the controlled conditions of clinical trials. The use of medical record data offers a greater amount of patient information, such as reasons for initiating LIRA or GLA treatment, bodyweight fluctuations and drug dosages (not limited to daily average consumption). Patients using GLA may have different practices for priming the insulin pen before each use. This priming requires injecting insulin into air[54,55]; some patients may inject 1 to 2 units at a time, and others may choose not to. This variability in patients' practices may affect the calculated total daily insulin doses, possibly up to 10% of the dose if patients are using <20 U/d. The average consumption of LIRA was less than 1.2 mg/d, which is the lower of the 2 recommended long-term treatment doses (1.2 and 1.8 mg/d). This may suggest issues with adverse effects from higher doses, financial constraints, etc. The use of a less-than-maximal dose may also impact overall drug costs; since patients are using, on average, only 60% to 70% of their maximal possible dose, ie, 1.2 mg/d instead of 1.8 mg/d, expected drug costs are ~40% to 50% lower.[37,56] Among patients using insulin, the average dose of insulin glargine of less than 30 U/d is probably sub-optimal when compared with clinical trials with forced titration protocols (averaging 45-70 U/d). The potential HbA1c-lowering effects of insulin glargine may therefore have been underestimated in this study because of under-dosing of insulin.

As a real-world study, the results of INITIATOR may be more likely to reflect conditions faced by healthcare providers. The consistency of clinical and cost outcomes between the 2 databases further validates the results. However, as noted in Table S1, baseline differences do exist between the 2 populations. These may be the source of those differences which were evident between the 2 individual cohorts, such as in hypoglycaemia rate and costs.

Our study has several limitations. First, because of the limited overlap between these 2 study cohorts in their baseline characteristics, it was not feasible to use a well-established method such as propensity score matching to conduct comparative effectiveness

analysis. Therefore, the outcomes reported in the current study reflect the observed changes and outcomes *within* treatment groups, rather than outcomes evaluated head-to-head *between* the 2 treatment groups. Future investigation should look into innovative approaches to address this issue. Second, this was an observational study and, as such, the analyses may be subject to selection bias and confounding, and cannot establish causality of drug effect on the observed outcomes, including costs. Third, the data analysed were from a commercially insured US managed-care population, and may not be fully representative of other populations or generalizable to all patients with T2DM. In particular, the lack of information on older Medicare patients is a limitation of the study. Fourth, the fact that patients with missing data (ie, baseline HbA1c or bodyweight) were excluded from the study population may influence the results, and therefore affect the generalizability of our findings. The reason patients had missing information is unknown, but it may be because the measurement was not taken during the study period of interest; the measurement was taken but not recorded in the medical chart; or the measurement was taken and recorded, but was taken by a physician other than the one from whom the patient's chart was obtained. Fifth, persistence with therapy was estimated using pharmacy claims data that reflect prescriptions filled by the patients; however, medication may not have been taken or consumed as prescribed. Several other factors may negatively impact treatment persistence in real-world studies, including younger patient age, lower income levels, increasing treatment-associated costs, reluctance to administer by injection, logistical problems (eg, traveling) or the presence of polypharmacy.[35,57–59] Sixth, healthcare claims data were used in this study, which are potentially subject to coding errors and contain limited information on some important clinical characteristics; we attempted to address this issue by linking claims to medical records data. Finally, the distinctive mechanisms of action of insulin analogues and GLP-1 receptor agonists may have caused some of the observed differences in outcomes.

In conclusion, this real-world study revealed significant and clinically relevant baseline differences between patients with T2DM initiating GLA and those initiating LIRA. Differences in baseline patient characteristics pose challenges when conducting comparative effectiveness research and in interpreting the results of such studies and, therefore, must be taken into account during future study design. Our results suggest that GLA and LIRA are being used to treat different patient groups. GLA appears to be prescribed for patients with less well controlled diabetes who are in need of a greater HbA1c reduction, while LIRA seems to be prescribed for patients with better glycaemic control but higher BMI, where weight loss may possibly have been a treatment goal. This highlights the challenges of translating clinical trial results to real-world practice. In addition, although each treatment approach has its clinical advantages, significant increases in healthcare costs, mainly driven by increased pharmacy costs, were observed in the LIRA group, warranting further cost-effectiveness analysis.

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Conflict of interest

W. W. is an employee of Sanofi US, Inc. E. B. and L. B. are employees of Optum, under contract with Sanofi US, Inc. M. G. and X. K. are employees of HealthCore, Inc., under contract with Sanofi US, Inc., for the conduct of this study. L. X. is an employee of STATinMED Research, under contract with Sanofi US, Inc. J. W. C. is a consultant and member of the lecture bureau for Sanofi US, Inc.; is a member of the lecture bureaus for AstraZeneca and for Eli Lilly and Company; and has received research funding from Novo Nordisk, Inc. P. A. L. is a consultant, member of the advisory panel, member of the speakers bureau for and has received research support from Sanofi US, Inc.; is a consultant, member of the advisory panel, member of the speakers bureau for and has received research support from Novo Nordisk, Inc.; is a member of the speakers bureau for and has received research support from Eli Lilly and Company; is a member of the speakers bureau for and has received research support from Amylin Pharmaceuticals; has received research support from Roche; and is a member of the speakers bureaus for BMS, Boehringer Ingelheim and AstraZeneca.

Author contributions

W. W. proposed and co-developed the study concept, co-developed the analysis plan, interpreted the results of the analyses throughout the manuscript development; reviewed the manuscript, provided comments and approved the final version for submission; and is willing to be accountable for the accuracy and integrity of the work. E. B. co-developed the concept and co-developed the analysis plan; collected the data, conducted statistical analyses and interpreted the results throughout the manuscript development, prepared the study report and conducted additional analyses; reviewed the manuscript, provided comments and approved the final version for submission; and is willing to be accountable for the accuracy and integrity of the work. M. G. co-developed the concept and co-developed the analysis plan; collected data, performed the analysis, interpreted the results of the analyses throughout the manuscript development and prepared the study report; reviewed the manuscript, provided comments and approved the final version for submission; and is willing to be accountable for the accuracy and integrity of the work. L. X. conducted the pooled analysis; interpreted the results of the analyses throughout the manuscript development; reviewed the manuscript, provided comments and approved the final version for submission; and is willing to be accountable for the accuracy and integrity of the work. L. B. co-developed the analysis plan; collected data, performed the analysis, interpreted the results of the analyses throughout the manuscript development and prepared the study report; reviewed the manuscript, provided comments and approved the final version for submission; and is willing to be accountable for the accuracy and integrity of the work. X. K. collected data, performed the analysis, interpreted the results of the analyses throughout the manuscript development and prepared the study report; reviewed the manuscript, provided comments and approved the final version for submission; and is willing to be accountable for the accuracy and integrity of the work. J. W. C. provided key clinical insights in interpreting the

results of the analyses from a clinician's point of view throughout the manuscript development; reviewed the manuscript, provided comments and approved the final version for submission; and is willing to be accountable for the accuracy and integrity of the work. P. A. L. provided key clinical insights in interpreting the results of the analyses from a clinician's point of view throughout the manuscript development; reviewed the manuscript, provided comments and approved the final version for submission; and is willing to be accountable for the accuracy and integrity of the work.

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SUPPORTING INFORMATION

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