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The Real-World Observational Prospective Study of Health Outcomes with Dulaglutide and Liraglutide in Patients with Type 2 Diabetes (TROPHIES): Patient disposition, clinical characteristics and treatment persistence at 12 months

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Abstract

Aims: The primary objective of the TROPHIES observational study is to estimate the duration of treatment on dulaglutide or liraglutide without a significant treatment change by 24 months in patients with type 2 diabetes (T2D) initiating their first injectable treatment with these glucagon-like peptide-1 receptor agonists (GLP-1 RAs). This manuscript presents 12-month interim data.

Materials and Methods: TROPHIES is a prospective, non-comparative, observational study of patients with T2D in Europe, naïve to injectable antihyperglycaemic treatments and initiating dulaglutide or liraglutide. Data on clinical characteristics, GLP-1 RA persistence and treatment patterns of glucose-lowering medication were collected at initiation of first injectable therapy and by 12 months.

Results: By 12 months, 1014 dulaglutide and 991 liraglutide patients were eligible across France, Germany and Italy. Both cohorts presented a high probability [95% confidence interval (CI)] of GLP-1 RA persistence [dulaglutide, 0.88 (0.86 to 0.90); liraglutide, 0.83 (0.80 to 0.85)] and reduction in mean glycated haemoglobin percentage (95% CI) from baseline [dulaglutide, −1.18 (−1.27 to −1.08); liraglutide, −1.15 (−1.26 to −1.05)] with 48.2% of dulaglutide and 41.2% of liraglutide patients reaching their individualized glycated haemoglobin percentage target set by the physician at baseline. Mean weight (95% CI) change from baseline was −3.2 kg (−3.6 to −2.8) for dulaglutide and −3.4 kg (−3.9 to −3.0) for liraglutide. Slight changes in concomitant medications were observed compared with baseline.

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Conclusions: In the real-world setting, dulaglutide and liraglutide cohorts achieved good persistence with similarly improved glycaemic control that was accompanied by weight loss at 12 months, consistent with previous clinical trial results.

KEYWORDS
antidiabetic drug, dulaglutide, liraglutide, type 2 diabetes, observational study

1 | INTRODUCTION

Real-world evidence (RWE) studies examine the effectiveness of pharmaceutical or biological therapies used in clinical practice, as well as routine clinical practice patterns in the real-world setting, and provide an important understanding of patients' treatment patterns.[1] Randomized controlled trials serve as the gold standard for evidence when assessing efficacy and safety, but do not provide information on how a compound would affect the larger, heterogeneous patient population in the real world because of their strict inclusion and exclusion criteria.

RWE studies that examine the effectiveness of glucose-lowering medication (GLM) for the treatment of type 2 diabetes (T2D) help to provide a better understanding of how therapies are perceived and implemented. As disease management is complex, such studies can also assist clinicians and decision makers in considering optimal treatment outcomes.[2] For instance, one challenge for people living with chronic diseases such as T2D is to agree with the prescription in terms of drug schedules and dosage, referred to as medication adherence. People with diabetes often point to cost, access, competing priorities, or lack of awareness when they have difficulty in continuing to take the medication for the prescribed period, referred to as medication persistence. Both medication adherence and persistence can be impacted by medication hesitancy, which reflects patients' individual medication experiences, personal beliefs, fears of adverse events including medical mistrust or stigma, and health literacy, among other factors.[3-5] Ideally, a partnership between the physician and the patient needs to be established to resolve concerns related to medication hesitancy, and the physician needs to discuss with the patient clinical scenarios that might lead to deprescribing (tapering, dose reduction, or discontinuation) of the prescribed treatment. Thus, understanding what factors contribute to increased adherence and persistence is important in achieving therapeutic goals with antihyperglycaemic therapy.

Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) are currently recommended as the first injectable GLM for the management of T2D for a majority of adult patients, particularly those with established cardiovascular disease or at high cardiovascular disease risk.[6,7] Several GLP-1 RAs are available, each with different profiles in relation to duration of action, efficacy, tolerability, ease of use and frequency of dosing.[8,9] GLP-1 RAs including dulaglutide, exenatide extended-release and injectable semaglutide allow once-weekly dosing, while others such as liraglutide and lixisenatide require daily dosing. Reducing the injection frequency might improve an individual's satisfaction, adherence and persistence, leading to better outcomes. In addition, data on long-term exposure and effectiveness over time are important to understand the real-world effect of these medications. Prospective studies usually have fewer potential sources of bias and confounding than retrospective studies, with most sources of error due to confounding and bias being more common in retrospective than prospective studies. Prospective observational studies allow for data that are not always available for retrospective studies to be collected, for example, reason for treatment discontinuation, weight, patient-reported outcomes and glycated haemoglobin (HbA1c) target goals. As prospective data that examine the persistence and long-term effectiveness of once-weekly and once-daily GLP-1 RA in the real-world setting are limited, specific prospective observational studies are needed.

Once-weekly dulaglutide and once-daily liraglutide are widely used GLP-1 RAs in the United States and European countries. The Real-World Observational Prospective Study of Health Outcomes with Dulaglutide and Liraglutide in Patients with Type 2 Diabetes (TROPHIES) is a two-arm, prospective, observational 24-month study that seeks to evaluate the use of dulaglutide and liraglutide in patients with T2D that are naïve to GLP-1 RA treatment. The primary objective is to estimate the duration of GLP-1 RA treatment without a significant treatment change because of treatment- or diabetes-related factors by 24 months. Additional study outcomes include treatment persistence, reasons for significant treatment change, clinical characteristics and treatment patterns of GLM. The TROPHIES study design, baseline clinical characteristics and treatment profiles have previously been described, in addition to patient-reported outcomes at the time of enrolment.[10,11] Data on the primary objective will be fully disclosed as part of the final analysis publication. This report describes interim treatment persistence and clinical outcomes at 12 months.

2 | MATERIALS AND METHODS

2.1 | Study design

TROPHIES is a prospective, observational, two-cohort (dulaglutide and liraglutide), 24-month study conducted in France, Germany and Italy. The study was initiated in July 2017, and study visits (data collection points) were scheduled at baseline and at approximately 6-, 12-, 18- and 24-months post-baseline as per routine clinical practice (Figure S4). For visits to the physician, a margin of ±6 weeks at the data collection point was advised.

Eligible patients were aged ≥18 years, had a diagnosis of T2D, were naïve to injectable treatment for T2D and were prescribed dulaglutide or liraglutide as their first injectable GLM by a physician during a routine health care visit. Patients initiating treatment with a GLP-1 RA in combination with insulin (defined as initiation of insulin within the first ≤30 days of GLP-1 RA treatment) or those being treated with an investigational drug or procedure were excluded.

Dulaglutide and liraglutide were administered by subcutaneous injection as per the labels.[12,13] The European Union (EU) label-recommended dulaglutide dose is 1.5 mg once-weekly as add-on therapy to other GLMs or 0.75 mg once-weekly as monotherapy in patients for whom metformin is inappropriate because of intolerance or contraindications. For potentially vulnerable patients, a starting dose of 0.75 mg once-weekly in combination therapy can be used. Per the EU label, the liraglutide starting dose of 0.6 mg once-daily should be increased to 1.2 mg once-daily after at least 1 week and can be further increased to 1.8 mg once-daily after at least one additional week. Initiation of treatment and any subsequent treatment changes during the observation period were at the discretion of the treating physician and the patient.

The study was conducted in accordance with the ethical principles of the Declaration of Helsinki and the applicable laws and regulations of the three countries. Appropriate local bodies approved the study. All patients provided authorization for the use and disclosure of their personal health information covering the collection and release of data regarding treatment and its outcomes for the entire study period. Following the EU General Data Protection Regulation 2016/679 (effective 25 May 2018), patients were asked to re-consent during a follow-up visit.

2.2 | Study objectives

For full definitions on the study outcomes, refer to García-Pérez et al.[10] Briefly, the primary objective of TROPHIES is to estimate the duration of treatment with the patients' first GLP-1 RA without a significant treatment change because of treatment- or diabetes-related factors by 24 months. A significant treatment change comprised discontinuation of the first GLP-1 RA or intensification of concomitant GLM. Discontinuation of the first GLP-1 RA was defined as stopping and not resuming the index GLP-1 RA during the remaining study period or stopping dulaglutide or liraglutide and initiating treatment with insulin, an oral GLM not taken at baseline, or a different GLP-1 RA. Discontinuation did not include reduction of dulaglutide or liraglutide doses.

Secondary objectives include description of patients' demographic and baseline clinical characteristics, treatment patterns (persistence with GLP-1 RA treatment regardless of the addition or discontinuation of other GLMs, discontinuation, switching and intensification), reasons underlying significant treatment changes (e.g. main reason for discontinuation, switching, or intensification), and changes in GLP-1 RA dose over time. Clinical outcomes of enrolled patients were described for each cohort at 12 months and included HbA1c, change in HbA1c from baseline, proportion of patients achieving specific glycaemic HbA1c targets, weight and changes in weight from baseline. The HbA1c target was determined by the physician at the baseline visit.

2.3 | Data collection

Data collected at baseline included information about prescribing physicians and patient demographic and clinical characteristics. Data relating to clinical outcomes and study objectives were collected at baseline and at each post-baseline visit. Documentation of treatment with GLMs included agents and doses used, any changes made, and the reasons for start, change, and/or discontinuation of each medication. This information was collected for all oral and injectable GLMs taken before baseline and newly initiated at baseline or post-baseline, the GLP-1 RA initiated at baseline, and concomitant non-diabetes-related medications. In addition, key clinical outcomes [e.g. HbA1c (%), met individual target HbA1c, HbA1c <7%, HbA1c ≤6.5%, weight (kg) and body mass index (kg/m^2)] were evaluated.

2.4 | Sample size and statistical measures

A sample size of 350 patients in each treatment group per country was considered sufficient to provide good precision for the estimation of the median time to the first significant treatment change for each GLP-1 RA.[10] All patients who fulfilled the eligibility criteria were included in the analyses. Patient data were analysed using descriptive statistics while persistence and time to meet HbA1c target were analysed using the Kaplan-Meier (KM) method. No imputation of missing data was performed. Visits were assigned to 6-, 12-, 18- and 24-month time points if within ±3 months of 6-month theoretical time points.

3 | RESULTS

3.1 | Study population

Demographic characteristics and treatment details at baseline have been published.[10] In summary, across France, Germany and Italy, enrolled patients had a mean age of ∼60 years, were more likely to be male and obese (mean body mass index ∼34 kg/m^2), were mostly White, and had a mean HbA1c of 8.2%.[10] By 12 months, a total of 2005 patients were eligible for inclusion in this analysis. Of these, 1774 (88.5%) continued while 231 (11.5%) discontinued the study (Table 1). A slightly greater percentage of patients in the liraglutide group, than the dulaglutide group, discontinued the study. The main reasons for study discontinuation included withdrawal from the study (4.4%) and lost to follow-up (4.0%). Baseline differences between those patients who withdrew from the study and those that completed were minimal. Attending a public practice was more often associated with withdrawal from the study (56.4% vs. 67.1% in completers vs. withdrawers,

TABLE 1 Patient status and reasons for study discontinuation at 12 months

	Dulaglutide	Liraglutide	Overall
Patient status at 12 months, n (%)			
Continued	919 (90.6)	855 (86.3)	1774 (88.5)
Discontinued[a]	95 (9.4)	136 (13.7)	231 (11.5)
Total, N	1014	991	2005
Reasons for discontinuation, n (%)			
Patient decision	41 (4.0)	48 (4.8)	89 (4.4)
Lost to follow-up	27 (2.7)	53 (5.3)	80 (4.0)
Adverse event	12 (1.2)	12 (1.2)	24 (1.2)
Other	5 (0.5)	10 (1.0)	15 (0.7)
Death	5 (0.5)	7 (0.7)	12 (0.6)
Physician decision	5 (0.5)	6 (0.6)	11 (0.5)
Total	95 (9.4)	136 (13.7)	231 (11.5)

For follow-up visits, a time window of ±91 days was allowed from the scheduled visit day, relative to the screening day.

[a]Includes patients who discontinued before 12 months or at 12 months; excludes those who had already had a visit in the time window. N/n, number of patients.

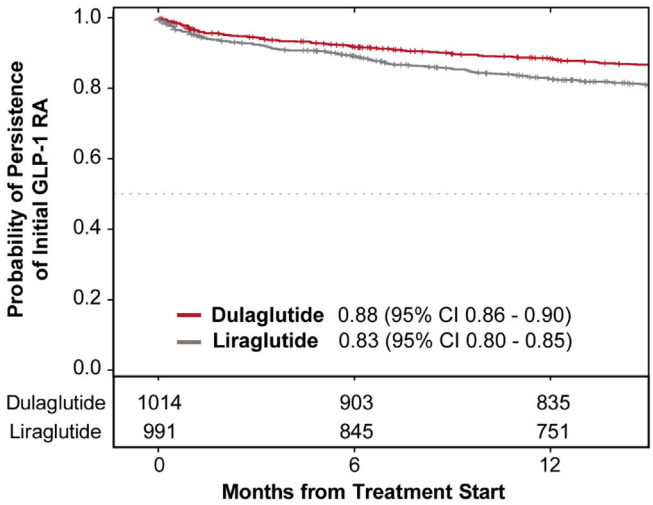

FIGURE 1 GLP-1 RA persistence. Kaplan-Meier curve for the probability of persistence with the initial GLP-1 RA up to 12 months of treatment. Persistence with the initial GLP-1 RA was defined as no discontinuation of the GLP-1 RA regardless of additions or stopping of antihyperglycaemic medications, or treatment intensification. The number shown below the Kaplan-Meier curve represents the number of patients at risk at 0, 6 and 12 months from initiation of treatment. CI, confidence interval; GLP-1 RA, glucagon-like peptide-1 receptor agonist

respectively) while hypertension was diagnosed more often in those patients completing the study (75.5%) versus withdrawers (68.4%).

3.2 | Treatment persistence

Figure 1 shows the persistence, defined as no discontinuation of the initial GLP-1 RA (dulaglutide or liraglutide) regardless of additions or stopping of antihyperglycaemic medications, or treatment intensification, at 6 and 12 months. At 12 months, a high probability [95% confidence interval (CI)] of persistence was observed in both the dulaglutide [0.88 (0.86-0.90)] and liraglutide [0.83 (0.80-0.85)] cohorts. Overall, 313 patients (15.6% of the total evaluable population) discontinued the index GLP-1 RA during this period (dulaglutide, 12.9%; liraglutide, 18.4%). The reasons for treatment discontinuation, as reported by the physician, are provided in Table S3, the main reasons for which included tolerability (6.0%), lack of glycaemic control (2.1%) and decision by the patient (1.8%).

3.3 | Clinical characteristics

Among patients with available HbA1c data, the overall mean HbA1c % at 12 months was 7.04% (n = 1559) compared with 8.24% (n = 1983) at baseline, reflecting a −1.16% mean change from baseline. The baseline and 12-month HbA1c values for dulaglutide and liraglutide cohorts are shown in Figure 2A. HbA1c % was decreased in both the dulaglutide (−1.18%) and liraglutide (−1.15%) groups, compared with baseline (Figure 2B). The HbA1c level targeted by the prescribing physicians for their patient was determined at baseline. Overall, 44.8% of patients (n = 695) had met their HbA1c target by 12 months. In addition, 52.3% of study patients had an HbA1c <7% (n = 811) while 35.6% had an HbA1c ≤6.5% (n = 552). Figure 2C highlights the breakdown of glycaemic HbA1c targets in the dulaglutide and liraglutide cohorts. In the dulaglutide group, 48.2% of patients met their target HbA1c while 41.2% of patients in the liraglutide group met their target HbA1c. Figure S5 shows the KM probability of meeting the individual HbA1c target in the dulaglutide and liraglutide groups up to 12 months. The probability (95% CI) of a patient meeting their individual HbA1c target by 12 months was 0.58 (0.55-0.61) and 0.55 (0.51-0.58) for dulaglutide and liraglutide, respectively.

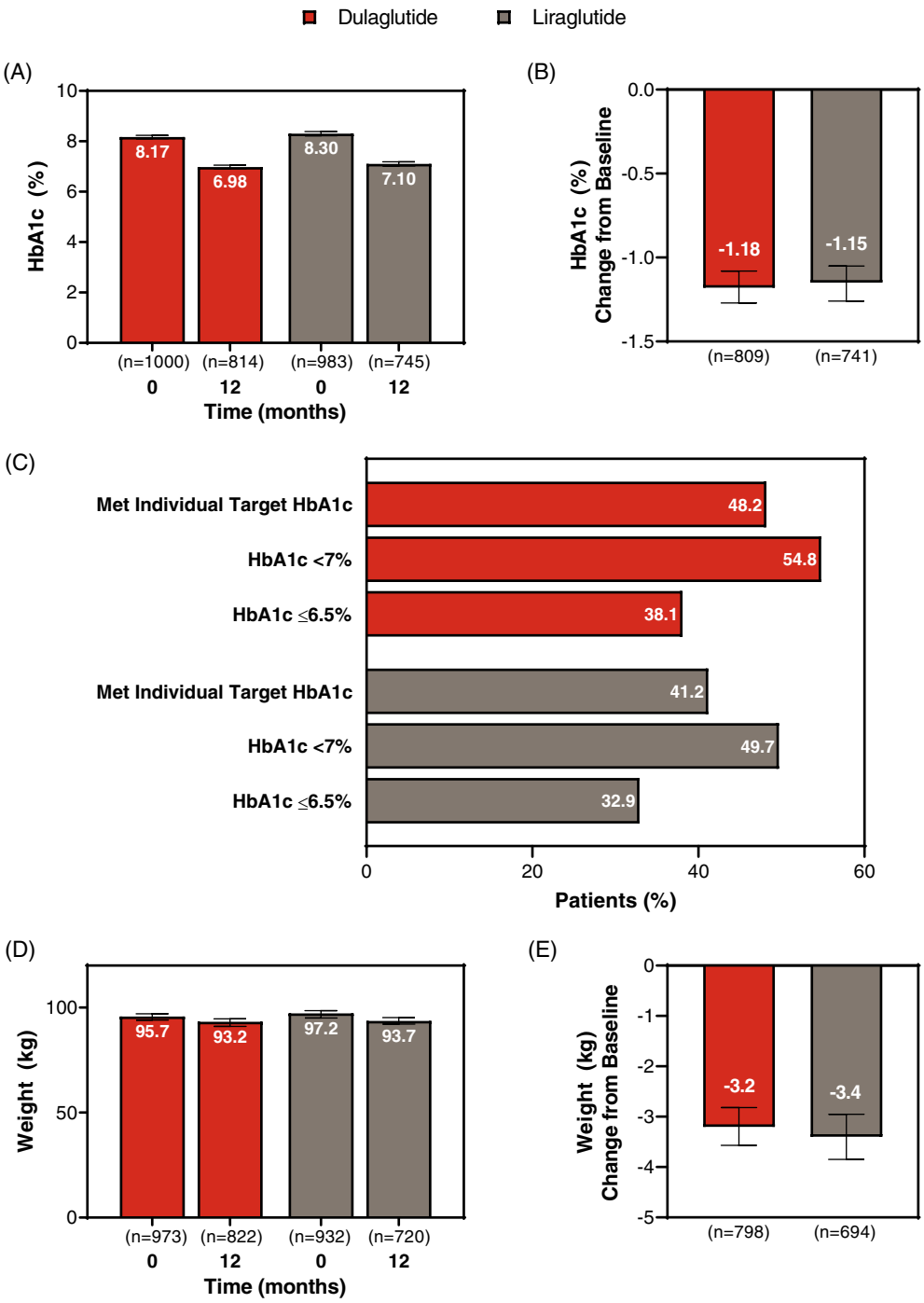

FIGURE 2 Clinical characteristics of HbA1c and weight. (A) HbA1c (%) at baseline (0 months) and at 12 months. (B) HbA1c (%) change from baseline to 12 months. (C) Proportions of patients who had an HbA1c ≤6.5% or <7%, and who met their individual target HbA1c. (D) Weight at baseline and at 12 months. (E) Weight change from baseline to 12 months. Error bars represent 95% confidence intervals. No comparisons were made between GLP-1 RAs because of the study design. HbA1c, glycated haemoglobin; GLP-1 RA, glucagon-like peptide-1 receptor agonist; n, number of patients

Among patients with available weight data, the overall mean weight at 12 months was 93.4 kg (n = 1542) compared with 96.5 kg (n = 1905) at baseline, reflecting a −3.3 kg mean change from baseline. The baseline and 12-month weight values for dulaglutide and liraglutide cohorts are shown in Figure 2D. Weight was decreased in both the dulaglutide (−3.2 kg) and liraglutide (−3.4 kg) groups, compared with baseline (Figure 2E). Using the threshold for weight loss of ≥5%, 31.6% (n = 471) of patients overall showed a weight loss, with similar percentages in the dulaglutide and liraglutide cohorts [dulaglutide, 29.4% (n = 235); liraglutide, 34.0% (n = 236)].

3.4 | Treatment patterns

By 12 months, in the dulaglutide cohort, 9.4% of patients were on the 0.75 mg dose and 81.3% were on the 1.5 mg dose. In the liraglutide cohort, 7.8% were on the 0.6 mg dose, 52.7% were on the 1.2 mg dose and 25.7% were on the 1.8 mg dose (see Figures S6 and S7 for further details). The mean ± standard deviation weekly dose for dulaglutide was 1.41 ± 0.23 mg and the mean daily dose for liraglutide was 1.20 ± 0.36 mg. The distribution of doses for dulaglutide and liraglutide from baseline to 12 months is provided in Figures S6 and S7.

TABLE 2 Oral GLM and insulin use at baseline (day 30) and at 12 months

	Dulaglutide		Liraglutide		Total	
	Baseline, N = 1004	12 months, N = 928	Baseline, N = 971	12 months, N = 883	Baseline, N = 1975	12 months, N = 1811
Number of oral GLM						
Mean ± SD	1.29 ± 0.66	1.31 ± 0.68	1.25 ± 0.68	1.26 ± 0.69	1.27 ± 0.67	1.29 ± 0.69
95% CI	1.25-1.33	1.27-1.36	1.21-1.29	1.21-1.30	1.24-1.30	1.25-1.32
Number of oral GLM, n (%)						
0	80 (8.0)	74 (8.0)	97 (10.0)	92 (10.4)	177 (9.0)	166 (9.2)
1	590 (58.8)	529 (57.0)	568 (58.5)	505 (57.2)	1158 (58.6)	1034 (57.1)
2	301 (30.0)	286 (30.8)	273 (28.1)	254 (28.8)	574 (29.1)	540 (29.8)
≥3	33 (3.3)	39 (4.2)	33 (3.4)	32 (3.6)	66 (3.3)	71 (3.9)
Oral medication class, n (%)						
Biguanides	849 (84.6)	778 (83.8)	814 (83.8)	737 (83.5)	1663 (84.2)	1515 (83.7)
Sulphonylureas	225 (22.4)	212 (22.8)	177 (18.2)	162 (18.3)	402 (20.4)	374 (20.7)
SGLT-2 inhibitors	108 (10.8)	115 (12.4)	96 (9.9)	89 (10.1)	204 (10.3)	204 (11.3)
DPP-4 inhibitors	66 (6.6)	70 (7.5)	70 (7.2)	66 (7.5)	136 (6.9)	136 (7.5)
Thiazolidinediones	15 (1.5)	16 (1.7)	18 (1.9)	19 (2.2)	33 (1.7)	35 (1.9)
α-glucosidase inhibitors	6 (0.6)	6 (0.6)	7 (0.7)	5 (0.6)	13 (0.7)	11 (0.6)
Insulin, n (%)	0 (0.0)	39 (4.2)	0 (0.0)	60 (6.8)	0 (0.0)	99 (5.5)

In contrast to Table 1, the 12-month time point in this table was defined as exactly day 365. Therefore, some patients who discontinued during the 12-month time-window but who were present at 365 days are accounted for at 12 months in Table 2 but considered as having discontinued in Table 1. CI, confidence interval; DPP-4, dipeptidyl-peptidase-4; GLM, glucose-lowering medication; N/n, number of patients not having discontinued at 12 months; SD, standard deviation; SGLT-2, sodium-glucose cotransporter-2.

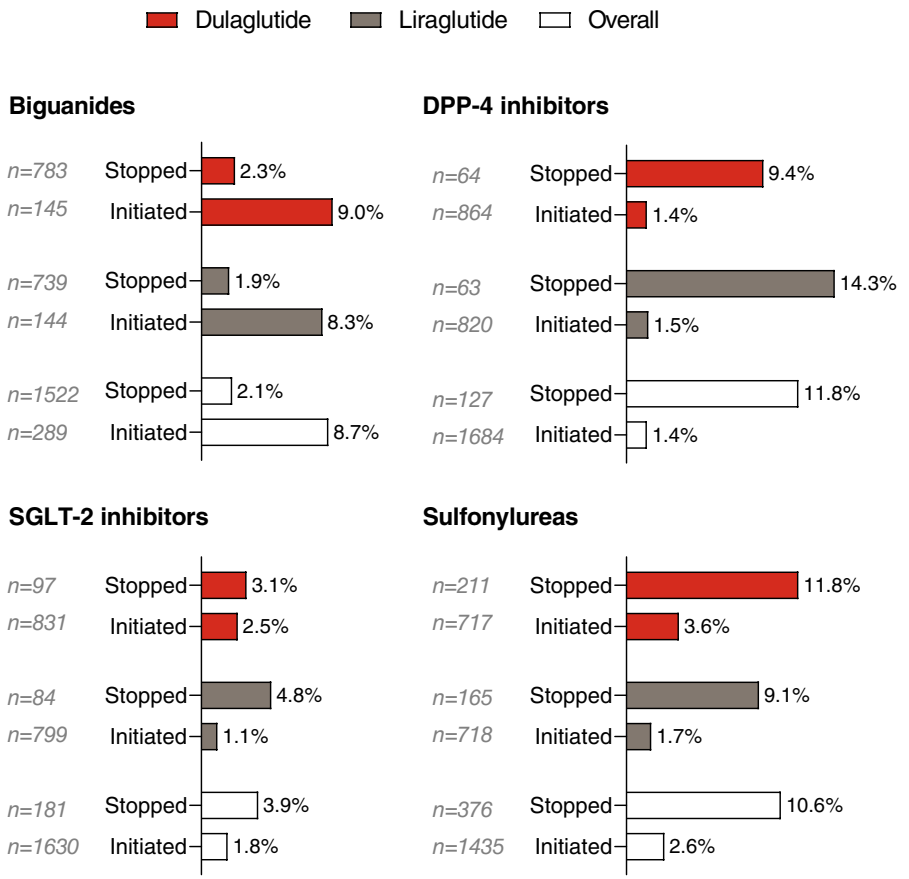

FIGURE 3 Patient-level changes in use of biguanides, sulphonylureas, SGLT-2 inhibitors and DPP-4 inhibitors from baseline (day 30) to 12 months. 'Stopped' was defined as patients who were taking the GLM at baseline (number presented as 'n' alongside percentages) but had ceased treatment by 12 months. 'Initiated' was defined as patients who were not taking the GLM at baseline (number presented as 'n' alongside percentages) but started the GLM by 12 months. DPP-4, dipeptidyl-peptidase-4; GLM, glucose-lowering medication; n = number of patients; SGLT-2, sodium-glucose cotransporter-2

The treatment patterns for concomitant oral GLM and insulin at 12 months post-index are summarized in Table 2. On average, patients used 1.29 ± 0.69 oral GLM at 12 months compared with 1.27 ± 0.67 oral GLM at baseline. By 12 months, the majority of patients were taking one concomitant oral GLM (57.1%) followed by those who were taking two concomitant oral GLM (29.8%), a similar treatment pattern to that observed at baseline. Biguanides were the most common oral GLM class used (83.7%), followed by sulphonylureas (20.7%), sodium-glucose cotransporter-2 (SGLT-2) inhibitors (11.3%) and dipeptidyl-peptidase-4 (DPP-4) inhibitors (7.5%). Figure 3 captures the patient-level changes during use of biguanides, DPP-4 inhibitors, SGLT-2 inhibitors and sulphonylureas from baseline to 12 months. A higher percentage of patients initiated, rather than stopped, biguanide treatment between baseline and 12 months. For DPP-4 inhibitors, SGLT-2 inhibitors and sulphonylureas, higher percentages of patients stopped, rather than initiated, these treatments, although for SGLT-2 inhibitors, the difference between these percentages was much less than for the other treatments. Overall, 5.5% of patients initiated insulin treatment by 12 months, with a slightly greater percentage in the liraglutide group (6.8%), than the dulaglutide group (4.2%) (Table 2).

4 | DISCUSSION

TROPHIES is a prospective, observational study conducted in patients with T2D initiating treatment with dulaglutide or liraglutide. At the time of the design and start of the study, dulaglutide was recently approved as a once-weekly treatment for T2D. Dulaglutide 3.0 and 4.5 mg doses were not marketed in the included countries; therefore, these doses were outside the scope of the study. Liraglutide was included as it was the most used GLP-1 RA at the time the study was designed and started. Other more recent GLP-1 RAs, such as semaglutide, were investigational and not approved at that time. The non-comparative aspect of our study is due to the nature of observational studies, in which the participating physicians simply observe the treatments received by patients and the health outcomes obtained under routine practice conditions. Formal comparisons between treatment arms were not carried out, as the study objectives were primarily to describe the treatment cohorts.

The number of patients at baseline noted in this interim analysis differ from those in a previous study analysis at baseline.[10] This can be explained by the fact that some patients failed to provide re-consent, which was because of the enforcement of EU General Data Protection Regulation 2016/679.

The level of persistence with dulaglutide and liraglutide in TROPHIES was much higher than that observed in published real-world data. In 2017, a retrospective database study evaluating real-world treatment patterns of patients with T2D initiating GLP-1 RA in five European countries found that, over a year of follow-up, the persistence ranged from 29.0% to 60.8% in patients initiating liraglutide and 17.5% to 44.4% in those initiating exenatide twice-daily.[14] Another retrospective study, which analysed the IQVIA Real-World Data Adjudicated Pharmacy Claims database to evaluate the treatment and dosing patterns of patients with T2D initiating GLP-1 RAs in Belgium, France, Germany, Italy, the Netherlands and Canada, showed persistence to be highest among patients treated with dulaglutide across six countries.[15] Based on outcomes from 10 RWE studies, 27.2%-61.0% of patients prescribed with dulaglutide were adherent (defined as proportion of days covered ≥0.80) with the mean persistence (defined as number of days of continuous therapy until discontinuation or the end of follow-up) being greater than 250 days in 12-month studies.[16]

The overall higher persistence observed in TROPHIES could be attributed to several reasons. First, there are differences in the definition of discontinuation. In the claims database, a gap of at least 2 months between prescriptions sufficed to declare discontinuation, while for TROPHIES, no restart of initial GLP-1 RA was allowed at any time in the study. Second, a difference exists between prescription databases such as the IQVIA, including longitudinal prescription datasets that might not capture all treatment exposure data, and TROPHIES that is more likely to capture complete exposure data because of the prospective study design. Third, in contrast to retrospective studies, TROPHIES is a prospective study, and arguably the high persistence may be influenced by the Hawthorne effect whereby patients persist because of a desire to please health care providers. Lastly, over time, the wider use of GLP-1 RAs in clinical practice has increased overall, perhaps related to greater confidence among patients and physicians in using the medication. Indeed, a recent study was more aligned with our results, finding approximately 85% of patients persistent with dulaglutide after 13 months.[17] Similarly, two other recent studies found that treatment with dulaglutide was discontinued by approximately 15% of patients within the first year of treatment.[18,19] It is also worth considering that differences may be related to the development of simpler and easier devices, and less frequent dosing regimens being recommended for certain GLP-1 RAs over time.

Despite the non-comparative study design of TROPHIES and no formal statistical testing being performed, the KM probability of persistence at 12 months for those initiating once-weekly dulaglutide was numerically higher (0.88) than for those taking once-daily liraglutide (0.83). A reduced injection frequency might improve patients' treatment satisfaction and persistence with antihyperglycaemic treatment.[20,21]

The current clinical practice recommendations on glycaemic goals provided by the American Diabetes Association and European Association for the Study of Diabetes recommend an HbA1c goal for non-pregnant adults of less than 7% without significant hypoglycaemia.[22] Before starting GLP-1 RA therapy, the mean HbA1c was approximately 8%, thus, largely exceeding these recommendations. By 12 months, a considerable reduction of HbA1c was observed in dulaglutide (−1.18%) and liraglutide (−1.15%) groups. Furthermore, 54.8% of dulaglutide patients and 49.7% of liraglutide patients had an HbA1c of less than 7% by the 12-month period. These findings were consistent with other RWE studies as well as clinical trial data. A recent review summarizing

the RWE for dulaglutide showed that it reduced HbA1c from baseline to 3 to 24 months by 0.5% to 2.2% across studies.[16] The authors also reported that 23.4%-55.7% of patients receiving prescribed dulaglutide at the doses of 0.75 and 1.5 mg achieved an HbA1c of less than 7%. Across the AWARD [The Assessment of Weekly AdministRation of LY2189265 (dulaglutide) in Diabetes] clinical trials, dulaglutide at both doses was associated with HbA1c reductions of −0.78% to −1.64% with study durations ranging from 24 weeks to 104 weeks.[23]

A systematic literature review of real-world data on the effects of liraglutide on reducing HbA1c showed an average reduction of 0.9%-2.26% in line with the findings reported here.[24] These reductions in HbA1c correspond with that reported in randomized controlled trials where liraglutide treatment resulted in an HbA1c reduction ranging from 0.8% to 1.83%.[24] In addition, the review showed that at least one-third of the patients taking liraglutide achieved a target HbA1c of less than 7% (29.5%-65.0%), compared with 49.7% of TROPHIES patients achieving this goal.[24] These reductions were similar to that observed in the Liraglutide Effect and Action in Diabetes (LEAD) clinical trial program where 35%-45% of patients reached this HbA1c target after 26 weeks of liraglutide treatment.[24]

Overall, these data indicate that dulaglutide and liraglutide are associated with clinically relevant reductions in HbA1c in patients with T2D. TROPHIES is a non-comparative study; however, the clinical trial AWARD-6, a head-to-head trial comparing the safety and efficacy of dulaglutide 1.5 mg with that of liraglutide 1.8 mg in patients treated with metformin, showed consistent results.[25]

By 12 months, weight was reduced by 3.2 kg in the dulaglutide cohort in line with other observational studies that reported a weight loss of 2.1-6.4 kg across studies of 3-12 months,[16] although marginally higher than that reported in the AWARD clinical trials (−0.9 to −3.0 kg).[23] A weight reduction of 3.4 kg was observed in the liraglutide cohort, which is also in line with other RWE (−1.3 to −8.65 kg)[24] and phase 3 clinical trial data (−4 to −6 kg).[26] In the AWARD-6 clinical trial, a reduction in weight over 26 weeks was observed for both the liraglutide and dulaglutide treatment groups [change from baseline to week 26 (SE); dulaglutide −2.90 kg (0.22), liraglutide −3.61 kg (0.22)].[25]

Several limitations should be considered when interpreting these findings. Formal comparisons between treatment arms were not carried out, as the study objectives were primarily to describe the treatment cohorts. No confirmatory statements can be derived and no statistical comparisons between cohorts can be made; therefore, a formal comparison cannot be drawn between dulaglutide and liraglutide. Study investigators may not have had patients' complete treatment records, so the numbers and types of GLMs received before baseline were probably underestimated. Per protocol, patients who had previously received insulin were excluded, but this may not reflect the therapeutic history of all patients who initiated GLP-1 RAs in real-world practice in the included countries, as the use of GLP-1 RA and insulin in combination is common in clinical practice. Moreover, health care systems and patient care vary across countries, so the findings of this study may not apply to other countries. For example, in Italy, all physicians are specialists, as Italian general practitioners are not allowed to prescribe GLP-1 RAs, while in France and Germany, both specialists and general practitioners can initiate treatment with GLP-1 RAs for patients with T2D. As mentioned earlier, the Hawthorne effect could be influencing the interactions that happened between the patient and physician, at least in part, which could have implications for the overall generalizability of the data.

There are limited prospective real-world data available that evaluate the treatment persistence associated with once-weekly and once-daily GLP-1 RA treatment. The current report provides important information on the treatment persistence, clinical characteristics and treatment patterns associated with two widely prescribed GLP-1 RAs in three large European countries. These data show that in the real-world setting, dulaglutide and liraglutide cohorts achieved good persistence with similarly improved glycaemic control that was accompanied by weight loss at 12 months, consistent with previous clinical trial results. Importantly, these findings from the prospective observational study, TROPHIES, showed higher levels of persistence than several previous reports from retrospective studies.

DATA SHARING AND DATA ACCESSIBILITY

Lilly provides access to all individual patient data collected during the trial, after anonymization, with the exception of pharmacokinetic or genetic data. Data are available on request 6 months after the indication studied has been approved in the United States and EU, and after primary publication acceptance, whichever is later. No expiration date of data requests is currently set once data are made available. Access is provided after a proposal has been approved by an independent review committee identified for this purpose and after receipt of a signed data sharing agreement. Data and documents, including the study protocol, statistical analysis plan, clinical study report, and blank or annotated case report forms, will be provided in a secure data sharing environment. For details on submitting a request, see the instructions provided at www.vivli.org.

AUTHOR CONTRIBUTIONS

FG, KB and LEGP contributed to the conception and/or design of the work. BG, HS, JL, EH and LEGP contributed to the acquisition and/or analysis of data for the work. BG, FG, HS, KB, MOF, EH, AD, MF and LEGP contributed to the interpretation of data for the work. All authors contributed to drafting of the work and/or critical revision of the work for important intellectual content.

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CONFLICT OF INTEREST

BG provides research support for Medtronic, Vitalaire, Sanofi, Eli Lilly and Novo Nordisk; is a clinical investigator for Sanofi, Eli Lilly, NovoNordisk, GSK, BMS, AstraZeneca, Medtronic, Abbott, Roche Diagnostics, MSD, Novartis, Janssen and Boehringer Ingelheim; has received speaker's fees and travel support from Eli Lilly; and is on the advisory boards for Sanofi, Eli Lilly, NovoNordisk, Novartis, GSK, MSD, Boehringer Ingelheim, AstraZeneca, Abbott, Medtronic and Roche Diagnostics. FG receives research support from Eli Lilly, Lifescan and Takeda; is a consultant for Boehringer Ingelheim, Lifescan, Merck Sharp & Dohme, Sanofi, AstraZeneca, Medimmune and Roche Diabetes Care; has received speaker's fees, support for attending meetings, and travel support from Eli Lilly; and is on the advisory boards for AstraZeneca, Eli Lilly, Novo Nordisk, Roche Diabetes Care and Sanofi. MF has received research support, consulting fees, speaker's fees, and travel support from Eli Lilly; and is on the advisory boards for Eli Lilly, Boehringer Ingelheim, Berlin Chemie AG and AstraZeneca. L-EG-P, KB, EH, MOF, AD and HS are full-time employees and shareholders of Eli Lilly and Company; JL is a consultant for Eli Lilly and Company.

PEER REVIEW

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DATA AVAILABILITY STATEMENT

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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