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ORIGINAL RESEARCH

Effectiveness and Persistence with Liraglutide Among Patients with Type 2 Diabetes in Routine Clinical Practice—EVIDENCE: A Prospective, 2-Year Follow-Up, Observational, Post-Marketing Study

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ABSTRACT

Introduction: The aim of this study was to investigate whether the efficacy of liraglutide observed in randomized controlled trials translates into therapeutic benefits in the French population during routine clinical practice.

Methods: This observational, prospective, multicenter study included 3152 adults with type 2 diabetes who had recently started or were about to start liraglutide treatment. During 2 years of follow-up, an evaluation of the reasons for prescribing liraglutide, maintenance dose of liraglutide, changes in combined antidiabetic treatments, level of glycemic control, change in body weight and body mass index (BMI), patient satisfaction with diabetes treatment and safety of liraglutide were investigated. The primary study endpoint was the proportion of patients still receiving liraglutide and presenting with HbA_{1c} <7.0% after 2 years of follow-up.

Results: At the end of the study, 29.5% of patients maintained liraglutide treatment and reached the HbA_{1c} target. Mean (±SD) HbA_{1c}, fasting plasma glucose concentration, body weight and BMI were significantly reduced from baseline [8.46% (±1.46) to 7.44% (±1.20); 180 (±60) to 146 (±44) mg/dL; 95.2 (±20.0) to 91.1 (±19.6) kg; 34.0 (±7.2) to 32.5 (±6.9) kg/m^2; respectively, all $P < 0.0001$]. Patient treatment satisfaction increased, with the mean diabetes treatment satisfaction questionnaire status version score increasing from 22.17 (±7.64) to 28.55 (±5.79), $P < 0.0001$. The main adverse event type was

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gastrointestinal, with a frequency of 10.9%, and the percentage of patients suffering ≥1 hypoglycemic episode decreased from 6.9% to 4.4%.

Conclusion: The results of the EVIDENCE study suggest that the effectiveness of liraglutide in real-world clinical practice is similar to that observed in randomized controlled trials.

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Keywords: BMI; Liraglutide; Observational; Type 2 diabetes; Weight

INTRODUCTION

Randomized controlled trials (RCTs) represent the reference standard in terms of assessing the efficacy and safety of any therapeutic agent, including glucagon-like peptide-1 receptor agonists (GLP-1RAs) such as liraglutide, which are considered in the American Diabetes Association/European Association for the Study of Diabetes 2015 position statement [1]. The results of the Liraglutide Effect and Action in Diabetes (LEAD) program demonstrated the anti-hyperglycemic efficacy of liraglutide as monotherapy and combined with other agents in the treatment of patients with type 2 diabetes (T2D) in RCTs. Furthermore, the LEAD program highlighted the low risk of hypoglycemia associated with liraglutide and the additional benefit of clinically relevant weight loss and decreased systolic blood pressure [2–8].

Observational studies are important to explore how treatments, such as liraglutide, are used in a real-life setting. Real-life data provide crucial information to evaluate the effectiveness of therapeutics in clinical practice and are being requested more and more frequently by health authorities. The Association of British Clinical Diabetologists (ABCD) conducted a nationwide audit in the UK to assess the safety and effectiveness of liraglutide in real-life clinical practice. Data from this audit demonstrated that, after 6 months of treatment, liraglutide 1.2 mg was effective in terms of reducing HbA_{1c} (more so in individuals with a higher baseline HbA_{1c}) and well tolerated [9, 10]. Furthermore, data from the IMS Health integrated claims database in the USA demonstrate that, in clinical practice, liraglutide (once daily) has greater effectiveness [in terms of HbA_{1c} reduction and improved glycemic goal attainment (HbA_{1c} <7.0%)] compared with either exenatide (GLP-1RA, twice daily) or sitagliptin [dipeptidyl peptidase-4 (DPP-4) inhibitor, once daily] in patients with T2D [11].

Following liraglutide's approval in France by the European Medicines Agency (EMA) in July 2009, the French Health Authority (FHA) requested the current study with 2 years of follow-up to evaluate conditions for prescription, maintenance dose, effectiveness, and safety of this therapy in routine clinical practice.

METHODS

Study Design

This observational, prospective, multicenter study was conducted (during the period September 2010 to November 2013) in adults with T2D who were starting treatment with liraglutide in mainland France. Study physicians (endocrinologists and general practitioners), already treating patients with

diabetes and prescribing injectable antidiabetic treatments were randomly recruited (by a contract research organization not connected to the survey sponsor) from the Centre de Gestion, de Documentation, d'Informatique et de Marketing (CEGEDIM) database and asked to include the first two or three consecutive patients meeting the eligibility criteria. Data were collected by physicians during routine care at inclusion (visit 1), then at approximately 3 months (visit 2), 6 months (visit 3), 12 months (visit 4), 18 months (visit 5), and 24 months (visit 6). Starting dose of liraglutide (0.6 mg/day), administration of liraglutide, and precautions for use were in accordance with the liraglutide summary of product characteristics (SmPC) [12]. This study was conducted in accordance with Good Pharmacoepidemiology Practices, the requirements in the Declaration of Helsinki and local legal requirements, the Consultative Committee on Information Processing in Health Research, and the National Committee of Data Processing and Freedom.

Patients

Patient recruitment took place from September 23, 2010 to November 15, 2011. Eligibility criteria for study inclusion were: age ≥18 years, diagnosed with T2D, recently started (for less than 1 week) or starting (prescribed during visit 1) liraglutide and ability to provide written consent and complete a diabetes treatment satisfaction questionnaire (DTSQ). Exclusion criteria were any of the following: hypersensitivity to liraglutide or to any of the excipients, already participating in a clinical trial at inclusion, high probability to be lost to follow-up, or diagnosed with type 1 diabetes (T1D).

Outcome Measures

The primary endpoint of the study was the percentage of patients still taking liraglutide and having HbA_{1c} <7.0% at 2 years of follow-up. Secondary endpoints included, at each visit: an evaluation of the reasons for prescription of liraglutide, maintenance dose of liraglutide, changes in combined antidiabetic treatments, level of glycemic control [change in HbA_{1c} and fasting plasma glucose (FPG) concentration], change in body weight and body mass index (BMI), patient satisfaction with diabetes treatment, and safety of liraglutide [hypoglycemic episodes, adverse events (AEs), and medical events of special interest (MESI)]. Hypoglycemic episodes were investigated with the question, "Did the patient suffer one or more hypoglycemic episode (symptomatic or not) documented (by the physician during the visit) since the last visit or within four weeks of the visit?", but the design of the study did not include any hypoglycemia verification test. Hypoglycemic episodes were classified as minor (not requiring third-party intervention) or major/severe (requiring third-party intervention to administer carbohydrates, glucagon, or another emergency treatment). MESI included pathologies such as pancreatitis, thyroid gland anomalies, malignant neoplasias, and major hypoglycemic episodes.

Study Populations for Specific Analyses

Full Analysis Set

The population in the full analysis set (FAS) included all patients having attended the inclusion visit and for whom liraglutide was prescribed. The objectives evaluated with this data set were the characteristics of patients at inclusion and the prescribing conditions, the

maintenance dose, and the safety (as requested by the FHA) at each visit.

Effectiveness Analysis Set

The population in the effectiveness analysis set (EAS) included all patients already included in the FAS and having completed the 2-year final visit under treatment with liraglutide and with at least one measurement of HbA_{1c}, FPG, body weight, or hypoglycemia information at the end of the study. Some patients (20 in total) had thoroughly completed the 2 years of follow-up, though the physician filled an end of study form out with a reason for withdrawal from study. These patients were also included in the EAS population. The objectives evaluated with this data set were changes in HbA_{1c}, FPG concentration, body weight, and BMI at each visit.

Population for Primary Endpoint Analysis

The population for the primary endpoint analysis (PEA) included all EAS patients plus patients who discontinued liraglutide treatment but remained in the study. The purpose of this pre-specified population was to prevent loss of data from patients who discontinued liraglutide before 2 years of follow-up.

Patient-Reported Outcomes Analysis Set

The population for the patient-reported outcomes set (PROAS) included all patients in the FAS who also filled in at least one item on the patient questionnaire at the inclusion visit and at least one follow-up visit. The DTSQs (status version) (satisfaction with treatment at each visit, which has a minimum score of zero and a maximum score of 36) and DTSQc (change version) (change in satisfaction with treatment between inclusion and 12 months, which has a minimum score of −18 and a maximum score of 18) were analyzed using the PROAS. Change in satisfaction with treatment was measured at 12 months due to the high number of missing data, with regard to this parameter, at 24 months.

Missing Data

No replacement of missing data was planned as part of the analysis of the primary endpoint.

Statistical Analysis

Calculating the sample size was based on the expected accuracy for the confidence interval (CI) of the number of patients still under treatment with HbA_{1c} <7.0% at 2 years. This calculation was based on an observed proportion of 40.0% not accessible for the primary endpoint based on a previous non-interventional study conducted by Novo Nordisk [13]. A sample size of 1707 patients would be adequate to achieve the goal with ±2.5% accuracy, the proportions observed with a significance of 95.0%. Therefore, at least 2845 patients had to be recruited. For qualitative parameters, data are expressed as number of patients and percentages and as mean value ± standard deviation (SD) for quantitative parameters. Quantitative parameters with normal distribution were analyzed by a Student test, otherwise by a non-parametric Wilcoxon–Mann–Whitney test, and qualitative parameters were analyzed by a Chi-square test with continuity correction or a Fisher's exact test if the hypothesis of the size of frequencies expected was not respected. If necessary, some ordinal levels were grouped. All tests were performed with a significance of 5.0%.

RESULTS

Patient Disposition

In total, 3590 patients with T2D were considered for inclusion. However, 438 patients were not included, mainly for the following reasons: patient refusal (36.0%), miscellaneous reasons (31.0%), well-controlled diabetes (11.0%), or issues with compliance or irregular follow-up in consultation (10.0%). In total, 1143 patients withdrew from the study early (before 2 years of follow-up)—41.0% were lost to follow-up or moved and 21.8% withdrew due to AEs. The distribution of patients during the study is shown in Fig. 1.

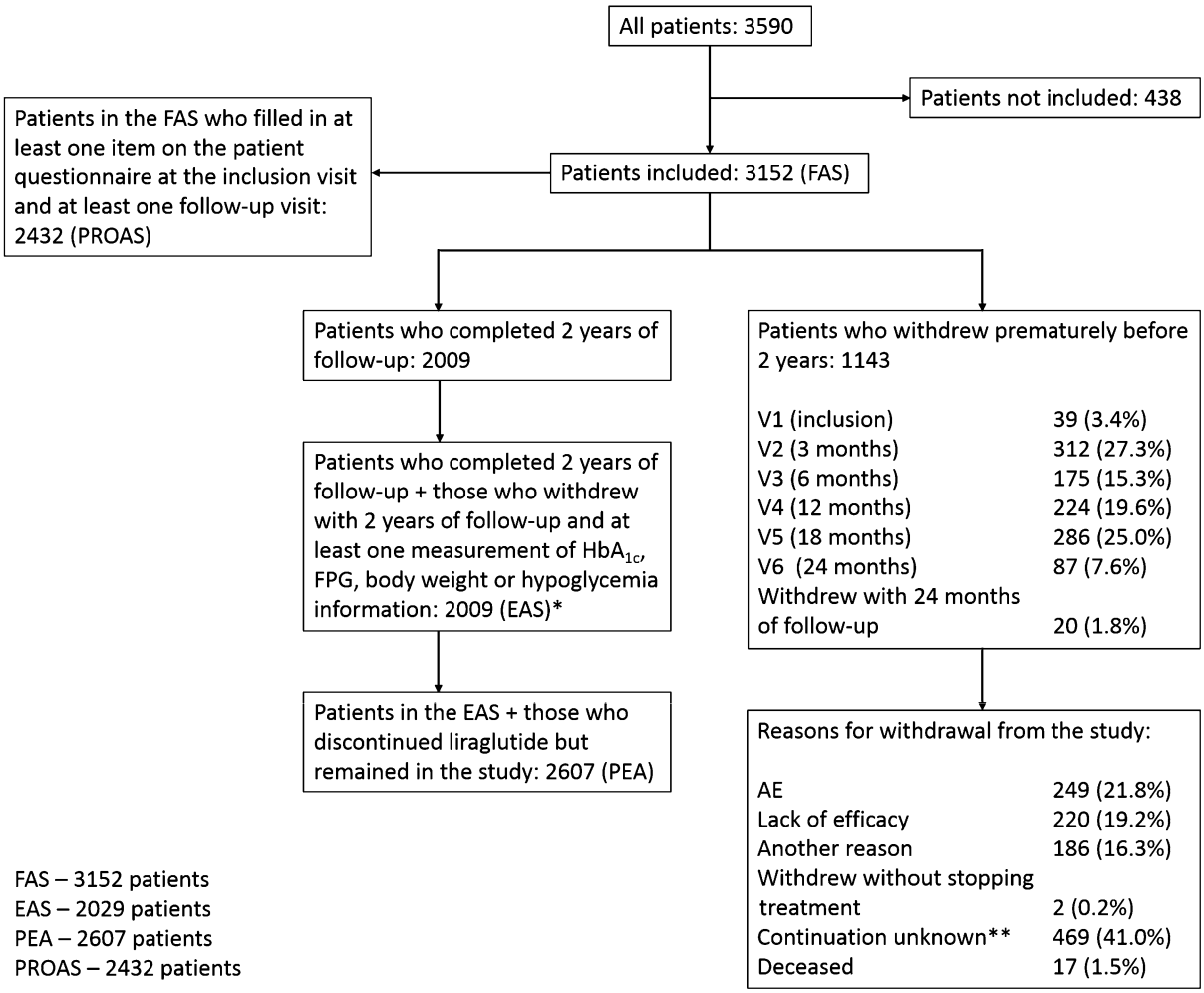

Fig. 1 Distribution of patients during the study. *Asterisks* some patients had thoroughly completed the 2 years of follow-up though the physician filled an end of study form out with a reason for withdrawal from study. These patients (20 in total) were included in the EAS population and counted as withdrawals from study. *Double asterisks* patients lost to follow-up or moved. *AE* adverse event, *EAS* effectiveness analysis set, *FAS* full analysis set, *FPG* fasting plasma glucose, *PEA* population for primary endpoint analysis, *PROAS* patient-reported outcomes analysis set

Baseline Characteristics

Baseline characteristics were collected from 3152 patients (FAS) enrolled in the EVIDENCE study and are shown in Table 1. Motivations of physicians to prescribe liraglutide and the description of antidiabetic treatments before and at liraglutide initiation in the FAS are shown in Tables 2 and 3, respectively.

Primary Endpoint

In total, 769 of 2607 patients (29.5%) in the PEA population maintained liraglutide treatment and reached the goal of HbA_{1c} <7.0% at the end of the study (95.0% CI 27.7; 31.2), confirmed by the sensitivity analysis in the FAS population (3152 patients): 24.4% (95.0% CI 22.9; 25.9).

Secondary Endpoints

Evolution of Antidiabetic Treatment

The most common reasons for prescribing liraglutide were desire for improvement of glycemic and weight control (Table 2). The evolution of antidiabetic treatment was analyzed using the EAS population (2029 patients). Liraglutide dose was initiated at 0.6 mg/day and, by 3 months, the percentage of patients prescribed 1.2 mg/day liraglutide had increased from 11.1% to 75.9%. Patients who demonstrated inadequate glycemic control on the 1.2 mg/day liraglutide dose were then transferred to the 1.8 mg/day dose. At the end of the study, 49.1% and 45.5% of patients received 1.2 mg/day or 1.8 mg/day of liraglutide, respectively (Fig. 2). However, due to concerns with tolerability of the higher doses or observed efficacy with the 0.6 mg/day dose, the remaining 5.4% of patients received

Table 1 Baseline characteristics of 3152 patients enrolled in the study—FAS

Characteristics	*n* (%) or mean (±SD)
Age (3146 patients analyzed)	
Mean (±SD), years	58.7 (±10.5)
Gender (3152 patients analyzed)	
Male, *n* (%)	1671 (53.0)
Female, *n* (%)	1481 (47.0)
Followed by another physician[a] (3147 patients analyzed)	
Yes, *n* (%)	1717 (54.6)
No, *n* (%)	1430 (45.4)
Social environment (3127 patients analyzed)	
Lives alone, *n* (%)	621 (19.9)
In family/couple, *n* (%)	2497 (79.9)
Retirement home, *n* (%)	9 (0.3)
Diabetes history	
Duration of diabetes (3140 patients analyzed)	
Mean (±SD), years	9.7 (±6.7)
Complication linked to diabetes[b] (3132 patients analyzed)	
Yes, *n* (%)	1048 (33.5)
No, *n* (%)	2084 (66.5)
If yes, type[c] (3131 patients analyzed)	
Coronary disease, *n* (%)	364 (11.6)
Neuropathy, *n* (%)	277 (8.8)
Retinopathy, *n* (%)	252 (8.0)
Nephropathy, *n* (%)	240 (7.7)
Lower limb arteritis, *n* (%)	176 (5.6)
Cerebrovascular disease, *n* (%)	69 (2.2)
Diabetic foot, *n* (%)	70 (2.2)
Other, *n* (%)	110 (3.5)
Clinical characteristics	
Body weight (3151 patients analyzed)	
Mean (±SD), kg	95.6 (±19.9)

Table 1 continued

Characteristics	*n* (%) or mean (±SD)
BMI (3147 patients analyzed)	
Mean (±SD), kg/m^2	34.1 (±6.9)
BMI distribution (3147 patients analyzed)	
<18.5 kg/m^2, *n* (%)	1 (0.0)
≥18.5; <25, *n* (%)	151 (4.8)
≥25; <30, *n* (%)	768 (24.4)
≥30; <40, *n* (%)	1706 (54.2)
≥40 kg/m^2, *n* (%)	521 (16.6)
Systolic blood pressure (3145 patients analyzed)	
Mean (±SD), mmHg	134.7 (±13.3)
Diastolic blood pressure (3144 patients analyzed)	
Mean (±SD), mmHg	77.8 (±8.8)
Biological characteristics	
HbA_{1c} (3109 patients analyzed)	
Mean (±SD), %	8.5 (±1.5)
Fasting plasma glucose (2629 patients analyzed)	
Mean (±SD), mmol/L	10.1 (±3.4)
Triglycerides (2701 patients analyzed)	
Mean (±SD), mmol/L	10.6 (±8.1)
High-density lipoprotein (2598 patients analyzed)	
Mean (±SD), mmol/L	2.6 (±0.9)
Low-density lipoprotein (2529 patients analyzed)	
Mean (±SD), mmol/L	5.9 (±2.1)

n number for subset, *SD* standard deviation

[a] A patient may have been included in the study by a general practitioner but also managed by an endocrinologist

[b] All historical medical events were registered on the basis of patient reporting or their medical record

[c] Patients may have had more than one complication. Due to missing data, the % value relates to the number of patients analyzed within the FAS population for that particular characteristic and not the total FAS population

Table 2 Motivations that influenced the decision of physicians to prescribe liraglutide—FAS

Motivation	*n*/total analyzed (%)
Improvement of glycemic control	2552/3145 (81.1)
Reduction of hypoglycemic episodes	290/3144 (9.2)
Improvement of weight control	2113/3145 (67.2)
Potential beneficial effect on beta-cell function	915/3145 (29.1)
Improvement of blood pressure	284/3143 (9.0)
Adverse effect of current treatment	324/3145 (10.3)
Patient dissatisfaction with current treatment	578/3144 (18.4)
Trying a new treatment	578/3144 (18.4)
Potential beneficial effect of other properties of GLP-1	956/3144 (30.4)

Due to missing data, the % value relates to the number of patients analyzed within the FAS population for that particular motivation and not the total FAS population. Physicians may have had more than one motivation for prescribing liraglutide

FAS full analysis set, *GLP-1* glucagon-like peptide-1, *n* number for subset

0.6 mg/day liraglutide. Liraglutide was added to current antidiabetic therapy and, by the end of the study, there was a reduction in oral antidiabetic drug (OAD) monotherapy and an increase in the number of patients receiving more than three therapies in combination. Throughout the study, rates of prescription of biguanides, sulfonylureas (SUs), glinides, and alpha-glucosidase inhibitors remained stable. In contrast, prescriptions of DPP-4 inhibitors and glitazones fell from baseline to end of study (40.1% to 9.7% and 14.1% to 3.0%, respectively) and those of insulin increased from baseline to end of study (12.9% to 24.0%) (Table 3).

Table 3 Change in antidiabetic treatment from before initiation of liraglutide to the end of study

	Before initiation of liraglutide (FAS)	Before initiation of liraglutide (EAS)	At end of inclusion (0 months) (FAS)	At end of inclusion (0 months) (EAS)	At end of study (2 years) (FAS/EAS)[a]
Therapeutic strategy					
Monotherapy	609 (19.5)	409 (20.4)	121 (3.9)	75 (3.8)	68 (3.8)
Double therapy	1233 (39.5)	821 (40.9)	1181 (38.2)	795 (39.9)	621 (34.8)
Triple therapy	1090 (34.9)	667 (33.2)	1415 (45.8)	888 (44.6)	733 (41.0)
>3 triple therapy	188 (6.0)	112 (5.6)	372 (12.0)	234 (11.7)	365 (20.4)
Treatments					
Biguanides	2561 (82.1)	1668 (83.0)	2521 (81.6)	1648 (82.7)	1623 (82.5)
SUs	1780 (57.1)	1131 (56.3)	1596 (51.6)	992 (49.7)	1002 (50.9)
DPP-4 inhibitors	1261 (40.4)	805 (40.1)	257 (8.3)	182 (9.1)	191 (9.7)
Insulin	488 (15.6)	260 (12.9)	283 (9.1)	165 (8.3)	440 (24.0)
Glitazones	425 (13.6)	284 (14.1)	190 (6.1)	121 (6.1)	60 (3.0)
Glinides	277 (8.9)	158 (7.9)	221 (7.1)	124 (6.2)	172 (8.7)
Alpha-glucosidase inhibitors	160 (5.1)	100 (5.0)	90 (2.9)	61 (3.1)	76 (3.9)
Total analyzed	3120 (100)	2009 (100)	3089 (100)	1992 (100)	1787 (100)

DPP-4 dipeptidyl peptidase-4, *EAS* effectiveness analysis set, *FAS* full analysis set, *n* number for subset, *SU* Sulfonylurea

[a] There were the same number of patients still remaining in both FAS and EAS populations at the end of the study; therefore, the percentages are the same in both populations. Values are expressed as *n* (%). Due to missing data, the % value relates to the number of patients analyzed within the FAS or EAS population for that particular time point and not the total FAS or EAS population

Glycemic and Weight Control

Changes in HbA_{1c}, FPG concentration, body weight, and BMI from baseline to 2 years were analyzed using the EAS population. From baseline to end of study, mean (±SD) HbA_{1c} was significantly ($P < 0.0001$) reduced [by 1.01% (±1.54)], from 8.46% (±1.46) to 7.44% (±1.20). At 2 years, 39.4% of the patients still on liraglutide maintained an HbA_{1c} <7.0%. Mean FPG concentration [from 180 (±60) to 146 (±44) mg/dL], mean body weight [from 95.2 (±20.0) to 91.1 (±19.6) kg], and mean BMI [from 34.0 (±7.2) to 32.5 (±6.9) kg/m^2] were also significantly (all $P < 0.0001$) reduced.

Treatment Satisfaction

Treatment satisfaction was analyzed in the PROAS population (2432 patients). Throughout the study, patient treatment satisfaction (with liraglutide) increased, with the DTSQs score increasing from a mean (±SD) of 22.17 (±7.64) at baseline to 28.55 (±5.79) at end of study, $P < 0.0001$. Change in satisfaction with treatment (compared with previous treatment) after 1 year of follow-up, measured

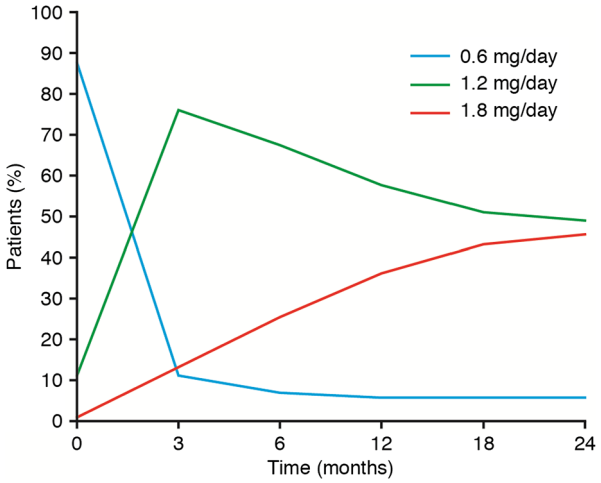

Fig. 2 Change in liraglutide dose by visits—EAS. *EAS* effectiveness analysis set

by the DTSQc, was, on average, 10.71 (±6.10) (95.0% CI 10.39; 11.03).

Hypoglycemia

Hypoglycemic episodes were analyzed using the FAS population. The percentage of patients experiencing at least one hypoglycemic episode (in the 4 weeks preceding each visit) decreased during the study, from 7.4% at 3 months to 4.4% at end of study. Most episodes were minor, not requiring third-party intervention. Nine patients reported severe hypoglycemia during the 2-year study period. These patients were also being treated with either biguanides and SUs or insulin and glinides, and there was no correlation with liraglutide dose.

AEs and MESI

AEs were analyzed using the FAS population. In total, 653 patients (20.7%) experienced at least one AE during the study period, with 458 patients (14.5%) experiencing an AE possibly related to liraglutide. AE categories affecting at least 1.0% of the population are listed in Table 4. There were six serious AEs involving digestive pathologies (one abdominal pain, two diarrhea, two nausea, and one vomiting). There were eight MESI related to pancreatic

Table 4 AE category affecting ≥1% of the population—FAS

AE	*n* (%)
GI	345 (10.9)
Nausea	144 (4.6)
Diarrhea	63 (2.0)
Vomiting	54 (1.7)
Dyspepsia	51 (1.6)
Abdominal pain	30 (1.0)
Constipation	20 (0.6)
Upper abdominal pain	19 (0.6)
Flatulence	13 (0.4)
Gastro-esophageal reflux	11 (0.3)
Metabolic and nutritional	82 (2.6)
Hypoglycemia	29 (0.9)
Inadequate control of diabetes	17 (0.5)
Hyperglycemia	10 (0.3)
Loss of appetite	23 (0.7)
General	73 (2.3)
Asthenia	21 (0.7)
Lack of efficacy with treatment	15 (0.5)
Medical and surgical procedures	57 (1.8)
Hospitalization	27 (0.9)
Cardiovascular disorders	41 (1.3)
Atrial fibrillation	10 (0.3)
Arrhythmia	6 (0.2)
Myocardial infarction	6 (0.2)
Coronary stenosis	5 (0.2)
Central nervous system	38 (1.2)
Neoplasias	37 (1.2)
Prostate cancer	5 (0.2)
Kidney cancer	3 (0.1)
Squamous cell carcinoma	2 (0.1)

The safety population for AEs included all patients who had been prescribed liraglutide at least once and had at least one available safety data point after inclusion (3152 patients). The *n* value relates to the number of AEs for each subset; the % value relates to proportion of the FAS population affected

AE adverse event, *FAS* full analysis set, *GI* gastrointestinal

pathologies (two pancreatitis, four acute pancreatitis, one increased lipasemia, and one hepato-pancreatic biological disorder) and eight linked to thyroid pathologies (two goiters, one hyperthyroidism, one hypothyroidism, one thyroid disorder, one thyroid nodule, one thyroid cancer [non-encapsulated papillary carcinoma], and one thyroidectomy with no known etiology). During the study, 17 people died. However, a causal relationship to liraglutide was considered unlikely by the physicians for all causes of death except in one patient who died of a pancreatic tumor 4 months after starting treatment with liraglutide, and in another patient who died of a multifocal hepatocellular carcinoma 23 months after inclusion. In these cases, a causal relationship of these two events to liraglutide was considered possible by the physicians.

DISCUSSION

The EVIDENCE study was a prospective, observational study that aimed to assess conditions for prescription, maintenance dose, effectiveness, and safety of liraglutide in routine clinical practice in France. To minimize the limitations associated with the design of an observational study, physicians were chosen at random from a large sample and the number of patients recruited by each physician was limited to prevent a cluster effect. In total, 992 physicians at 992 sites in mainland France participated in the study. Therefore, this study can be considered representative of the national profile. Throughout the study, all contact between the sites and the sponsor went through the research organization to avoid bias in the delivery of routine care, and quality control was applied to each step of data handling, ensuring the correctness of all data, specifically regarding safety reporting. As this was an observational study, with no control group, the results are indicative of certain combinations and cannot give rise to cause-and-effect relationships. Furthermore, the complete data are not available for analysis for all patients, as any missing data were not replaced.

In the EVIDENCE study, the main motivation for physicians to prescribe liraglutide was to improve glycemic control. The studies in the LEAD program have shown that liraglutide may provide greater benefit when used earlier in the course of disease progression [2, 4]. In the EVIDENCE study, only ~20.0% of patients were receiving OAD monotherapy at the time of initiation of liraglutide. Additionally, compared with patients in the LEAD studies, patients included in the EVIDENCE study were slightly older (mean age 58.7 vs. ~52.0 to ~58.0 years) and more obese (70.8% of patients had a BMI $\geq$30 kg/m^2 in the EVIDENCE study vs. 59.6% of patients across the six LEAD studies) [2–8, 14]. Taken together, this may suggest that liraglutide was initiated later in the disease course in the EVIDENCE study than in the LEAD studies. Indeed, the mean duration of diabetes for patients was 9.7 years in the EVIDENCE study and between 6.5 and 9.4 years in the LEAD studies [2–8]. One possible explanation for this is related to the guidelines available during the course of the EVIDENCE study that recommended the use of GLP-1RAs as second-line therapy [15]. Furthermore, 15.6% of patients were treated with insulin prior to liraglutide introduction in the EVIDENCE study, while this was not permitted in the LEAD studies [2–8], thus confirming that the EVIDENCE study included a different patient population compared with the LEAD studies. It is of note, however, that

patients included in the EVIDENCE study had similarly poorly controlled diabetes (mean HbA_{1c} 8.5%) to those in the LEAD studies (mean HbA_{1c} 8.1–8.6%) [2–8].

Mean HbA_{1c} reduction, amounting to −1.0%, at the end of the EVIDENCE study, was clinically relevant and compared well with that in the LEAD RCTs (−0.8% to −1.5%) [2–8] and other real-world studies (−0.9% to −1.6%) [16–18]. Furthermore, liraglutide was associated with optimal glycemic control (HbA_{1c} <7.0%) in ~30.0% of patients after 2 years of treatment, while only 9.8% of patients had HbA_{1c} <7.0% at baseline. The proportion of patients achieving optimal glycemic control in the EVIDENCE study is almost identical to results from a recent 26-week UK-based real-world study (29.3%) [16] and only slightly below the ~35.0% to ~45.0% reported after 26 weeks of treatment in the LEAD RCTs, which shows liraglutide's effectiveness under standard conditions for use [2–5, 7, 8]. When comparing data from the EVIDENCE study with that from the LEAD-3 extension study (18 months in duration), a greater difference in patients achieving optimal glycemic control (HbA_{1c} <7.0%) is apparent, i.e., ~30.0% in EVIDENCE vs. ~53.0–58.0% in the LEAD-3 extension study [19]. However, it is possible that the proportion of patients achieving optimal glycemic control in the LEAD-3 extension study is influenced by survivor bias.

Real-world data demonstrate that most T2D patients starting GLP-1RA therapy have a high BMI [20], and previous studies have shown that liraglutide is associated with weight loss [21, 22]. Moreover, a recent study showed that, across the LEAD studies, higher initial BMI was associated with slightly greater weight loss with liraglutide [14]. Therefore, unsurprisingly, the desire for improved weight control was an important motivation for physicians to prescribe liraglutide in the EVIDENCE study. In total, 95.2% of patients involved in the EVIDENCE study had a baseline BMI ≥25 kg/m^2 and, as reported in RCTs [2–8] and other real-world studies with liraglutide [16–18], the reductions in both weight and BMI seen throughout the EVIDENCE study were statistically significant. Although the impact of such weight loss in T2D remains to be demonstrated in terms of prognosis, this trend may be enough to at least improve patient quality of life.

Throughout the study, the most commonly prescribed oral antidiabetic treatments remained stable with the introduction of liraglutide. However, there was a reduction in the use of DPP-4 inhibitors from 40.1% to 9.7%. This may be expected, as data from an open-label extension study demonstrate the switch from DPP-4 inhibitor to liraglutide to be beneficial, both in terms of glycemic and weight control [23]. Moreover, liraglutide is not indicated for use in combination with DPP-4 inhibitors [12], and combinations of incretin-based therapies are not well studied to date and the theoretical benefits appear to be relatively limited [24]. Finally, it is not currently known whether there may be an increased risk of AEs when GLP-1RAs and DPP-4 inhibitors are used in combination. At the end of study, 191 patients were still being treated by a combination of liraglutide and a DPP-4 inhibitor. This may be interpreted as a lack of interaction between the sponsor and the physicians. Throughout the study, there was a reduction in the prescription of glitazones from 14.1% to 3.0%. This observation may have been largely due to the withdrawal of these drugs from the French market during the study period and physicians' concerns regarding patients' weight.

Patients initiating liraglutide treatment should be transferred from the starting dose of 0.6 to 1.2 mg/day after at least 1 week [12]. This dose can then be increased further to 1.8 mg/day for patients who require increased glycemic control. Consequently, at the end of study, about half of the study population were on the 1.2 mg/day dose and half were on the 1.8 mg/day dose. At the 12-month timepoint, 36.2% of patients were on the 1.8 mg/day dose and about 58.0% were on 1.2 mg/day. This finding compares well with results from a recent real-world study (32.7% and 64.6%, respectively) [17].

Throughout the study, even though the use of SUs and glinides remained stable and the use of insulin increased, the percentage of patients suffering at least one hypoglycemic episode (during the 4 weeks of preceding visits) decreased from 6.9% (baseline measure) to 4.4% and only nine patients experienced a severe hypoglycemic episode during the entire 2 years of follow-up. To put this into perspective, 11 patients experienced a severe hypoglycemic episode during the 4 weeks preceding inclusion in the study. All patients who experienced a severe hypoglycemic episode were also being treated with both biguanides and SUs or with insulin and glinides. Therefore, it is likely that liraglutide was not the cause of the severe hypoglycemic episodes, and data from the LEAD-3 trial demonstrated no cases of severe hypoglycemia when liraglutide was used as monotherapy [6]. However, with the lack of a control arm in the EVIDENCE study, it is difficult to conclusively evaluate this.

The most frequently reported AE type in this study was classified as belonging to gastrointestinal (GI) disorders, and the frequency reported (10.9%) was similar to that reported in another real-world study (11.4%) [17]. However, this occurrence is considerably lower than that observed with liraglutide in the LEAD RCTs (~33.0% to ~56.0%) [2–8]. This may be due to the less controlled nature of safety reporting in this observational study which is a well-known phenomenon in non-RCTs [25]. However, it may also be possible that a prolonged dose escalation period in the EVIDENCE study may have contributed to this observation.

Based only on very limited data [26–30], some researchers have suggested that therapy with GLP-1RAs may increase the risk of pancreatitis [31, 32]. During this study, there were four cases (0.1%) of acute pancreatitis, which is in agreement with the current SmPC for liraglutide (<0.2%) [12]. The incidence of acute pancreatitis in this study was 0.8 cases per 1000 patient-years, which compares well with a rate of 1.6 cases per 1000 patient-years reported in a recent meta-analysis of 18 clinical trials involving liraglutide [33], and is less than the background incidence (4.2 cases per 1000 patient-years) in people with T2D [34]. This finding also relates well to another recent study, which suggests that the use of incretin-based drugs appears not to be associated with an increased risk of acute pancreatitis [35]. However, vigilance still needs to be conducted, as a recently published analysis suggests that, compared with other anti-hyperglycemic agents, use of incretin-based drugs is associated with an increased risk of reported pancreatitis in France [36]. At present, neither the US Food and Drug Administration (FDA) nor the EMA have reached a final conclusion regarding a causal relationship between GLP-1RAs and pancreatitis or pancreatic cancer. However, both agencies do agree that assertions concerning a causal association between incretin-based drugs and pancreatic safety, as expressed recently in the scientific literature

and in the media, are inconsistent with the current data [37]. Overall, the safety profile for this study is in accordance with what is reported in the SmPC for liraglutide [12] and does not, therefore, alter liraglutide's risk–benefit profile.

Finally, results from the EVIDENCE study show an increase in patients' treatment satisfaction after initiating liraglutide therapy in a real-world setting, and treatment satisfaction has been shown to be associated with increased adherence to treatment [38] and lower HbA_{1c} values [39, 40].

CONCLUSIONS

The results of the EVIDENCE study suggest that the effectiveness of liraglutide in real-world clinical practice is similar to that observed in RCTs, even though there were important demographic and clinical differences between the patient populations. In addition, the incidence of GI events was considerably lower in EVIDENCE than in RCTs. Overall, the results from this observational study suggest that treatment with liraglutide translates into therapeutic benefits for patients with T2D in routine clinical practice.

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