Diabetes Ther (2021) 12:1475–1489
https://doi.org/10.1007/s13300-021-01053-7

ORIGINAL RESEARCH

Semaglutide Once-Weekly Persistence and Adherence Versus Other GLP-1 RAs in Patients with Type 2 Diabetes in a US Real-World Setting

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Received: December 18, 2020 / Accepted: March 22, 2021 / Published online: April 10, 2021

ABSTRACT

Introduction: The superior efficacy and safety of semaglutide once-weekly (QW), compared with dulaglutide, liraglutide, or exenatide QW, have been demonstrated in the SUSTAIN trials. This study assessed treatment persistence and adherence to semaglutide QW versus dulaglutide, liraglutide, or exenatide QW in a real-world setting.

Methods: This retrospective, database study used Optum's de-identified Clinformatics® Data Mart Database to identify glucagon-like peptide 1 receptor agonist (GLP-1 RA) treatment-naïve adult patients with type 2 diabetes (T2D) initiating semaglutide QW, dulaglutide, liraglutide, or exenatide QW between January 1, 2018 and April 30, 2019. Persistence (time remaining on treatment) was assessed with Kaplan–Meier survival estimates and Cox proportional hazard models. Adherence was assessed using proportion of days covered (PDC) and proportion of patients with PDC > 80%.

Results: Of 56,715 patients included, 3279 received semaglutide QW, 27,891 dulaglutide, 17,186 liraglutide, and 8359 exenatide QW. Patients initiating semaglutide QW were younger and with lower percentage of Medicare coverage than patients initiating the comparators. Persistence at 360 days was significantly higher for semaglutide QW (67.0%) versus dulaglutide (56.0%), liraglutide (40.4%), and exenatide QW (35.5%); $p < 0.001$ for all comparisons. Compared with semaglutide QW, the discontinuation rate was significantly higher for dulaglutide (hazard ratio [HR] 1.22; 95% confidence interval [CI] 1.13, 1.32; $p < 0.001$), liraglutide (HR 1.80; 95% CI 1.66, 1.95; $p < 0.001$), and exenatide QW (HR 2.12; 95% CI 1.96, 2.30; $p < 0.001$). Adherence to semaglutide QW versus liraglutide at 360 days and to exenatide QW was 39.1% versus 30.0% [$p = 0.07$] and 27.7% [$p = 0.02$], respectively. Adherence to dulaglutide at 360 days was numerically higher than semaglutide QW (43.2% versus 39.1%; $p = 0.45$) but did not reach statistical significance.

Conclusion: Persistence with semaglutide QW was significantly greater than comparators, while adherence was comparable or greater. Together with earlier results from double-blind clinical studies, these data support semaglutide QW use for treatment of patients with T2D.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s13300-021-01053-7.

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Keywords: Diabetes mellitus; Glucagon-like peptide 1; Medication adherence; Medication persistence; Semaglutide; Type 2

Key Summary Points

Why carry out this study?

In patients with T2D, good persistence and adherence to treatment are associated with better glycemic control, fewer complications, and lower healthcare utilization. Approximately 50% of patients with T2D do not achieve adequate glycemic control, an outcome often related to poor adherence to medication.

To address the need for real-world evidence on adherence and persistence to GLP-1 RAs, we conducted a retrospective analysis of a patient claims database to examine adherence and persistence to semaglutide QW, dulaglutide, exenatide QW, and liraglutide.

What was the hypothesis of the study?

We speculated whether there was a difference in treatment persistence and adherence among patients with T2D initiating semaglutide QW, compared with other long-acting GLP-1 RAs such as dulaglutide, liraglutide, and exenatide QW.

What were the study outcomes/conclusions?

Our findings show that persistence with semaglutide QW was significantly greater than with dulaglutide, exenatide QW, and liraglutide, while adherence was comparable or greater.

What has been learned from the study?

The greater persistence and adherence demonstrated in this study support the use of semaglutide QW for treatment of patients with T2D.

DIGITAL FEATURES

This article is published with digital features, including a summary slide, to facilitate understanding of the article. To view digital features for this article go to https://doi.org/10.6084/m9.figshare.14248778.

INTRODUCTION

The joint American Diabetes Association and European Association for the Study of Diabetes guidelines recommend the use of glucagon-like peptide 1 receptor agonists (GLP-1 RAs) or sodium-glucose cotransporter protein 2 inhibitors (SGLT2is) with demonstrated cardiovascular (CV) benefit as a second-line therapy in patients with type 2 diabetes (T2D) who have or are at high risk of established atherosclerotic CV disease (ASCVD), established kidney disease, or heart failure. This recommendation applies independent of baseline glycated hemoglobin (HbA_{1c}) or individualized HbA_{1c} target [1].

GLP-1 RAs have been shown to have a number of beneficial physiological effects, including the glucose-dependent stimulation of insulin secretion from beta cells [2], inhibition of glucagon secretion [2], slowed gastric emptying [3], and increased satiety [4]. As a result of their glucose-dependent mode of action, treatment with GLP-1 RAs has a low risk of hypoglycemia, compared to other antihyperglycemic agents [5]. Gastrointestinal (GI) disorders are the most commonly reported adverse events associated with GLP-1 RA use, although these are often transient in nature and resolve over time [6]. A number of long-acting GLP-1 RAs are approved for the treatment of T2D in the US [7, 8], including semaglutide once-weekly (QW) [9], dulaglutide [10], liraglutide [11], and exenatide QW [12]. Of these injectable GLP-1 RAs, semaglutide QW was the most recently approved by the US Food and Drug Administration (December 2017) and was marketed in the US from February 2018.

The superior safety and efficacy of semaglutide QW have previously been demonstrated in the SUSTAIN phase 3 clinical trial program,

with SUSTAIN 1–5 and SUSTAIN 7–10 clinical trials comparing semaglutide QW with other comparators in patients with T2D [13–21]. Similarly, real-world data from a liraglutide-to-semaglutide QW observational switch study and EXPERT (a study involving switching from any other GLP-1 RA to semaglutide QW) have demonstrated the effectiveness of semaglutide QW in a real-world setting [22, 23].

As with any regular medication, non-adherence is an issue, and in patients with T2D, good persistence and adherence to treatment are associated with better glycemic control, fewer complications, and lower healthcare utilization [24]. Low treatment persistence can lead to inadequate glycemic control and higher risk of morbidity and mortality [24]. It is therefore important to obtain real-world evidence on treatment persistence and adherence; however, such real-world evidence on semaglutide QW, either alone or in comparison to other GLP-1 RAs, is limited.

Given the evidence to date from the SUSTAIN 7 clinical trial, which demonstrated the superior efficacy on HbA_{1c} and weight reduction of semaglutide QW compared to dulaglutide 1.5 mg [21], and from an early real-world evidence study showing a similar level of effectiveness [25], we speculated whether this was attributable to greater persistence with and adherence to semaglutide QW. Therefore, the co-primary outcomes of this study were to evaluate treatment persistence and adherence among patients with T2D initiating semaglutide QW compared with other long-lasting GLP-1 RAs (dulaglutide, liraglutide, and exenatide QW) in a US real-world setting by analyzing a large, retrospective claims database.

METHODS

This was a retrospective, database study to assess treatment persistence and adherence of patients with T2D receiving semaglutide QW in comparison with existing GLP-1 RAs (dulaglutide, exenatide QW, and liraglutide). At the time of this study, the available doses of semaglutide QW were 0.5 and 1.0 mg, whilst dulaglutide was available in 0.75 and 1.5 mg doses [9, 10]. All analyses in this study were performed on de-identified claims data from the Optum Clinformatics® database.

Data Source

Optum's Clinformatics® Data Mart is derived from a database of administrative health claims for members of large commercial and Medicare Advantage health plans in the US. The de-identified data pertain to both medical and pharmacy coverage and include information on demographics, enrolment, inpatient and outpatient encounters, and pharmacy prescription fills. Data collected from January 1, 2017 until June 30, 2019 were analyzed for this study; a timeline of the study is presented in Supplementary Fig. S1 (including definitions of the baseline period, index date, and follow-up periods). Costs stated within the results were taken from the Optum Clinformatics® database and include sums that were paid by the patient and their health plan and others that were paid by the health plan alone.

Eligibility Criteria

Patients were eligible for inclusion in the study if they were aged at least 18 years during the index period (January 1, 2018–April 30, 2019), had a diagnosis of T2D, and were GLP-1 RA treatment-naïve in the 360 days prior to the index period. In addition, patients were required to have at least one pharmacy claim for the index drug during the index period, with the first claim being set as the index date, continuous enrolment for 360 days prior to the index date (baseline period), and continuous enrolment extending past the index date with variable follow-up (Supplementary Fig. S1).

Ethics

As this was a non-interventional, retrospective analysis of claims data from de-identified patients, institutional review board approval was not required. As the data were secondary and based on a commercially available database (https://www.optum.com/), no data were

Table 1 Baseline patient characteristics for the total persistence study population and total adherence study population at 180 days and 360 days

	Persistence *n* = 56,715				Adherence (180 days) *n* = 35,358				Adherence (360 days) *n* = 16,187			
	Sema QW *n* = 3279	Dula *n* = 27,891	Lira *n* = 17,186	Exe QW *n* = 8359	Sema QW *n* = 447	Dula *n* = 17,073	Lira *n* = 11,996	Exe QW *n* = 5842	Sema QW *n* = 87	Dula *n* = 7280	Lira *n* = 6137	Exe QW *n* = 2683
Age, years (mean)	55.80	62.20	61.12	60.64	60.89	62.01	61.20	60.70	59.53	63.2	62.0	61.60
Gender, %												
F	49.1	51.2	55.2	50.0	52.1	51.3	55.0	50.2	40.2	50.8	54.2	51.1
M	50.9	48.8	44.8	50.0	47.9	48.7	45.0	49.8	59.8	49.2	45.8	48.9
Region, %												
Midwest	20.9	19.5	21.9	19.7	26.4	19.4	21.2	19.3	28.7	19.6	21.1	18.2
Northeast	8.9	9.3	7.9	5.8	13.9	9.0	7.5	5.8	20.7	8.9	7.1	5.5
South	57.5	54.7	52.6	57.3	44.7	55.1	53.4	57.7	35.6	54.1	53.4	58.3
West	12.6	16.1	17.2	16.8	14.8	16.1	17.4	17.0	14.9	16.8	18.0	17.6
Unknown	0.2	0.4	0.5	0.4	0.2	0.5	0.5	0.4	–	0.6	0.5	0.5
Medical cost, US $	13,073.95	16,213.42	18,521.23	14,419.98	14,427.75	15,722.96	18,102.73	14,188.90	14,266.24	15,981.36	17,791.76	15,239.81
COM/MCR, %												
COM	82.3	43.8	43.7	49.0	53.0	44.6	43.4	48.5	59.8	39.7	40.1	42.3
MCR	17.7	56.2	56.3	51.0	47.0	55.4	56.6	51.5	40.2	60.3	59.9	57.7
Insurance, %												
EPO	11.2	6.1	5.9	7.2	5.2	6.2	5.6	7.2	10.3	5.1	4.6	6.1
HMO	16.5	21.4	22.0	21.8	34.9	21.6	22.1	22.4	31.0	22.7	23.4	24.9
IND	0.5	0.4	0.3	0.4	0.2	0.5	0.4	0.5	–	0.6	0.4	0.4
OTH	12.4	36.6	35.9	30.8	30.7	35.7	35.8	30.6	26.4	38.8	37.9	33.1
POS	57.6	31.2	31.6	36.2	25.3	31.7	31.7	35.8	25.3	28.3	29.3	31.3
PPO	1.8	4.2	4.4	3.5	3.8	4.3	4.4	3.7	6.9	4.5	4.8	4.2
CCI score, mean	2.4	3.0	3.0	2.8	3.0	2.9	3.0	2.8	2.8	3.0	3.0	2.9
CCI score, %												
≤ 1	41.5	30.3	29.4	32.3	26.9	30.9	29.4	32.1	29.9	29.0	28.2	30.5
2–3	38.9	37.4	36.5	38.7	42.5	37.5	36.6	38.7	44.8	38.1	37.1	37.7
≥ 4	19.7	32.3	34.1	29.0	30.6	21.6	34.0	29.3	25.3	32.9	34.7	31.8
DCSI score, mean	2.5	3.2	3.2	3.0	3.1	3.1	3.2	3.0	3.0	3.2	3.2	3.1
DCSI score, %												
≤ 1	30.4	24.1	26.6	26.3	22.2	24.6	27.1	26.0	21.8	23.7	26.2	24.8
2–3	44.3	37.5	34.5	38.1	41.8	37.9	34.3	38.3	46.0	37.0	35.1	37.2
≥ 4	25.3	38.4	38.9	35.6	36.0	37.5	38.6	35.7	32.2	39.3	38.8	38.1

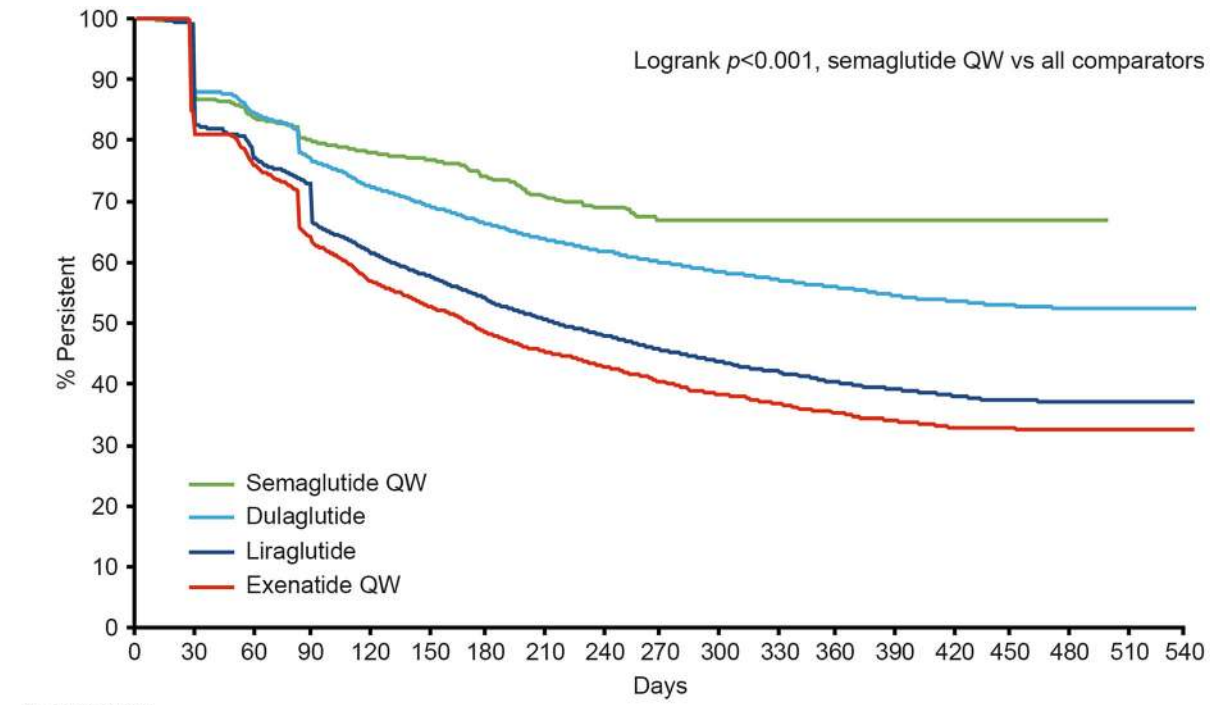
Table 1 continued

	Persistence *n* = 56,715				Adherence (180 days) *n* = 35,358				Adherence (360 days) *n* = 16,187			
	Sema QW *n* = 3279	Dula *n* = 27,891	Lira *n* = 17,186	Exe QW *n* = 8359	Sema QW *n* = 447	Dula *n* = 17,073	Lira *n* = 11,996	Exe QW *n* = 5842	Sema QW *n* = 87	Dula *n* = 7280	Lira *n* = 6137	Exe QW *n* = 2683
ASCVD*, %	23.0	34.6	37.1	32.5	30.9	33.9	37.2	33.0	26.4	34.8	37.6	35.0
Hyperlipidemia, %	80.0	81.5	79.8	81.5	85.0	81.7	79.9	82.3	87.4	83.0	80.9	82.8
Hypertension, %	77.8	83.9	83.7	83.1	83.0	83.7	83.9	83.5	89.7	84.6	84.7	84.5
Prior antidiabetics, %												
Metformin	73.5	70.8	66.5	71.7	69.6	71.1	66.8	72.8	67.0	70.7	67.5	75.5
Insulin	37.9	39.8	41.0	35.4	49.4	40.4	41.0	36.1	46.0	40.8	41.1	36.5
SU	26.9	38.8	32.9	38.1	29.8	38.6	33.4	39.4	34.5	39.7	34.1	40.9
SGLT2i	27.5	19.7	14.4	23.6	27.3	19.7	14.5	24.5	27.6	19.8	15.1	23.9
DPP4i	21.7	26.2	18.8	25.9	26.4	26.8	19.4	27.0	32.2	27.8	20.1	28.1
TZD	8.5	9.1	7.7	10.7	8.3	8.8	8.0	11.0	8.1	9.0	8.4	11.8
Meglitinide	0.6	1.3	0.9	1.1	1.8	1.2	1.0	1.2	1.2	1.3	1.0	1.3
AGI	0.3	0.5	0.4	0.4	0.2	0.5	0.4	0.4	–	0.6	0.3	0.4
AMY	0.1	0.0	0.0	0.0	0.2	0.0	0.0	0.1	–	0.0	0.0	0.0

Data are presented for the full analysis set. The data (including costs) were taken from the Optum Clinformatics® database

AGI alpha-glucosidase inhibitors, *AMY* amylinomimetics, *ASCVD* atherosclerotic cardiovascular disease, *CCI* Charlson comorbidity index, *COM* commercial, *DCSI* diabetes complications severity index, *DDP4i* dipeptidyl peptidase 4 inhibitor, *Dula* dulaglutide, *EPO* exclusive provider organization, *Exe* exenatide, *HMO* health maintenance organization, *IND* indemnity, *Lira* liraglutide, *MCR* Medicare, *OTH* other, *POS* point of service, *PPO* preferred provider organization, *QW* once-weekly, *Sema* semaglutide, *SGLT2i* sodium glucose cotransporter 2 inhibitor, *SU* sulfonylurea *TZD* thiazolidinedione

*ASCVD comprised the following diagnoses: acute coronary syndrome (diagnosis code—I24, I25 ex. I25.3, I25.4), angina (I20), myocardial infarction (I21, I22, I23), peripheral artery disease (I70, I73.9, I74, I75, I99, Z86.7), revascularization (Z95.1, Z95.5, Z95.8, Z95.9, Z98.6, Z98.6), ischemic stroke (I63, I65, I66, I67.2, I67.81, I67.82, I67.83, I67.84), hemorrhagic stroke (I60, I61, I62), stroke effects (I69, R29.7 ex. R29.700), and transient ischemic attack (G45)



Number at risk																		
Semaglutide QW	2845	2452	1745	1144	716	280	216	168	115	81	61	45	30	16	6	4	1	–
Dulaglutide	24320	22344	17938	14838	12456	10493	8945	7595	6336	5204	4187	3423	2723	2066	1485	976	480	61
Liraglutide	16743	12865	10907	8280	7050	5969	5122	4377	3705	3044	2536	2092	1694	1317	978	660	510	41
Exenatide QW	6853	6033	4611	3751	3160	2601	2202	1861	1501	1206	984	782	605	466	347	201	85	10

	Estimated persistence at 180 days (%)	Estimated persistence at 360 days (%)	Discontinuation rate, HR (95% CI) vs semaglutide QW	*p*-value (semaglutide QW vs comparators)
Semaglutide QW	74.0	67.0	-	-
Dulaglutide	66.4	56.0	1.22 (1.13, 1.32)	<0.001
Liraglutide	54.2	40.4	1.80 (1.66, 1.95)	<0.001
Exenatide QW	48.6	35.5	2.12 (1.96, 2.30)	<0.001

Fig. 1 Unadjusted Kaplan–Meier survival curve estimates for all study drugs. Data are presented for the unadjusted analysis set. CI confidence interval, HR hazard ratio, QW once-weekly

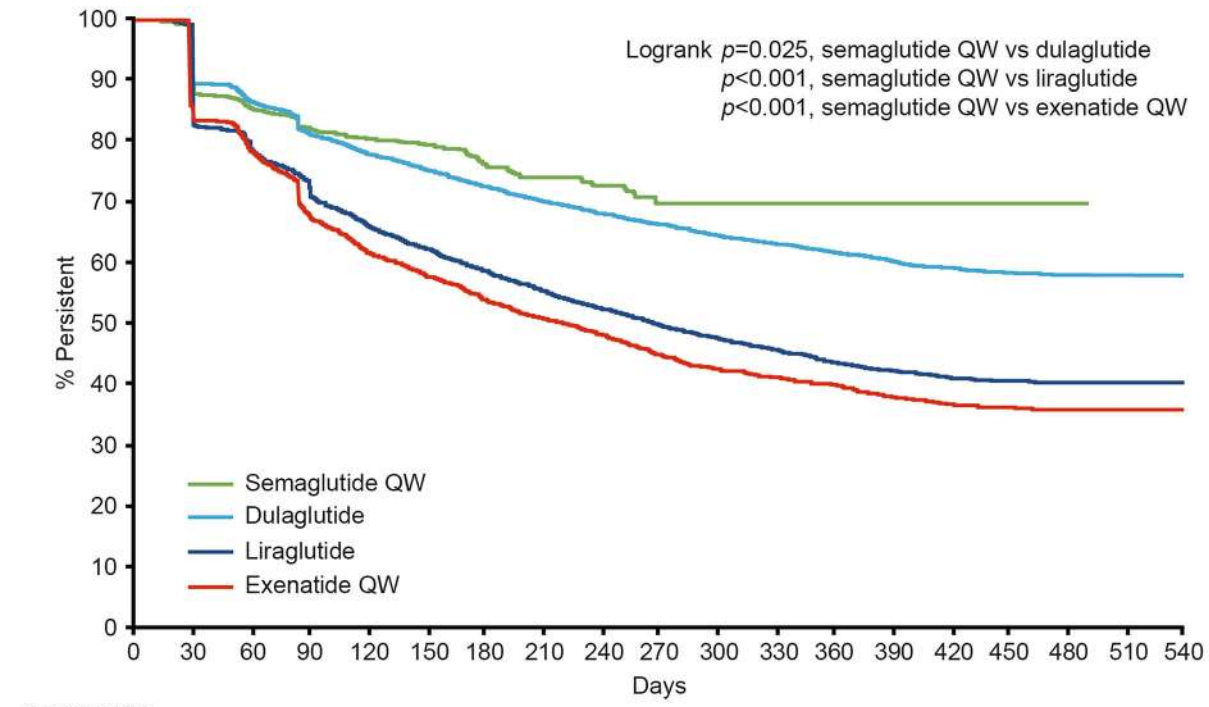
collected directly from human participants or animals by any of the authors.

Persistence Analysis of Semaglutide QW Versus Other GLP-1 RAs

The primary endpoint of treatment persistence among patients initiating semaglutide QW compared with dulaglutide, exenatide, and liraglutide was assessed using a variable follow-up by Kaplan–Meier survival estimate (KMSE). Patients were considered persistent if they did not discontinue GLP-1 RA treatment. Analysis was performed from GLP-1 RA initiation to discontinuation (defined as a more than 60-day gap in supply), end of enrolment, or end of available data (June 30, 2019). Hazard ratios (HRs) were calculated from Cox proportional hazard models for all drugs. We also estimated treatment persistence at the endpoints of 180 days and 360 days.

Persistence Analysis: Stratification According to Payer Type (Medicare Versus Commercial Insurance)

Following review, major differences among patient demographics with reference to payer type (Medicare versus commercial) were



Number at risk																		
Semaglutide QW	2350	2046	1443	939	564	162	125	99	68	51	41	31	19	10	4	3	–	–
Dulaglutide	10669	9837	8228	7047	6058	5197	4449	3776	3102	2522	2035	1646	1313	982	695	452	229	26
Liraglutide	7250	5538	4681	3819	3284	2829	2419	2048	1738	1408	1164	952	760	579	425	425	153	15
Exenatide QW	3356	2968	2363	1951	1667	1385	1162	974	766	766	501	396	295	420	156	156	41	5

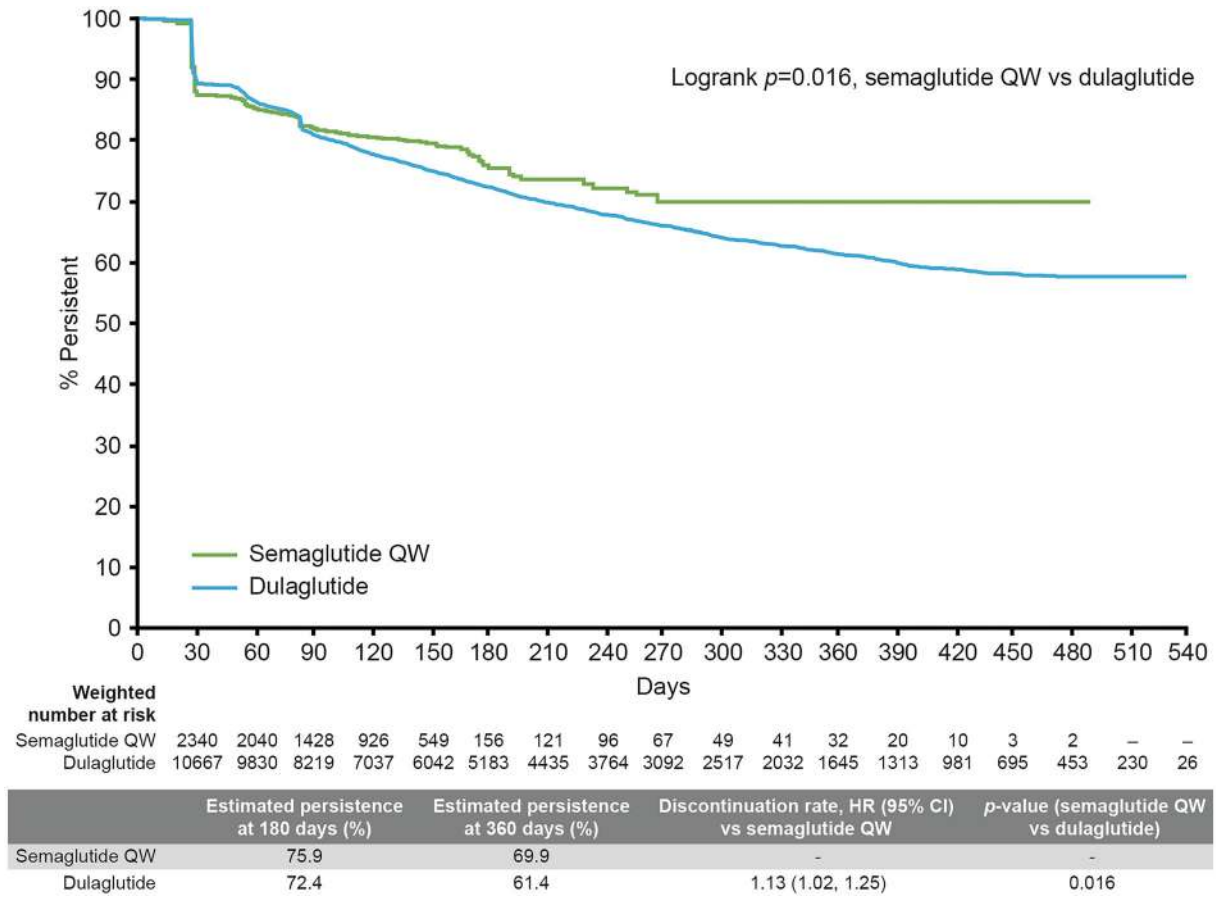
	Estimated persistence at 180 days (%)	Estimated persistence at 360 days (%)	Discontinuation rate, HR (95% CI) vs semaglutide QW	*p*-value (semaglutide QW vs comparators)
Semaglutide QW	76.1	69.7	-	-
Dulaglutide	72.5	61.5	1.10 (1.00, 1.21)	0.025
Liraglutide	58.7	43.4	1.79 (1.63, 1.97)	<0.001
Exenatide QW	53.8	39.9	2.07 (1.88, 2.29)	<0.001

Fig. 2 Unadjusted Kaplan–Meier survival curve estimates for all study drugs stratified for the commercial claim subgroup. Data are presented for the unadjusted set. CI confidence interval, HR hazard ratio, QW once-weekly

observed. Therefore, patients were stratified according to payer type to reduce selection bias.

Persistence Analysis: Propensity Score Adjusted (Semaglutide QW Versus Dulaglutide) According to Payer Type

Following stratification according to payer type, propensity score adjustment was performed for only the semaglutide QW and dulaglutide groups to account for remaining differences between patient demographics. Propensity scores were generated from a logistic regression model considering all baseline covariates; here, we reported the demographic covariates of age (18–44, 45–64, and 65+ years), gender, region (North East, South, Midwest, West), and payer type (commercial/Medicare and exclusive provider organization [EPO]/health maintenance organization [HMO]/point of service [POS]/indemnity/other). The remaining covariates measured during the baseline period are reported in Supplementary Table S1. Propensity scores were used to generate inverse probability of treatment weights to weight samples. The balance of the sample was assessed by computing and comparing standardized differences among all covariates before and after weighting.



	Estimated persistence at 180 days (%)	Estimated persistence at 360 days (%)	Discontinuation rate, HR (95% CI) vs semaglutide QW	*p*-value (semaglutide QW vs dulaglutide)
Semaglutide QW	75.9	69.9	-	-
Dulaglutide	72.4	61.4	1.13 (1.02, 1.25)	0.016

Fig. 3 Adjusted Kaplan–Meier survival curve estimates for semaglutide QW and dulaglutide after propensity score adjustment stratified for the commercial claim subgroup. CI confidence interval, HR hazard ratio, QW once-weekly

Adherence Analysis of Semaglutide QW Versus Other GLP-1 RAs

The co-primary endpoint of adherence was measured by the proportion of days covered (PDC), with the assumption of zero stockpiling, and was assessed in fixed timeframes of 180 and 360 days for patients having sufficient follow-up. PDC was defined as the count of days covered by medication starting from the index date to the end of the fixed follow-up timeframe, divided by the length of the follow-up period.

Adherence Analysis: Propensity Score Adjustment (Semaglutide QW Versus Dulaglutide) Without Stratification

Propensity score adjustment was also exclusively performed in the semaglutide QW versus dulaglutide arms for adherence analysis to account for remaining differences between patient demographics; however, unlike the persistence analysis, we did not stratify by payer type as this was no longer a major discrepancy as in the full sample.

Post Hoc Adherence Analysis

We hypothesized that the original adherence results may have been impacted by the titration schedule for semaglutide QW; therefore, we conducted an additional sensitivity analysis. This analysis was performed on patients who had a second prescription fill, with the PDC defined as the count of days covered from the second fill to the end of the follow-up period, divided by the variable time between the second fill and end of the follow-up period. PDC was

Table 2 Adherence in patients receiving semaglutide QW versus patients receiving dulaglutide after propensity score adjustment for original analysis and post hoc analysis

Outcome variable	Semaglutide QW	Dulaglutide	*p* value (semaglutide versus dulaglutide)
Original analysis			
PDC at 180 days, *n*	447	17,073	–
Mean	0.65	0.72	< 0.001
PDC > 80%, %	41.9	53.6	0.59
PDC at 360 days, *n*	87	7280	–
Mean	0.64	0.62	< 0.001
PDC > 80%, %	44.7	43.3	0.86
Post hoc analysis			
PDC at 180 days, *n*	370	14,480	–
Mean	0.79	0.80	0.54
PDC > 80%, %	63.3	66.7	0.32
PDC at 360 days, *n*	71	6111	–
Mean	0.75	0.69	0.05
PDC > 80%, %	63.4	52.3	0.20

PDC proportion of days covered, *QW* once-weekly

compared using Student's *t* test, and the proportion meeting the common adherence threshold of PDC > 80% was compared with the chi-square test via logistic regression.

RESULTS

Overall, a total of 56,715 patients fulfilled the inclusion criteria and initiated GLP-1 RA treatment. This comprised 5.8% ($n = 3279$) of patients receiving semaglutide QW, 49.2% ($n = 27{,}891$) receiving dulaglutide, 30.3% ($n = 17{,}186$) receiving liraglutide, and 14.7% ($n = 8359$) receiving exenatide QW. Baseline patient characteristics for all study drugs assessed are presented in Table 1. Differences were observed between semaglutide QW and all the comparators in age, comorbidities, and prior antidiabetic medication. Patients initiating semaglutide QW were, on average, younger and a smaller percentage had Medicare coverage (mean age ± standard deviation [SD] 55.8 years ± 11.14; Medicare 17.7%) compared with dulaglutide (62.2 years ± 12.15; 56.2%), liraglutide (61.1 years ± 12.11; 56.3%), and exenatide QW (60.6 years ± 11.93; 51.0%) ($p < 0.001$ for all) (Table 1).

Persistence Analysis: Semaglutide QW Versus Other GLP-1 RAs

Persistence associated with semaglutide QW use was significantly greater than that observed for all comparators ($p < 0.001$ all comparisons; Fig. 1). The KMSE of persistence at 180 days was 74.0% for semaglutide QW compared with 66.4% for dulaglutide. The KMSE of persistence at 180 days was 54.1% for liraglutide and 48.6% for exenatide QW. Similarly, at 360 days, 67.0% of patients were estimated to be persistent with semaglutide QW, versus 56.0% for dulaglutide, 40.4% for liraglutide, and 35.5% for exenatide

QW ($p < 0.001$ for all). Compared with semaglutide QW, treatment discontinuation rate was significantly higher for dulaglutide (HR 1.22; 95% confidence interval [CI] 1.13, 1.32; $p < 0.001$), liraglutide (HR 1.80; 95% CI 1.66, 1.95; $p < 0.001$), and exenatide QW (HR 2.12; 95% CI 1.96, 2.30; $p < 0.001$) (Fig. 1).

Persistence Analysis: Stratification According to Payer Type (Medicare Versus Commercial Insurance)

Commercial Claim Subgroup

The majority of baseline differences were well balanced through stratification by payer type (Supplementary Table S2). Differences were observed in prior antidiabetic medication between semaglutide QW and all the comparators. Prior use of dipeptidyl peptidase 4 inhibitors, insulin, metformin, SGLT2is, and thiazolidinediones in patients receiving semaglutide QW versus patients receiving dulaglutide was 20.4%, 34.4%, 76.0%, 28.6%, and 8.1% versus 24.4%, 30.6%, 75.9%, 25.8%, and 8.3%, respectively.

Semaglutide QW was associated with a significantly greater treatment persistence compared with dulaglutide at both 180 days (76.1% versus 72.5%, respectively) and 360 days (69.7% versus 61.5%, respectively); logrank test $p = 0.025$ (Fig. 2). Similarly, a statistically significant difference was observed in the KMSE of persistence at 180 days favoring semaglutide QW (76.1% for semaglutide QW versus 58.7% for liraglutide and 53.8% for exenatide QW) and 360 days (69.7% for semaglutide QW versus 43.4% for liraglutide and 39.9% for exenatide QW); logrank $p < 0.001$ for both (Fig. 2). Compared with semaglutide QW, the treatment discontinuation rate was higher for liraglutide (HR 1.79; 95% CI 1.63, 1.97; $p < 0.001$) and exenatide QW (HR 2.07; 95% CI 1.88, 2.29; $p < 0.001$) and similar for dulaglutide QW (HR 1.10; 95% CI 1.00, 1.21; $p = 0.05$; Fig. 2).

Medicare Claim Subgroup

Baseline characteristics within the Medicare claim subgroup for all study groups were well balanced. Differences in patient comorbidities were observed between semaglutide QW and all the comparators groups. A higher number of patients receiving semaglutide QW (51.8%) had a Charlson comorbidity index (CCI) score ≥ 4 compared with patients receiving dulaglutide (46.9%).

There was a trend favoring semaglutide QW but no significant difference in the treatment persistence between semaglutide QW and dulaglutide at 180 days (64.1% versus 61.6%, respectively) and 360 days (57.1% versus 51.6%, respectively); logrank test $p = 0.746$ (Supplementary Fig. S2). Significant differences favoring semaglutide QW were observed in persistence versus liraglutide at 180 and 360 days (50.7% and 38.1%, respectively) and exenatide QW at 180 and 360 days (43.8% and 31.4%, respectively); logrank $p < 0.001$ for all (Supplementary Fig. S2). Compared with semaglutide QW, there was no statistically significant difference in the treatment discontinuation rate for dulaglutide QW (HR 0.97; 95% CI 0.84, 1.12; $p = 0.654$). However, the rate of discontinuation was significantly higher with liraglutide (HR 1.33; 95% CI 1.15, 1.55; $p < 0.001$) and exenatide QW (HR 1.64; 95% CI 1.41, 1.90; $p < 0.001$), compared with semaglutide QW (Supplementary Fig. S2).

Persistence Analysis: Propensity Score Adjusted (Semaglutide QW Versus Dulaglutide) According to Payer Type

Commercial Claim Subgroup

Baseline patient characteristics after propensity score adjustment for the commercial claim subgroup receiving semaglutide QW and dulaglutide are presented in Supplementary Table S3A, and the adjusted KMSE and HR for persistence are presented in Fig. 3. Baseline characteristics after propensity score adjustment were well balanced between the two claim subgroups and had minimal effect on the results compared with stratification alone. A significant difference ($p = 0.016$) in persistence was observed between semaglutide QW and dulaglutide at 180 days (75.9% versus 72.4%, respectively) and 360 days (69.9% versus 61.4%, respectively), and the rate of discontinuation

was higher with dulaglutide (HR 1.13; 95% CI 1.02, 1.25; $p = 0.017$) (Fig. 3).

Medicare Claim Subgroup

Baseline patient characteristics after propensity score adjustment for the Medicare claim subgroup receiving semaglutide QW and dulaglutide are presented in Supplementary Table S3B, while the adjusted KMSE and HR for persistence for semaglutide QW and dulaglutide are presented in Supplementary Fig. S3. Adjustment showed minimal effect on the results compared with stratification alone. The difference in persistence between semaglutide QW and dulaglutide at 180 days (62.4% versus 61.7%, respectively) and 360 days (56.2% versus 51.7%, respectively) was not significant ($p > 0.05$), though the trend was in favor of semaglutide QW. Likewise, the rate of discontinuation for semaglutide QW was similar to dulaglutide (HR 0.89; 95% CI 0.74, 1.08; $p > 0.05$) (Supplementary Fig. S3).

Adherence Analysis: Semaglutide QW Versus Other GLP-1 RAs

As a result of the relatively short period of time from the launch of semaglutide QW to the index date, fewer patients receiving semaglutide QW were included in the adherence analysis at both 180 and 360 days ($n = 447$ and $n = 87$, respectively), compared with patients receiving dulaglutide ($n = 17{,}073$ and $n = 7280$, respectively) (Table 2), liraglutide ($n = 11{,}996$ and $n = 6137$, respectively), and exenatide QW ($n = 5842$ and $n = 2683$, respectively). Differences in baseline characteristics were observed between semaglutide QW and all the comparators regarding age, region, and prior antidiabetic medication (Table 1).

The measurement of PDC > 80% showed that treatment adherence was significantly higher for patients receiving semaglutide QW compared with patients receiving liraglutide and exenatide QW (44.7% versus 39.9% [$p = 0.04$] and 38.8% [$p = 0.01$], respectively), whereas it was significantly lower compared with those receiving dulaglutide (44.7% versus 53.8%; $p < 0.001$). Similarly, the treatment adherence at 360 days was higher for patients receiving semaglutide QW compared with exenatide QW (39.1% versus 27.7% [$p = 0.02$], respectively), but there were no significant differences found between semaglutide QW compared with liraglutide or dulaglutide (39.1% versus 30.0% [$p = 0.07$] and 43.2% [$p = 0.45$], respectively; data not shown).

Adherence Analysis: Propensity Score Adjusted (Semaglutide QW Versus Dulaglutide) Without Stratification

Following propensity score adjustment, a significantly higher treatment adherence was observed for dulaglutide compared with semaglutide QW at day 180 (53.4% versus 41.9%; $p < 0.001$), a result which was similar to that observed for the unadjusted data. However, there were no significant differences in the proportion of patients with PDC $\geq$ 80% at day 360 for semaglutide QW (44.7%) compared with dulaglutide (43.3%, $p = 0.86$) (Table 2).

Post Hoc Adherence Analysis

As a result of the opposing results observed between semaglutide QW treatment adherence and persistence, we performed a post hoc treatment adherence analysis to test the hypothesis that the titration for semaglutide QW may have impacted the original adherence results. To account for this hypothesis, we analyzed PDC starting from eligible patients' second fill among those with at least two fills.

Post hoc treatment adherence analysis was performed on a smaller number of patients receiving semaglutide QW at 180 days and 360 days ($n = 370$ and $n = 71$, respectively) compared with patients receiving dulaglutide ($n = 14{,}480$ and $n = 6111$, respectively) (Table 2). In the unadjusted post hoc results, there were no significant differences in the proportion of patients with PDC $\geq$ 80% at day 180 or day 360 for semaglutide QW (61.9% and 59.2%, respectively) compared with dulaglutide (66.6% [$p = 0.06$] and 52.2% [$p = 0.24$], respectively). Similarly, in the propensity score adjusted post hoc results, there were no

significant differences in the semaglutide QW adherence at day 180 or day 360 (63.3% and 63.4%, respectively) compared with dulaglutide adherence (66.7% [$p = 0.32$] and 52.3% [$p = 0.20$], respectively) (Table 2).

DISCUSSION

This study provides real-world evidence that persistence with medication in patients with T2D who are GLP-1 RA-naïve is greater in those receiving semaglutide QW than those receiving dulaglutide, liraglutide, or exenatide QW. Additionally, adherence to semaglutide QW was greater than adherence to liraglutide and exenatide QW. Adherence to semaglutide QW was similar to dulaglutide once the data from two prescription fills were used to account for the confounding titration.

Previous real-world evidence studies have shown dulaglutide to be associated with greater treatment persistence and adherence compared with semaglutide QW, liraglutide, and exenatide QW [26–29]. In this study, the greater treatment persistence and comparable adherence of semaglutide QW versus these other GLP-1 RAs may be a result of the associated clinical benefits of semaglutide QW such as improved glycemic control and greater weight loss [21, 25]. Additionally, the favorable persistence and adherence are likely to contribute to improved clinical outcomes.

Interestingly, patients receiving semaglutide QW were more likely to be part of the commercial claim subgroup versus the Medicare claim subgroup, which suggests that the major differences in baseline characteristics observed were primarily driven by the commercial/Medicare ratio. One explanation for the differences in the commercial/Medicare ratio may be due to the data collection period taking place soon after launch of semaglutide QW.

When the commercial and Medicare claim subgroups were analyzed separately, persistence was greater in those patients with commercial claims. The degree of persistence was heavily dependent on the commercial/Medicare split, indicating that the overall result was driven by the commercial claim subgroup, and this in turn carries over to the overall comparison due to the relative sizes of the commercial/Medicare population. The results of the adjusted data reflected those following stratification, with only minimal differences.

In the unadjusted analysis, adherence to semaglutide QW at day 180 and day 360 was superior to exenatide QW. In contrast, adherence to dulaglutide was significantly higher than adherence to semaglutide QW at day 180. Interestingly, the observed PDC for semaglutide QW at day 180 and 360 was similar; this finding was not observed with dulaglutide, suggesting that the adherence rates for semaglutide QW are more consistent over time compared with the adherence rates for dulaglutide. However, the smaller patient population in the semaglutide group compared with the other GLP-1 RAs makes it difficult to draw conclusions.

As with any claims database analysis, there are limitations to the current study. First, the data were derived from medical claims, which may have contained undetected coding errors and, given that the primary use of claims data is in the arbitration of any payment issued, data confounding errors as a result of incomplete patient medical histories cannot be ruled out. During the study, uptake of semaglutide QW increased over time from its launch in February 2018, and the majority of patients had an index date in 2019. This resulted in differing numbers of patients influencing either end of the Kaplan–Meier survival curves and the possibility that the behavior of the patients at the beginning of the analysis may have differed from that of the patients nearer the end of the analysis. It is noteworthy that the study only included data from the US and comprised a smaller number of patients receiving semaglutide QW, likely as a result of recent product launch, compared with those receiving the comparators; as such, the power of the statistical analyses may not have been robust and the generalizability of the results should be interpreted with caution. Consequently, future analyses involving a larger study population may be warranted. A further possible limitation is that the distribution of GLP-1 RAs and the resulting observed persistence may have been influenced by the baseline characteristics. Covariate and propensity score

adjustments were performed to account for these differences, although unmeasured baseline characteristics that were not accounted for may have affected the observed results (e.g., body mass index). Specific to the semaglutide QW versus dulaglutide comparison, the difference in the pens used to administer the GLP-1 RAs may have affected adherence and persistence; for example, semaglutide QW is administered via a multi-use pen, whereas dulaglutide is administered via a single-use pen [9, 10]. This may have affected differences in the number of prescription fills meeting adherence and persistence definitions and calculations between semaglutide QW and dulaglutide for the current study. Finally, it is important to note that the original cost measures were not used during database entry, which may have introduced errors.

Strengths to our analysis include the use of real-world evidence on the persistence with and adherence to semaglutide QW as well as using multiple comparators to semaglutide QW: dulaglutide, liraglutide, and exenatide QW. Furthermore, our analysis involved two different time points at 180 and 360 days for both treatment persistence and adherence, which is important in informing medium- and longer-term persistence and adherence. While clinical trials are considered the gold standard for internal validity of safety and efficacy, the persistence and adherence rates are typically higher than those observed in real-world clinical practice [30]. This in turn causes difficulty in extrapolating results from randomized controlled trials to the general public. Therefore, real-world evidence provides greater understanding of the effects of these therapeutic options on the population in a real-world setting.

CONCLUSION

This study provided real-world persistence data for semaglutide QW, and the results of this retrospective, database analysis showed that patients with T2D receiving semaglutide QW had greater persistence than patients receiving dulaglutide, liraglutide, or exenatide QW. However, the degree of persistence was heavily dependent on insurance type. The greater persistence and adherence demonstrated in this study support the use of semaglutide QW for treatment of patients with T2D.

ACKNOWLEDGEMENTS

Data contained within this manuscript have previously been presented as a poster at the Academy of Managed Care Pharmacy (AMCP) congress, 21–24 April 2020, Houston, Texas, US.

Funding. This study and the journal's Rapid Service Fee were funded by Novo Nordisk Inc.

Medical Writing Assistance. Medical writing and submission support were provided by Deborah Porter, MS, and Izabel James, MBBS, of Watermeadow Medical, an Ashfield company, part of UDG Healthcare plc, funded by Novo Nordisk Inc.

Authorship. All authors reviewed and interpreted the data, and were involved in drafting and critically revising the manuscript. Yuanjie Liang provided the statistical analysis of data. All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published.

Authors' Contributions. Chioma Uzoigwe, Yuanjie Liang, and Yurek Paprocki contributed to the concept and design of the study. Chioma Uzoigwe, Yuanjie Liang, Yurek Paprocki and Sarah Whitmire all critically analyzed and interpreted the data included in the manuscript, as well as drafting and revising the manuscript. Yuanjie Liang provided the statistical analysis of the data. Chioma Uzoigwe is the lead author 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.

Disclosures. Chioma Uzoigwe is a full-time employee and shareholder of Novo Nordisk Inc. Yuanjie Liang is a full-time employee and shareholder of Novo Nordisk Inc. Sarah Whitmire was employed at Real World Analytics & Insights at the time of the study and has also received funding from Novo Nordisk Inc. Sarah Whitmire's affiliation has changed since the completion of the study, and since Jan 2020 she is a full-time employee of Novo Nordisk Inc. Yurek Paprocki is a full-time employee and shareholder of Novo Nordisk Inc.

Compliance with Ethics Guidelines. As this was a non-interventional, retrospective analysis of claims data from de-identified patients, institutional review board approval was not required. As the data were secondary and based on a commercially available database (https://www.optum.com/), no data were collected directly from human participants or animals by any of the authors.

Data Availability. The datasets generated and/or analyzed during the current study are not publicly available. Data are proprietary to the owner of the database and licensed by agreement to Novo Nordisk Inc. Data presented in the publication are available from the corresponding author upon request.

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