ORIGINAL ARTICLE

The Multicenter, Open-Label, Observational LEAD-Ph Study: Real-World Safety and Effectiveness of Liraglutide in Filipino Participants with Type 2 Diabetes

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Abstract

Objective. Assess safety and effectiveness of liraglutide among Filipino participants with type 2 diabetes (T2D) in routine clinical practice.

Methodology. A 26-week, prospective, multicenter, open-label, observational study was conducted in adults with T2D prescribed liraglutide (1.2 mg or 1.8 mg) in routine clinical practice in the Philippines. Primary endpoint: incidence rate and type of serious adverse drug reactions (SADRs). Secondary endpoints included other aspects of safety, and effectiveness.

Results. Participants (n=1056) had a mean (standard deviation) age of 53.2 (12.0) years, and glycated hemoglobin (HbA$_{1c}$) level of 8.8% (2.0). Of 19 ADRs reported in 17 participants, none were SADRs (primary endpoint). No serious adverse events were reported. From baseline to week 26: the proportion of participants with major hypoglycemic episodes (requiring assistance) decreased from 2.0% to 0.2%; and with minor episodes (plasma glucose <3.1 mmol/L [<56 mg/dL]) decreased from 6.1% to 1.5%; serum creatinine remained unchanged. Among secondary effectiveness endpoints, improvements were seen from baseline to week 26 in HbA$_{1c}$ level, fasting and postprandial blood glucose levels, body weight, blood pressure, and fasting lipid profile.

Conclusion. During routine clinical use of liraglutide for T2D in the Philippines, no new safety concerns were identified and blood glucose was lowered effectively.

Key words: glucagon-like peptides, liraglutide, type 2 diabetes mellitus, safety, observational study, Philippines

INTRODUCTION

Core pathophysiologic defects in the progression of type 2 diabetes (T2D) include progressive pancreatic β-cell failure resulting in insulin deficiency and increased tissue insulin resistance compounding the problem.[1] It has been recognized that impairments in the incretin effect (in which insulin secretion is amplified by incretin hormones in response to the ingestion of glucose), particularly the action of glucagon-like peptide 1 (GLP-1), also play a key role in the progression of T2D[2,3] and may be an important contributor to the observed hyperglycemia.[4] Targeting this impairment can form part of a dynamic management approach to counteract the progressive nature of T2D.[5,6] GLP-1-mediated effects include glucose-dependent stimulation of endogenous insulin secretion, modulation of glucagon secretion, reduced appetite and food intake,

delayed gastric motility and emptying, inhibition of β-cell apoptosis and improvement of β-cell function.[4,7] Multiple physiologic effects of GLP-1, beyond glucose metabolism, mean that drugs that mimic the action of GLP-1 can target several core pathophysiological defects underlying the development of T2D.[7,8] GLP-1 receptor agonists (GLP-1 RAs) are therefore among the second-line treatment options for T2D according to the treatment algorithm from the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD), and can be added after 3 months of initial monotherapy if the target glycated hemoglobin (HbA$_{1c}$) level is not achieved.[9] Furthermore, the American Association of Clinical Endocrinologists (AACE) includes GLP-1 RAs as an acceptable first-line monotherapy – an alternative to metformin for patients with mild hyperglycemia (HbA$_{1c}$ <7.5%).[10]

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The GLP-1 RA liraglutide has 97% homology to native GLP-1, with the addition of a fatty acid side chain that confers a substantially prolonged half-life, enabling once-daily dosing.[11] The efficacy and safety of liraglutide as monotherapy or in combination with oral antidiabetic drugs (OADs) were demonstrated in the randomized, controlled trials of the Liraglutide Effect and Action in Diabetes (LEAD) study series.[12-17] Compared with active comparators in these trials, liraglutide generally improved HbA$_{1c}$, fasting plasma glucose, postprandial blood glucose (PPBG) levels, and β-cell function. It also demonstrated favorable effects on body weight.[12-17] Improvements in glycemic control and weight loss were sustained for up to 1–2 years of follow-up.[18-20] Based on findings from clinical trials, liraglutide was generally well tolerated with an acceptable incidence of hypoglycemic episodes; the most common adverse events (AEs) reported were gastrointestinal, including nausea, vomiting and diarrhea.[12-17,21] However, the gastrointestinal AEs tended to be transient and their incidence subsided over time.[22] Liraglutide was approved for the treatment of T2D in Europe in 2009 and subsequently in the USA in 2010.[23,24]

Studies of liraglutide in Asian populations with T2D to date include a double-blind active-control trial in participants from China, South Korea, and India,[25] an open-label active comparator trial in Chinese participants,[26] and an observational study in India.[27] Liraglutide was approved in the Philippines in February 2011 for the treatment of adults with T2D, as monotherapy or in combination with OADs and/or basal insulin when these agents, together with diet and exercise, do not provide adequate glycemic control.[28] Despite the studies, this approval, and the inclusion of GLP-1 RAs in the ADA/EASD and AACE guidelines (commonly referred to by healthcare practitioners in the Philippines),[9,10] local guidelines do not include GLP-1 RAs,[29] and experience of liraglutide use in the Philippines remains limited.

This prospective study was undertaken as a post-marketing surveillance commitment to the Philippine Food and Drug Administration (FDA). The data provide an assessment of the safety and effectiveness of liraglutide 1.2 mg and 1.8 mg among the Filipino population in a clinical practice setting.

METHODOLOGY

Study design

This was a 26-week, prospective, open-label, observational study in participants with T2D who were prescribed liraglutide in routine clinical practice. The study was conducted from September 1, 2011 to July 26, 2013 in 85 study centers in the Philippines by specialists and primary care physicians with experience in the management of T2D. The study is registered with ClinicalTrials.gov (NCT01345734).

Participants provided written informed consent prior to any study-related activity. This study was approved by the Ethics Review Board of the University of the Philippines-Philippine General Hospital and was conducted in accordance with the Declaration of Helsinki, and the Guidelines for Good Pharmacoepidemiology Practices.

Patient inclusion and exclusion criteria

Participants were included if they were adults (aged ≥18 years) with T2D, either newly diagnosed and not on anti-diabetic medication or already receiving other antidiabetic medications, who required treatment intensification with liraglutide according to the clinical judgment of their treating physician and were capable of giving informed consent. Participants were excluded if they had type 1 diabetes, were or had previously been treated with liraglutide, were participating in another clinical study, had hypersensitivity to liraglutide or to any of the excipients (disodium phosphate dihydrate, propylene glycol, phenol, water for injections), were pregnant, breast-feeding or had the intention of becoming pregnant within the following 6 months, or had a high probability of being lost to follow-up during the study period, as assessed by the treating physician.

Treatment

Liraglutide was administered (when deemed clinically warranted by the treating physician) in accordance with approved local labeling, as monotherapy or in combination with one or more OADs (dipeptidyl peptidase-4 inhibitors and/or exenatide therapy were discontinued at baseline, prior to liraglutide initiation) and/or basal insulin. Liraglutide was started at a dose of 0.6 mg once daily and increased by 0.6 mg, at intervals of at least 1 week, to a maintenance dose of 1.2 or 1.8 mg once daily by the investigator according to approved prescribing information. The study drug was self-administered at any (consistent) time, independent of meals, using an injection pen device.

Assessments

Visits occurred at baseline (Visit 1), at approximately 13 weeks (Visit 2) and finally at approximately 26 weeks (Visit 3). The suggested frequency and timing of visits were based on accepted clinical practice for the management of T2D. Further, any procedure carried out during this study was conducted according to routine practice.

Participants were instructed to maintain a diary to record AEs and hypoglycemic episodes. Investigators asked about adverse drug reactions (ADRs), serious adverse events (SAEs), and medical events of special interest (MESIs; which included major and minor hypoglycemic episodes) at study visits and additionally gathered information on laboratory assessments (fasting lipid profile values and serum creatinine levels). ADRs were considered to be AEs (any undesirable medical event) for which a causal relationship with the product was suspected (i.e., judged possible or probable by the reporting healthcare professional) and any abnormalities from laboratory assessments that were regarded as clinically significant (i.e., of a severity requiring active management). Serious ADRs (SADRs) and SAEs were considered to be AEs or ADRs that resulted in death, a life-threatening experience, hospitalization, persistent or significant disability/incapacity, a congenital anomaly/birth defect, or which required intervention to avoid one of these outcomes. As standard, MESIs were considered to be events such as medication errors or transmission of an infectious agent via the study drug; in this study, MESIs additionally included pancreatitis, thyroid gland disorders, neoplasms,

and major hypoglycemia. Major hypoglycemia was defined as episode of hypoglycemia that the patient was unable to self-treat (including those events requiring administration of glucagon or intravenous glucose by another person); plasma glucose levels prior to the incident were recorded if available. (Minor hypoglycemia applied to events in which the patient was able to self-treat and for which plasma glucose <3.1 mmol/L [<56 mg/dL] was recorded. Episodes of minor hypoglycemia were reported in the case report form [CRF].)

Participants were also asked to record concomitant medications, and self-monitored blood glucose (SMBG) levels in their diaries. Most recent values of HbA_{1c}, fasting blood glucose (FBG), and PPBG and the dates of measurement since the last visit prior to starting liraglutide treatment (if available) were obtained from patient medical records at baseline. Most recent values of HbA_{1c}, FBG, and PPBG and date of measurement since last visit were obtained at study Visits 2 and 3. Serum creatinine levels, systolic blood pressure (SBP) and diastolic blood pressure (DBP) were recorded at each visit only when available from the patient's medical record or patient recall.

Endpoints

The primary endpoint was the incidence of SADRs during the study period (26 weeks of liraglutide therapy). Secondary safety endpoints comprised: numbers of SAEs and ADRs during the study period; numbers of major hypoglycemic events registered during the 13 weeks preceding each study visit and minor hypoglycemic events registered during the 4 weeks preceding each study visit, in both cases during liraglutide therapy; changes in serum creatinine levels, SBP and DBP.

Secondary effectiveness endpoints comprised: changes in HbA_{1c} (by visit, and change from baseline to week 13 and week 26); percentages of participants reaching HbA_{1c} targets of ≤6.5% and <7.0% at the end of the study; changes in FBG and PPBG levels (after breakfast, lunch, or dinner); and changes in body weight and related parameters (body mass index [BMI], waist circumference, and hip circumference) (by visit, and changes from baseline to week 13 and week 26). Other parameters monitored were changes, if any, in fasting lipid profile (by visit), frequency of SMBG (at baseline and week 26), and the prescription of antidiabetic (at baseline before and after initiation of liraglutide), antihypertensive, and lipid-lowering medications (by visit).

Statistical analysis

A sample of 812 participants was required to obtain a 95% confidence interval (CI) (±1.5%) for an estimated SADR incidence of 5%. To allow for an expected 20% discontinuation rate, recruitment of 1000 participants was planned. Statistical analyses were performed using SAS version 9.3 (SAS Institute, Cary, NC, USA). Differences across visits for continuous variables (such as weight, HbA_{1c}, FBG, or PPBG) were analyzed using a one-way analysis of variance (ANOVA) with study visit as a classification variable (two-sided p value). For continuous variables that reached statistical significance across visits using ANOVA, differences between study visits were then analyzed using a one-sided Dunnett's test and the p value presented (lower tail [except high-density lipoprotein cholesterol, upper tail]). Changes from baseline were expressed as least squares means with standard error (SE) and 95% CI from one-way ANOVA and, where appropriate, a one-sided p-value from the Dunnett's test. The number of hypoglycemic events was analyzed using the Wilcoxon signed-rank test. Discrete variables were summarized using frequency tables (N, %). Proportions of participants with missing data were indicated as % where appropriate.

RESULTS

Participants

Of 1056 participants enrolled and exposed to liraglutide (full analysis set [FAS]), 75.2% completed the study and were included in the effectiveness analysis set (EAS) (Figure 1). Commonly cited reasons for non-completion were discontinuation of liraglutide (n=137), lost to follow-up (n=115), and ADRs (n=5).

Baseline demographic and disease characteristics are shown in Table 1. There was a higher proportion of females than males (52.9% versus 47.1%). The population had a mean (SD) age of 53.2 (12.0) years, HbA_{1c} of 8.8% (2.0), and diabetes duration of 9.2 (8.0) years. The most frequent diabetes complications at baseline were peripheral neuropathy (19.7%) and coronary heart disease (16.6%). The most frequently cited reason given by participants as to why they accepted the physician's suggestion for starting liraglutide was to improve weight control (cited by 90.2% of participants) (Table 2).
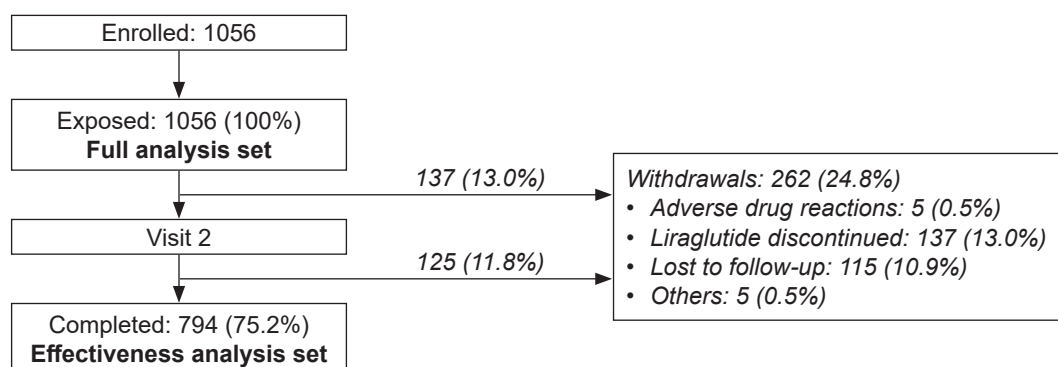

Figure 1. Participant disposition.

Table 1. Baseline demographic and disease characteristics

	n*	Mean ± SD or n (%)
Sex, male / female	1056	497 (47.1) / 559 (52.9)
Age, years	1056	53.2 ± 12.0
BMI, kg/m^2	1056	33.1 ± 5.9[†]
HbA$_{1c}$, %	881	8.8 ± 2.0
FBG, mg/dL	719	185.7 ± 74.4
PPBG, mg/dL	190	235.7 ± 99.6
Diabetes duration, years	523	9.2 ± 8.0
SBP, mmHg	998	127.9 ± 13.3
DBP, mmHg	998	80.2 ± 8.9
Diabetes complications	1056	
Peripheral neuropathy		208 (19.7)
Coronary heart disease		175 (16.6)
Nephropathy		109 (10.3)
Macroangiopathy[‡]		106 (10.0)
Retinopathy		90 (8.5)
Autonomic neuropathy		41 (3.9)
Stroke		7 (0.7)

*Data collection based on FAS; where n<1056, data were missing or unknown for the remaining participants. [†]Although the mean BMI is classified as obese, the range was from 18.7 (underweight) to 50.0 kg/m^2 (morbidly obese), and a number of participants with low BMIs were included in the study. [‡]Including peripheral vascular disease. BMI, body mass index; DBP, diastolic blood pressure; FAS, full analysis set; FPG, fasting blood glucose; HbA$_{1c}$, glycated hemoglobin; PPBG, postprandial blood glucose; SBP, systolic blood pressure.

Table 2. Participants' reasons* for starting liraglutide treatment

Reason cited	n (%)
Improve weight control	953 (90.2)
Improve HbA$_{1c}$	874 (82.8)
Improve β-cell function	720 (68.2)
Improve FBG	543 (51.4)
Participant dissatisfied with previous therapy	239 (22.6)
Improve PPBG	227 (21.5)
Reduce risk of hypoglycemia	113 (10.7)
Side effects from previous therapy	31 (2.9)
Others	7 (0.7)

*More than one reason could be stated.
β, beta; FPG, fasting plasma glucose; HbA$_{1c}$, glycated hemoglobin; PPBG, postprandial blood glucose.

Safety

SADRs, SAEs and ADRs

No SADRs were reported during the study (primary endpoint), and there were also no reports of SAEs. There were 19 reported ADRs from 17 participants (Table 3). Although hypoglycemia events were to be reported on the CRF, separately from ADRs, four events of hypoglycemia were in fact recorded as ADRs; as ADRs, severities were thus not classified as major or minor hypoglycemia but instead as mild, moderate, or severe (three events were considered mild, one was moderate). Contrary to the protocol, an AE that was neither considered related to study drug (i.e., an ADR) nor serious (i.e., an SAE) was also recorded. This AE, frozen shoulder (periarthritis), occurred in a 33-year-old patient, was considered to be moderate in severity, and the patient did not recover fully by the end of the study.

The majority (16/19) of ADRs were mild, and all but one of the participants recovered fully. The exception was a 51-year-old participant with a mild case of diarrhea, deemed possibly related to study drug and for whom liraglutide was permanently withdrawn. A further four participants also withdrew from the study due to ADRs, specifically cushingoid features (moon face), hypoglycemia, nausea and vomiting, and dizziness. The

Table 3. Summary of adverse drug reactions

Type of Event/Outcome	Participants, n (%)	Number of Events
Any ADR	17 (1.6)	19
Probably/possibly related	10 (0.9)/7 (0.7)	10/9
Severe/moderate/mild	0/3 (0.3)/14 (1.3)	0/ 3/16
SADR	0	0
Outcome		
Fatal	0	0
Not recovered	1 (0.1)	1
Recovered without sequelae	16 (1.5)	18
ADRs leading to withdrawal*	5 (0.5)	6

Data for full analysis set (n=1056). One further participant was reported as experiencing frozen shoulder (periarthritis); as this was not considered to be an ADR, the event is not included in the data above. *Includes one participant for whom treatment was withdrawn but who was not originally reported by the investigator as having withdrawn.
ADR, adverse drug reaction; SADR, serious adverse drug reaction.

Table 4. Summary of ADRs by system organ class and preferred term

Type of Event	Participants, n (%)	Events (n)
All ADRs*	**17 (1.6)**	**19**
Metabolism and nutrition disorders	**4 (0.4)**	**4**
Hypoglycemia[†]	4 (0.4)	4
Gastrointestinal disorders	**3 (0.3)**	**5**
Abdominal pain upper	1 (0.1)	1
Diarrhea	1 (0.1)	1
Nausea	1 (0.1)	1
Vomiting	2 (0.2)	2
General disorders and administration site conditions	**3 (0.3)**	**3**
Fatigue	1 (0.1)	1
Injection site rash	1 (0.1)	1
Malaise	1 (0.1)	1
Cardiac disorders	**2 (0.2)**	**2**
Palpitations	2 (0.2)	2
Skin and subcutaneous tissue disorders	**2 (0.2)**	**2**
Alopecia	1 (0.1)	1
Rash	1 (0.1)	1
Endocrine disorders	**1 (0.1)**	**1**
Cushingoid[‡]	1 (0.1)	1
Nervous system disorders	**1 (0.1)**	**1**
Dizziness	1 (0.1)	1
Psychiatric disorders	**1 (0.1)**	**1**
Insomnia	1 (0.1)	1

Data for full analysis set (n=1056). *Two further events (increased alanine aminotransferase and aspartate aminotransferase, severity and outcome not reported) in one participant were reported but were invalid due to lack of participant identifiers. [†]Four events of hypoglycemia were mistakenly recorded as ADRs instead of MESIs. [‡]Moon face.
ADR, adverse drug reaction; MESI, medical events of special interest.

participant with dizziness was not originally reported as a treatment withdrawal by the investigator but, because liraglutide was permanently discontinued, the participant has been included in these analyses.

Other than the four events of hypoglycemia inadvertently included as ADRs, the most commonly reported ADRs by system organ class (Table 4) were gastrointestinal disorders (five events in three participants [0.3%]: two ADRs of vomiting and one each of diarrhea, nausea, and upper abdominal pain) and general disorders and administration-site conditions (three events in three participants [0.3%]: fatigue, injection-site rash, and malaise).

Hypoglycemia

The proportion of participants reporting hypoglycemic episodes decreased during the study period. At baseline

(i.e., for the 13 weeks preceding initiation of treatment with liraglutide), the proportion of participants with major hypoglycemic episodes was 2.0% (21/1056); this decreased to 0.6% (6/1056) of participants at week 13, and decreased further to 0.2% (2/1056) at week 26. The proportion of participants with minor hypoglycemic episodes at baseline was 6.1% (64/1056); this decreased to 2.5% (26/1056) of participants at week 13, and to 1.5% (16/1056) at week 26. It is important to note, however, that at each of these timepoints data were missing or unknown for a varied proportion of participants (ranging from 5.4 to 24.8%). Furthermore, these events did not include the four episodes reported as ADRs.

Serum creatinine

Differences in serum creatinine during the course of the study did not reach statistical significance (mean [SE] change from baseline to week 26 was 0.02 ± 0.02 mg/dL [95% CI: –0.03; 0.06]; $p=0.2327$ [ANOVA], FAS, n=183).

Effectiveness

Glycemic control

There was a significant reduction in HbA_{1c} levels from baseline to week 26 with liraglutide treatment (Figure 2); the mean (SE) change from baseline in HbA_{1c} was -1.81% $\pm$ 0.05 [95% CI: -1.92; -1.71], $p<0.0001$ (n=577; baseline to week 26). The target HbA_{1c} level <7.0 (the goal identified by the ADA/EASD) was reached by 197/794 (24.8%) participants in the EAS at week 13 (data missing for 171/794 [21.5%] participants) and by 322/794 (40.6%) participants at week 26 (missing data: 151/794 [19.0%] participants). The proportions of participants achieving HbA_{1c} levels $\leq$6.5% (the AACE goal) at weeks 13 and 26 were 126/794 (15.9%) and 234/794 (29.5%), respectively (missing data as for target <7.0%).

FBG levels were also significantly reduced from baseline to week 26 with liraglutide treatment (Figure 3), with a mean

a) HbA$_{1c}$ during the study

b) Change from baseline in HbA$_{1c}$
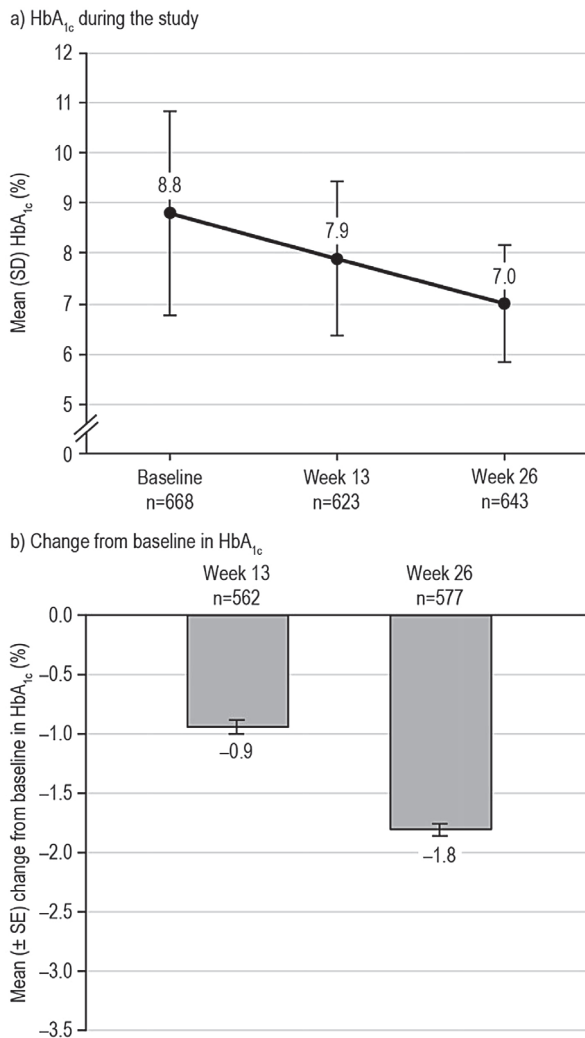
Figure 2. Glycemic control during the LEAD-Ph study: HbA$_{1c}$. From participants in the EAS with available data. The mean ($\pm$ SE) change from baseline in HbA$_{1c}$ level at week 13 was –0.94 $\pm$ 0.06%, $p<0.0001$* (n=562), and –1.81 $\pm$ 0.05%, $p<0.0001$* (n=577) at week 26. *Statistical difference at the 5% level, one-tailed. EAS, effectiveness analysis set; HbA$_{1c}$, glycated hemoglobin; SD, standard deviation; SE, standard error.
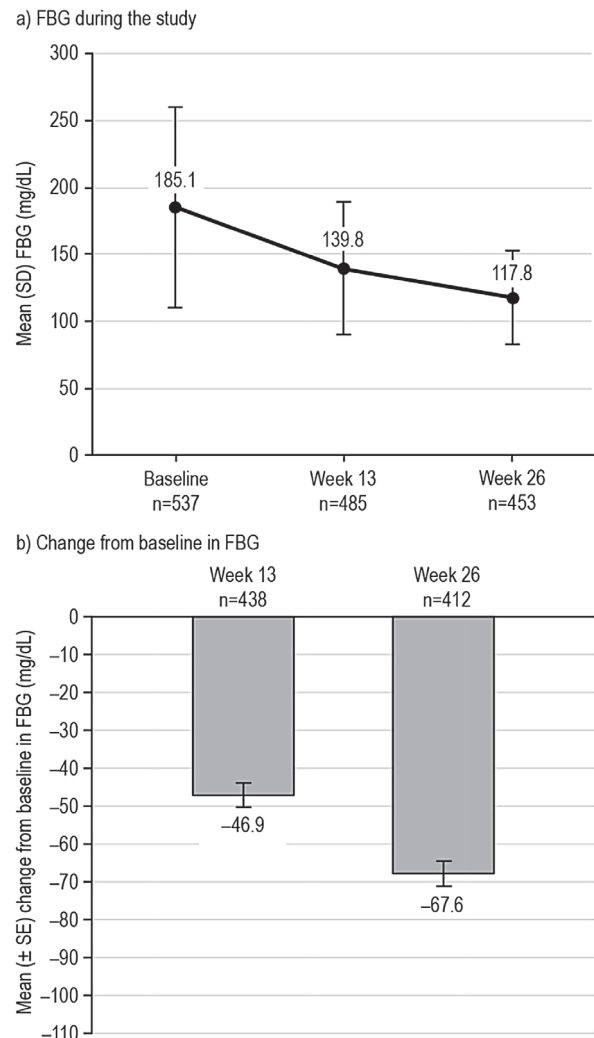
a) FBG during the study

b) Change from baseline in FBG

Figure 3. Glycemic control during the LEAD-Ph study: FBG. From participants in the EAS with available data. The mean ($\pm$ SE) change from baseline in FBG level at week 13 was –46.94 $\pm$ 3.16 mg/dL, $p<0.0001$* (n= 438), and –67.61 $\pm$ 3.26 mg/dL, $p<0.0001$* at week 26 (n=412). *Statistical difference at the 5% level, one-tailed. EAS, effectiveness analysis set; FBG, fasting blood glucose; SD, standard deviation; SE, standard error.

(SE) change of -67.61 ± 3.26 mg/dL [95% CI: -74.00; -61.22], $p<0.0001$ (n=412). Similarly, for the few participants with PPBG assessments after the same meal (breakfast) at each study visit available for analysis, there was a significant reduction in PPBG levels across visits with liraglutide treatment (Figure 4). The mean (SE) change in post-breakfast PPBG (baseline to week 26) was -109.27 ± 14.01 mg/dL [95% CI: -137.02; -81.52], $p<0.0001$ (n=51). Nevertheless, these PPBG data should be interpreted with caution, due to the low numbers of participants with data available (n=51–67).

Body weight, BMI and body measurements

Body weight decreased during the study (Figure 5, Table 5). Accordingly, there was a concomitant significant change in BMI from baseline to week 26, and mean (SE) change of -1.37 ± 0.04 kg/m^2 [95% CI: -1.44; -1.29], $p<0.0001$ (both EAS, n=794). Participants with a higher BMI at baseline lost more weight during the study than participants with a lower baseline BMI. Participants with BMI ≥35 kg/m^2 had a significant reduction in body weight (baseline to week 26) with a mean (SE) weight change of -4.35 ± 0.19 kg [95% CI: -4.73; -3.98], $p<0.0001$ (n=291), compared with participants with BMI <25 kg/m^2 having a mean (SE) weight change of -2.05 ± 0.31 kg [95% CI: -2.65; -1.44] (n=53), which did not reach statistical significance. Waist and hip circumference measurements tended to decrease in participants with available data, although the participant numbers were low for these endpoints and differences did not reach statistical significance (Table 3).

Blood pressure

Mean (SE) changes for SBP were -3.11 ± 0.41 mmHg [95% CI: -3.91; -2.30], $p<0.0001$ (n=750; baseline to week 13), and -5.31 ± 0.41 mmHg [95% CI: -6.12; -4.50], $p<0.0001$ (n=746; baseline to week 26). Mean (SE) changes for DBP were -2.93 ± 0.32 mmHg [95% CI: -3.57; -2.30]; $p<0.0001$ (n=750; baseline to week 13), and -5.35 ± 0.32 mmHg [95% CI: -5.99; -4.71]; $p<0.0001$ (n=746; baseline to week 26).

a) PPBG (post-breakfast) during the study

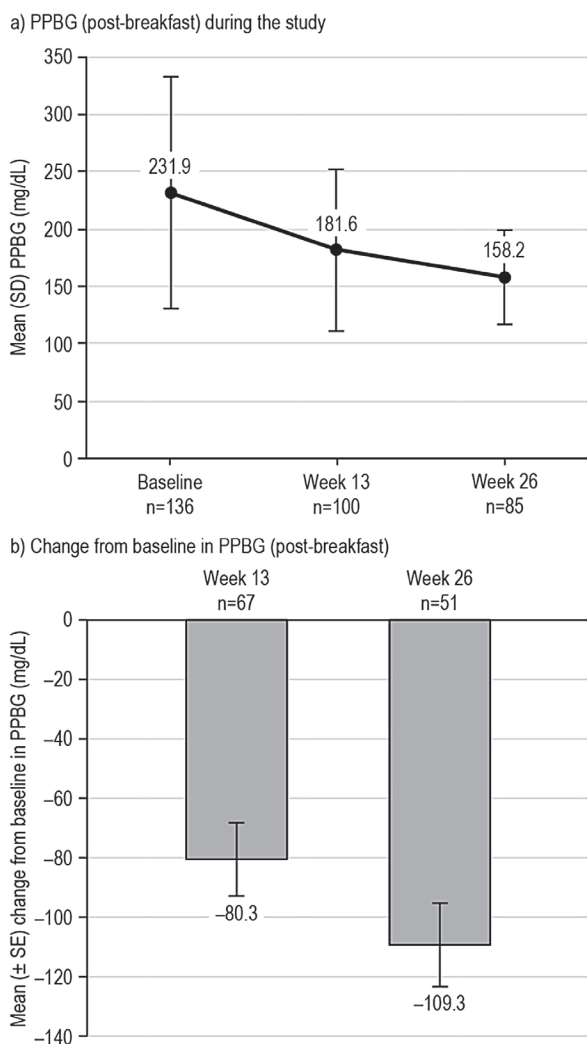b) Change from baseline in PPBG (post-breakfast)

Figure 4. Glycemic control during the LEAD-Ph study: PPBG. From participants in the EAS with available data. The mean (± SE) change in post-breakfast PPBG level at week 13 was −80.32 ± 12.23 mg/dL, $p<0.0001$* (n=67), and −109.27 ± 14.01 mg/dL, $p<0.0001$* at week 26 (n=51). *Statistical difference at the 5% level, one-tailed. EAS, effectiveness analysis set; PPBG, postprandial blood glucose; SD, standard deviation; SE, standard error.
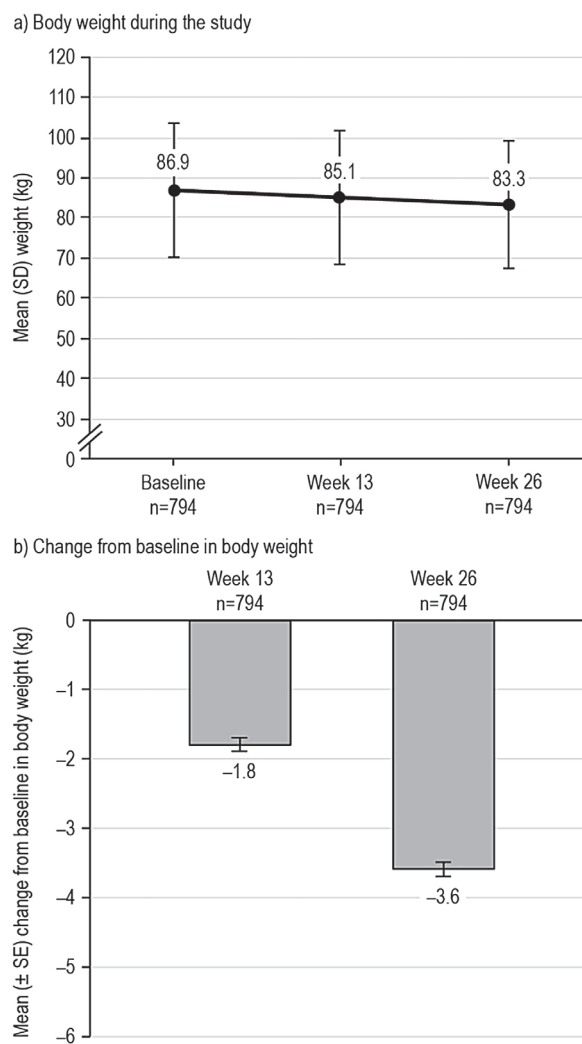

a) Body weight during the study

b) Change from baseline in body weight

Figure 5. Changes in body weight during the LEAD-Ph study. From participants in the EAS with available data. The mean (± SE) change from baseline in body weight at week 13 was −1.79 ± 0.10 kg, $p=0.0267$* (n=794), and −3.58 ± 0.10 kg, $p<0.0001$* at week 26 (n=794). *Statistical difference at the 5% level, one-tailed. EAS, effectiveness analysis set; SD, standard deviation; SE, standard error.

Table 5. Changes to body weight, BMI, waist and hip circumference

Parameter	Baseline	Week 13	Week 26
Weight, kg			
N	794	794	794
Mean ± SD	86.9 ± 16.7	85.1 ± 16.2	83.3 ± 15.9
Median [min, max]	85.5 [42.0, 146.5]	84.0 [42.0, 144.4]	82.3 [41.0, 142.7]
Change from baseline, mean ± SE	-	−1.79 ± 0.10; p=0.0267*; n=794	−3.58 ± 0.10; p<0.0001*; n=794
BMI, kg/m²			
N	794	794	794
Mean ± SD	33.4 ± 5.9	32.7 ± 5.7	32.0 ± 5.6
Median [min, max]	33.0 [18.7, 50.0]	32.2 [18.6, 49.3]	31.6 [17.8, 48.8]
Change from baseline, mean ± SE	-	−0.68 ± 0.04; p=0.0174*; n=794	−1.37 ± 0.04; p<0.0001*; n=794
Waist circumference, cm			
N	87	85	84
Mean ± SD	105.1 ± 13.9	104.2 ± 12.2	101.7 ± 12.8
Median [min, max]	105.0 [76.0, 142.0]	103.0 [79.0, 140.0]	101.5 [78.0, 137.0]
Change from baseline, mean ± SE	-	−1.74 ± 0.69; n.s.; n=65	−4.35 ± 0.71; n.s.; n=62
Hip circumference, cm			
N	42	25	20
Mean ± SD	110.1 ± 12.5	108.0 ± 10.8	104.0 ± 7.8
Median [min, max]	109.0 [88.0, 148.0]	106.0 [93.0, 148.0]	105.0 [92.0, 122.0]
Change from baseline, mean ± SE	-	−0.29 ± 1.59; n.s.; n=21	−2.75 ± 1.82; n.s.; n=16

Data for participants in the effectiveness analysis set with available data. *Statistical difference at the 5% level, one-tailed (Dunnett's test). BMI, body mass index; n.s., not significant across visits (ANOVA); SD, standard deviation; SE, standard error.

Table 6. Changes to fasting lipid profile

Lipid, mg/dL	Baseline	Week 13	Week 26
Total cholesterol			
N	439	250	209
Mean ± SD	182.4 ± 53.7	149.6 ± 41.1	139.3 ± 44.7
Median [min, max]	172.4 [53.7, 394.0]	145.5 [51.8, 302.2]	134.2 [39.4, 327.0]
Change from baseline, mean ± SE	-	−32.60 ± 3.30; p<0.0001*; n=206	−45.56 ± 3.55; p<0.0001*; n=179
HDL cholesterol			
N	391	226	189
Mean ± SD	48.9 ± 17.4	54.1 ± 16.8	55.0 ± 13.4
Median [min, max]	47.3 [11.6, 166.2]	54.0 [16.0, 138.5]	54.1 [20.8, 108.6]
Change from baseline, mean ± SE	-	5.15 ± 1.14; p=0.0001*; n=179	4.50 ± 1.21; p<0.0001*; n=156
LDL cholesterol			
N	394	226	190
Mean ± SD	101.6 ± 44.5	74.3 ± 34.6	69.2 ± 34.2
Median [min, max]	93.0 [17.0, 339.4]	71.1 [17.2, 292.3]	64.6 [17.0, 237.4]
Change from baseline, mean ± SE	-	−27.41 ± 3.38; p<0.0001*; n=175	−32.63 ± 3.56; p<0.0001*; n=158
Triglycerides			
N	424	239	192
Mean ± SD	156.7 ± 69.5	135.2 ± 52.4	128.8 ± 43.9
Median [min, max]	141.5 [44.3, 406.0]	126.0 [37.0, 364.0]	120.5 [53.1, 317.1]
Change from baseline, mean ± SE	-	−30.00 ± 4.91; p<0.0001*; n=196	−36.59 ± 5.40; p<0.0001*; n=162

Data for participants in the effectiveness analysis set with available data. *Statistical difference at the 5% level, one-tailed (Dunnett's test). HDL, high-density lipoprotein; LDL, low-density lipoprotein; SD, standard deviation; SE, standard error.

Fasting lipid profile

Improvements in fasting lipid profiles were shown across the variables studied (Table 6). In the EAS, the mean (±SE) change in total cholesterol was -45.56 ± 3.55 mg/dL [95% CI: -52.53; -38.59]; p<0.0001 (n=179; baseline to week 26). High-density lipoprotein cholesterol increased by a mean (SE) of 4.50 ± 1.21 mg/dL [95% CI: 2.12; 6.88]; p<0.0001 (n=156; baseline to week 26), while the mean ± SE change in low-density lipoprotein cholesterol was -32.63 ± 3.56 [95% CI: -39.63; -25.63] mg/dL; p<0.0001 (n=158; baseline to week 26). Triglycerides similarly showed a reduction (mean [SE] change: -36.59 ± 5.40 mg/dL [95% CI: -47.21; -25.98]; p<0.0001 [n=162; baseline to week 26]).

Diabetes management

Participants were asked to self-monitor their blood glucose levels; however, most did not. At baseline, a total of 301/794 (37.9%) participants reported checking their blood glucose levels. This number comprised 153 (19.3%) who checked daily, 118 (14.9%) who checked weekly, and 30 (3.8%) who

Table 7. Antidiabetic therapy before and after liraglutide initiation (at baseline)

Concomitant Medications	n (%)
Before liraglutide prescription	
OAD – combinations (including metformin)	438 (41.5)
OAD and insulin	277 (26.2)
OAD – metformin only	170 (16.1)
OAD and GLP-1 RA	65 (6.2)
Insulin	48 (4.5)
No therapy (but diagnosed T2D)	35 (3.3)
OAD, insulin and GLP-1 RA	18 (1.7)
GLP-1 RA only	4 (0.4)
Insulin and GLP-1 RA	1 (0.1)
After liraglutide prescription	
OAD and insulin	293 (27.7)
OAD – metformin only	290 (27.5)
OAD combinations (including metformin)	249 (23.6)
None (liraglutide only)	166 (15.7)
Insulin	58 (5.5)

GLP-1 RA, glucagon-like peptide-1 receptor agonist; OAD, oral antidiabetic drug; T2D, type 2 diabetes.

checked monthly. The remaining 493/794 (62.1%) did not regularly monitor their blood glucose levels. At week 26, the proportions of participants who reported undertaking regular SMBG decreased slightly to a total of 265/794 (33.4%), with 136 (17.1%) reporting daily monitoring, 110 (13.9%) weekly and 19 (2.4%) monthly (with 66.6% not reporting regular monitoring).

Before beginning treatment with liraglutide, most participants were treated with a combination of OADs (including metformin) (438 [41.5%]) or OADs and insulin (277 [26.2%]) (Table 7). After initiation of liraglutide (at baseline), similar proportions of participants were treated with a combination of liraglutide, OADs and insulin (293 [27.7%]), liraglutide and metformin alone (290 [27.5%]), and liraglutide combined with more than one OAD including metformin (249 [23.6%]), while 58 (5.5%) participants were treated with liraglutide and insulin. A total of 166 (15.7%) participants were treated with liraglutide monotherapy.

Changes in lipid-lowering and antihypertensive medications
Use of lipid-lowering medication remained fairly stable during the study. At baseline, 20.0% (148/739) of participants in the EAS were treated with fibrates, and 90.0% (665/739) were treated with statins. After 26 weeks of treatment with liraglutide, these proportions were 20.9% (89/426) and 89.4% (381/426), respectively.

At baseline, most participants (570/664, 85.8%) were being treated with angiotensin II receptor blockers. Over the course of the study, this proportion increased slightly to 93.9%, although from considerably fewer participants with available data (355/378). There were decreases in all other types of antihypertensive treatment (angiotensin-converting enzyme inhibitors, beta-blockers, calcium channel blockers, and diuretics; data not shown).

DISCUSSION

The LEAD-Ph study was a post-marketing surveillance commitment to the Philippine FDA, and was conducted to assess the safety and effectiveness of liraglutide over 26 weeks in participants with T2D during routine clinical practice in the Philippines. Overall, this study found no new safety concerns and demonstrated the clinical effectiveness of liraglutide in participants with T2D within this setting. There were no reports of SADRs (the primary endpoint), and participants treated with liraglutide for 26 weeks, as prescribed in the course of routine care, experienced statistically significant and clinically relevant improvements in HbA_{1c}, FBG, and PPBG levels. No SAEs, and few ADRs, were reported (19 events in 17 participants), and the reported incidence of hypoglycemia was also low.

A higher frequency of ADRs and SADRs might have been expected in LEAD-Ph, based on other observational studies of liraglutide use in European participants with T2D.[30,31] In a 12-month Belgian study, 58/245 (24%) of the participants reported ADRs and 6/245 (2.4%) reported an SADR, while in a French study, 458/3152 (14.5%) of the participants experienced an AE possibly related to liraglutide during 2 years of follow up.[30,31] There are limited data on the frequency of treatment-related AEs in

observational studies involving Asian populations. In a 26-week, open-label, active-comparator trial of liraglutide, of 183 Chinese participants treated with liraglutide, the proportion of patients with AEs possibly/probably related to treatment was 43.2%.[26] However, in the observational 26-week LEAD-In study of liraglutide in routine clinical use in India, only 19/1416 (1.3%) of the participants reported 20 AEs, of which 19 were considered to be treatment-related, and no participant reported an SADR, which resonates with the findings of LEAD-Ph.[27] Other than the four events of hypoglycemia, the most frequently reported ADRs by system class during LEAD-Ph were gastrointestinal disorders. This accords with the findings from the LEAD clinical trials for liraglutide and the safety profile of the GLP-1 RA class, in which gastrointestinal AEs are the commonly observed AEs.[12-17,19,21,32-34] However, withdrawals due to gastrointestinal events are uncommon, as these events are generally transient and can be mitigated by weekly dose escalation.[12-17,19,21,32,33] During this study, 24.8% of participants in the FAS had withdrawn by week 26, approximately half of these withdrawals occurred by week 13, yet only 0.5% of participants in the FAS withdrew due to ADRs. Most withdrawals in LEAD-Ph were attributed to liraglutide discontinuations (13.0%), a reason for which may be financial constraints (participants were required to pay for liraglutide prescriptions and were not reimbursed in this observational study).

Notwithstanding similarities between LEAD-Ph and the Indian LEAD-In study, the absence of SADRs and the low frequency of ADRs for a study of the size of LEAD-Ph (n=1056 [FAS]) should be interpreted with caution. While training on safety reporting was provided to investigators at the start of the study and at site initiation visits, and repeated reminders were provided throughout the study, insufficient event reporting may have occurred. Additionally, the varied and significant proportion of participants with missing data may also have been a contributing factor.

The inadvertent reporting of an AE (frozen shoulder [periarthritis]) among the ADRs, and of four episodes of hypoglycemia as ADRs, suggests that there may have been confusion for some investigators regarding the reporting procedure. In addition, the study physicians may also have implemented slower titration protocols than was recommended in the package insert, with dose increases routinely separated by more than 1 week (data on liraglutide dose escalation were not collected during the study). Therefore, collection of data on liraglutide starting dose and dose changes, as well as compliance to therapy, might have provided additional insight for clinicians, and the absence of these data limits the conclusions that can be drawn from this study.

It is possible that a lower frequency of ADR reporting may occur generally in the Philippines and other Asian populations than in European countries where liraglutide has been studied, with perhaps less experience of the concept of pharmacovigilance monitoring. This supposition cannot be explored at this time, as there are no public databases from which to gather local data on ADR reporting, and studies examining the issue of underreporting are lacking. Thus, there are no solid data for comparison with other populations, but this gap in itself suggests that the

importance of safety reporting might be less prominent in the Philippines than elsewhere.

The significant improvements in HbA_{1c}, FBG, and PPBG levels while on treatment with liraglutide in this study provide confirmation of the real-world effectiveness of this treatment in Filipino participants with T2D. The change from baseline to week 26 in HbA_{1c} levels (mean change -1.81%, $p<0.0001$, from 8.8% at baseline) was similar to that seen in LEAD-In (-1.6%, $p<0.0001$, from 8.8% at baseline),[27] and these effectiveness results are consistent with the LEAD clinical trials.[12-17,19,21,32,33] Given that liraglutide is also associated with a low risk of hypoglycemia,[35] it is perhaps not surprising that the incidence of hypoglycemia in the present study was low despite improvements in glycemic control. Importantly, the incidence was low even though 351/1056 (33.2%) participants were receiving concomitant insulin (with or without OAD); it is unclear to what extent Filipino participants receiving insulin may have additionally mitigated the risk of hypoglycemia by a habit of snacking. The trend towards weight reduction observed while on liraglutide among Filipino participants was also encouraging and is similar to that seen in the phase 3 LEAD clinical trials, with concomitant improvements in BMI and body measurements. Collectively, these findings are important for meeting physicians' and patients' expectations; improved weight control was the most frequently cited reason for starting liraglutide (90% of participants). Besides improvements in body weight and BMI, other clinical parameters included in this surveillance also point towards a lowering in the overall cardiovascular risk profile. Specifically, there were numerical improvements in fasting lipid profile, and there was a trend towards reductions in SBP and DBP.

In terms of the management of diabetes and use of concomitant medications, there were no notable changes during the study. A similar proportion of participants took OADs in combination with insulin before and after liraglutide initiation at baseline. The frequency of SMBG was low and reduced slightly from baseline to study end. Use of lipid-lowering and antihypertensive medication also remained fairly stable during the course of the study.

In addition to those limitations already mentioned, the varied and significant proportion of participants with missing data and high discontinuation rate (262/1056 [24.8%]) should be acknowledged. Further limitations include the absence of data for heart rate, which may be useful to include as an endpoint in subsequent studies, and self-monitoring of blood glucose was not performed by the majority of participants. Finally, this study was limited by the absence of a control group and lack of adjustment for missing data. It is also subject to the inherent limitations of its observational nature. Nevertheless, this study reports the first data on the use of liraglutide in the Philippines, and provides a useful insight into the safety and effectiveness of liraglutide in routine clinical practice among Filipino participants.

CONCLUSIONS

During this observational study of the routine clinical use of liraglutide for T2D in the Philippines, no SADRs were reported, less than 2% of participants reported an ADR, and the incidence of hypoglycemia was reduced at the end of the study compared with baseline. Improvements in glycemic control, body weight, BMI, blood pressure, and fasting lipid profile were also observed. There were no notable changes in the management of diabetes during the study, or notable changes in concomitant medication use after liraglutide initiation at baseline. In summary, no new safety concerns were identified with the routine clinical use of liraglutide as a treatment for T2D in the Philippines and effectiveness results were generally consistent with previous studies.

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