Original Article

Liraglutide effect and action in diabetes-In (LEAD-In): A prospective observational study assessing safety and effectiveness of liraglutide in patients with type 2 diabetes mellitus treated under routine clinical practice conditions in India

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ABSTRACT

Background: This 26-week, open-label observational study assessed the incidence and type of adverse events (AEs) associated with liraglutide use according to the standard clinical practice settings and the local label in India. **Materials and Methods:** A total of 1416 adults with type 2 diabetes (T2D) treated with liraglutide in 125 sites across India were included in the study. Participants were newly diagnosed or already receiving antidiabetic medications. Safety and efficacy data were collected at baseline and at approximately weeks 13 and 26. The primary outcome was incidence and type of AEs while using liraglutide, with events classified by Medical Dictionary for Regulatory Activities system organ class and preferred term. The secondary objective was to assess other clinical parameters related to effective T2D management. **Results:** Twenty AEs, predominately gastrointestinal, were reported in 1.3% of the study population in scheduled visits up to week 26. No serious AEs, including death, were reported. Hypoglycemic episodes were reported in 7.3% of participants at baseline and 0.7% at week 26. No major hypoglycemic events were reported up to week 26 (baseline: 0.4%). Glycated hemoglobin was reduced from baseline (8.8 ± 1.3%) to week 26 by 1.6 ± 1.1% ($P < 0.0001$); significant improvements in fasting blood glucose, and 2-h postprandial blood glucose (post-breakfast, -lunch, and -dinner) were also observed. Mean body weight decreased by 8.1 ± 6.5 kg from baseline (92.5 ± 14.6 kg; $P < 0.0001$). **Conclusions:** From the number of AEs reported, it is suggested that liraglutide was well tolerated in subjects with T2D treated under standard clinical practice conditions in India. Liraglutide was effective, and no new safety concerns were identified.

Key words: Adverse events, India, liraglutide, real-world, routine clinical practice, type 2 diabetes

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INTRODUCTION

Treatment of type 2 diabetes (T2D) should be individualized according to the patient- and disease-related factors as per

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the American Diabetes Association (ADA) and European Association for the Study of Diabetes position paper.[1] Patient needs differ and it is, therefore, important to have a range of treatment options available to optimize according to individuals. Liraglutide is a once-daily human glucagon-like peptide-1 (GLP-1) analog first approved for the treatment of T2D in Europe in 2009 and subsequently approved in India in 2010. Approval was based on outcomes from the liraglutide effect and action in diabetes (LEAD) trial program, which demonstrated the antihyperglycemic efficacy of liraglutide as monotherapy and combined with other glucose-lowering agents in the treatment of patients with T2D.[2-7]

The LEAD trials also demonstrated that liraglutide was associated with higher incidences of gastrointestinal disorders (nausea, vomiting, and diarrhea), although these gastrointestinal adverse events (AEs) are mostly transient and tend to subside with time.[8] Preclinical studies have suggested a possible link between long-term GLP-1 mimetic therapy and an increased risk of pancreatitis, and medullary thyroid carcinoma has been reported in rodent models.[9-13] As such, caution is advised in patients with a history of pancreatitis and those with preexisting thyroid disease.[14] No firm conclusions regarding an increased link of pancreatitis with incretin-based drugs could be made from extensive assessments by the United States Food and Drug Administration and the European Medicines Agency.[15] Furthermore, a recent *post hoc* analysis of pancreatitis cases from 9016 patients enrolled in Phase 2 and Phase 3 randomized clinical trials with liraglutide was inconclusive regarding the potential risk of pancreatitis.[16]

While randomized controlled trials (RCTs), such as those comprising the LEAD program,[2-7] represent the reference standard in terms of assessing the efficacy and safety of therapeutic agents, extrapolation of findings to a real-world setting is difficult due to strict inclusion and exclusion criteria.[17] Observational studies are important to determine how treatments are used in real-life settings, where guidelines and/or prescribing information may not always be followed.

The aim of this study was to assess the safety and effectiveness of liraglutide in routine clinical practice in India, according to the local label and guidelines.

Materials and Methods

Study design
LEAD-In was a 26-week, prospective, observational study including patients with T2D, who were treated with liraglutide according to the local label under standard clinical practice conditions in 125 sites across India.

Safety and effectiveness data were collected during scheduled visits at baseline, after ~13 weeks, and after ~26 weeks.

Liraglutide was administered once daily as monotherapy or as combination therapy as per the approved labeling. Administration was subcutaneous, in the abdomen, thigh, or upper arm. Patients were instructed to select their own injection time, but to continue to inject at the same time each day regardless of meal times.

The trial was registered with ClinicalTrials.gov (NCT01212133) and was conducted in accordance with the Declaration of Helsinki.[18] The protocol was approved by the Drug Controller General of India and the Institutional Review Board/Independent Ethics Committees of respective sites. All patients gave study-specific signed informed consent before the collection of any information.

The study period ran from November 29, 2010, to April 30, 2012.

Participants
Liraglutide was initiated as per the local label. Eligible participants were adults (aged ≥18 years) with T2D. All participants were either newly diagnosed or were already receiving antidiabetic medications (which could include GLP-1 analogs), and in whom liraglutide was determined to be an appropriate new treatment according to the clinical judgment of their treating physician.

Patients were excluded if they had type 1 diabetes or any current or previous exposure to liraglutide.

Study outcome measures
The primary objective was to assess the incidence and type of AEs in a routine clinical practice setting in India. The secondary objective was to assess other clinical parameters related to the effective management of T2D.

The primary outcome measure (i.e., AEs) was summarized by number of events, number of subjects, and percentage of subjects with events classified by Medical Dictionary for Regulatory Activities system organ class and preferred term. In addition, summary tables were presented for AEs by severity, outcome, and causality.

Data on all hypoglycemic episodes were reported. Major episodes were defined as events requiring third-party assistance (administration of glucagon or intravenous glucose to the subject by another person). Minor episodes were defined as events in which plasma glucose (PG) was <3.1 mmol/L (56 mg/dL) and which were self-treated. Episodes for which there were no PG measurement or PG

was ≥3.1 mmol/L (56 mg/dL) and which were self-treated were classified as symptoms only. Minor hypoglycemia was recorded as the number of hypoglycemic events in the 4 weeks before week 13 and week 26, and major hypoglycemia used the number of events in the 13 weeks before week 13 and week 26.

Any medical events of special interest (MESI) were recorded, including medication errors, suspected transmission of an infectious agent via a study product, or the incidence of pancreatitis, thyroid gland disorders, neoplasms, or major hypoglycemia.

Secondary outcome measures included glycemic parameters (glycated hemoglobin [HbA$_{1c}$], fasting blood glucose [FBG], postprandial blood glucose [PPBG]), defined by ADA as 1–2 h after the start of a meal.[19] Other variables measured included fasting lipid profile (total cholesterol [TC], low-density lipoprotein-cholesterol [LDL-C], high-density lipoprotein-cholesterol [HDL-C], triglycerides, and free fatty acids), change in systolic blood pressure (SBP) and diastolic blood pressure (DBP), body measurements (body weight, body mass index [BMI], waist circumference, and hip circumference), and frequency of self-monitoring blood glucose (SMBG).

Statistical analysis
Continuous variables were summarized with descriptive statistics. Categorical data were summarized with the number and percentage of patients in each category.

Statistical testing and comparison of before and after liraglutide therapy were performed with paired *t*-tests for continuous variables (weight, HbA$_{1c}$, FBG, or PPBG), and with the Wilcoxon signed-rank test for the proportion of patients experiencing at least one hypoglycemic event.

All statistical tests were two-sided with the level of significance set at $\alpha = 0.05$. All results were interpreted in a descriptive manner, and missing data were not imputed.

Odds ratios were calculated by logistic regression to assess the association between the incidence of AEs and selected end-points.

RESULTS

Demographics and baseline characteristics
A total of 1416 patients were enrolled from 125 sites in India. These patients constituted the full analysis set (FAS) and were considered for safety evaluations. Of these, 1262 completed the 26-week study and were considered as the effectiveness analysis set (EAS).

A total of 154 patients (10.9%) discontinued the study by week 26; of this number, liraglutide was discontinued by 14 patients. The major reason for the study discontinuation was loss to follow-up (129 patients).

Baseline characteristic data are shown in Table 1.

Adverse events
Nineteen subjects (1.3% of the FAS population) reported a total of twenty AEs (excluding hypoglycemia) in this 26-week study [Table 2]; this included two subjects who were lost to follow-up between baseline and week 13. All but one of the twenty AEs was gastrointestinal: Ten (0.7%) were nausea and nine (0.6%) were vomiting. Nineteen AEs were considered by trial investigators to be related to liraglutide, and most AEs were mild. No serious AEs were reported. Information on the timing of AEs was not consistently recorded throughout the study.

Liraglutide was temporarily withdrawn from five subjects reporting nausea events, two subjects reporting vomiting

Table 1: Participant demographics and baseline characteristics

	n*	FAS (n=1416)
Sex, male/female (%)	1416	57.1/42.9
Age (years)	1416	46.8±9.7
Weight (kg)	1410	92.5±14.6
BMI (kg/m²)	1339	34.4±5.5
Diabetes duration (years)	973	7.2±5.6
Diabetes complications, n (%)	1416	
Autonomic neuropathy		137 (9.7)
Peripheral neuropathy		286 (20.2)
Nephropathy		110 (7.8)
Retinopathy		106 (7.5)
Macroangiopathy†		19 (1.3)
Coronary heart disease		96 (6.8)
Stroke		14 (1.0)
SBP (mmHg)	1365	134.4±15.3
DBP (mmHg)	1365	85.5±8.8

Data are mean±SD until otherwise stated. *Data collection based on FAS; where n<1416, data were missing or unknown for the remainder. †Including peripheral vascular disease. BMI: Body mass index, DBP: Diastolic blood pressure, FAS: Full analysis dataset, HbA$_{1c}$: Glycated hemoglobin, HDL-C: High-density lipoprotein cholesterol, LDL-C: Low-density lipoprotein cholesterol, SBP: Systolic blood pressure, SD: Standard deviation

Table 2: Number of subjects reporting at least one adverse event during the 26-week study period*

	Severity			Total
	Mild	Moderate	Severe	
All adverse events, n	15	5	0	20
Gastrointestinal, n (%)				
Nausea	8 (0.6)	2 (0.1)	0	10 (0.7)
Vomiting	7 (0.5)†	2 (0.1)	0	9 (0.6)
Back pain, n (%)	0	1 (0.1)	0	1 (0.1)

*Information on timing of adverse events, narrative information and the number of subjects in which each adverse event occurred were not consistently recorded. †Two patients who were lost to follow-up reported adverse events between baseline and week 13

events, and one subject reporting back pain. The duration of withdrawal (not recorded) was at the investigator's discretion. Liraglutide dose was reduced after one nausea event. Subjects recovered from all AEs reported during the study, irrespective of whether temporary withdrawal or dose reduction was required.

No MESI or deaths were reported.

Hypoglycemia
At baseline, 104 (7.3%) patients reported to have had a minor hypoglycemic event in the previous 4 weeks before initiating treatment with liraglutide [Table 3]. The number of patients reporting a minor hypoglycemic event in the previous 4 weeks at week 13 and week 26 was 64 (4.8%) and 9 (0.7%) patients, respectively. Information on hypoglycemic events was not recorded at any other time points.

No major hypoglycemic events were reported after initiation of liraglutide from baseline to week 26.

Glycemic measures from baseline to week 26
Change in glycemic control from baseline to week 26 was assessed using HbA_{1c}, FBG, and PPBG among the 1262 patients in the EAS. From a mean of 8.8 ± 1.3% at baseline, HbA_{1c} was reduced by 1.0% and 1.6% at weeks 13 and 26, respectively ($P < 0.0001$ vs. baseline for both) [Table 4].

A total of 21.9% and 35.2% of patients achieved the HbA_{1c} targets of ≤6.5% and <7.0%, respectively, at week 26. Mean decreases in FBG were 30.3 mg/dL at week 13 and 44.0 mg/dL at week 26 ($P < 0.0001$ vs. baseline for both) [Table 4]. Significant decreases were also observed in PPBG at weeks 13 and 26, whether measured post-breakfast, -lunch, or -dinner ($P < 0.0001$ vs. baseline) [Table 4].

Other secondary end-points from baseline to week 26
Fasting lipid profiles
Statistically significant decreases in mean TC, LDL-C, and triglycerides were observed from baseline to week 13 and to week 26 ($P < 0.0001$ for all vs. baseline) [Tables 4 and 5].

Body measurements
Significant reductions were also observed at week 13 and week 26 in mean weight (−4.1 kg and −8.1 kg, respectively), BMI (−1.5 kg/m² and −2.9 kg/m²), and waist circumference (−3.2 cm and −5.3 cm) ($P < 0.0001$ for all vs. baseline) [Table 5].

Blood pressure
There were significant decreases in mean SBP and DBP at week 13 and week 26 (SBP, −7.9 mmHg and −10.7 mmHg; DBP, −3.2 mmHg and −5.0 mmHg, respectively; $P < 0.0001$ for all vs. baseline) [Table 5].

Table 3: Hypoglycemic events from baseline to week 26*

	Baseline† (*n*=1416)	Week 13 (*n*=1322)	Week 26 (*n*=1262)
Minor hypoglycemia in past 4 weeks, *n* (%)			
Yes	104 (7.3)	64 (4.8)	9 (0.7)
No	1139 (80.4)	1177 (89.0)	1149 (91.0)
Unknown	173 (12.2)	81 (6.1)	104 (8.2)
Major hypoglycemia in past 13 weeks, *n* (%)			
Yes	5 (0.4)	0 (0.0)	0 (0.0)
No	1247 (88.1)	1243 (94.0)	1158 (91.8)
Unknown	164 (11.6)	79 (6.0)	104 (8.2)

*Information on the number of subjects experiencing at least one hypoglycemic event was not recorded. †Before initiation of treatment with liraglutide

Table 4: HbA_{1c}, fasting plasma glucose and postprandial blood glucose from baseline to week 26

	Baseline	Week 13	Week 26
HbA_{1c}, mean±SD (%)	8.8±1.3 (*n*=1191)	7.8±0.9 (*n*=1212)	7.2±0.8 (*n*=1215)
Mean±SD change from baseline	NA	−1.0±0.9* (*n*=1157)	−1.6±1.1* (*n*=1170)
Fasting blood glucose, mean±SD (mg/dL)	170.6±47.8 (*n*=1171)	139.9±34.4 (*n*=1234)	126.7±28.1 (*n*=1212)
Mean±SD change from baseline	NA	−30.3±33.6* (*n*=1157)	−44.0±39.7* (*n*=1144)
Postprandial blood glucose, mean±SD (mg/dL)			
Post-breakfast	247.4±61.7 (*n*=842)	190.4±45.4 (*n*=930)	166.6±41.5 (*n*=916)
Post-lunch	251.4±68.0 (*n*=405)	190.7±41.9 (*n*=393)	171.4±31.7 (*n*=377)
Post-dinner	303.8±72.5 (*n*=115)	215.0±41.0 (*n*=95)	187.9±35.3 (*n*=96)
Mean±SD change from baseline	NA		
Post-breakfast		−58.2±52.3* (*n*=799)	−79.5±57.3* (*n*=785)
Post-lunch		−58.5±48.1* (*n*=332)	−80.0±57.5* (*n*=321)
Post-dinner		−108.6±46.3* (*n*=92)	−134.7±50.8* (*n*=90)

*P<0.0001 versus baseline. HbA_{1c}: Glycated hemoglobin, NA: Not analyzed, SD: Standard deviation

Table 5: Other secondary outcomes from baseline to week 26			
	Baseline	**Week 13**	**Week 26**
Total cholesterol, mean±SD (mg/dL)	187.3±42.6 (*n*=1009)	172.8±33.0 (*n*=665)	164.3±29.4 (*n*=570)
Mean±SD change from baseline	NA	−16.9±24.2* (*n*=642)	−28.9±31.0* (*n*=562)
HDL-C, mean±SD (mg/dL)	43.6±12.1 (*n*=1008)	46.7±14.1 (*n*=661)	45.6±13.4 (*n*=569)
Mean±SD change from baseline	NA	+1.9±11.5* (*n*=635)	+0.4±15.6† (*n*=559)
LDL-C, mean±SD (mg/dL)	109.2±36.8 (*n*=1006)	102.5±29.3 (*n*=668)	96.9±25.0 (*n*=564)
Mean±SD change from baseline	NA	−8.4±23.3* (*n*=643)	−15.0±25.7* (*n*=554)
Triglyceride, mean±SD (mg/dL)	152.0±66.9 (*n*=1019)	130.8±52.7 (*n*=668)	116.9±43.0 (*n*=563)
Mean±SD change from baseline	NA	−15.7±34.3* (*n*=647)	−26.1±38.9* (*n*=554)
Serum creatinine, mean±SD (mg/dL)	1.0±0.7 (*n*=941)	0.9±0.4 (*n*=626)	0.9±0.2 (*n*=555)
Mean±SD change from baseline	NA	−0.2±0.9* (*n*=605)	−0.2±0.7* (*n*=545)
Urine albumin, mean±SD (mg/dL)	12.1±15.7 (*n*=364)	10.9±13.3 (*n*=283)	6.7±9.6 (*n*=249)
Mean±SD change from baseline	NA	−1.1±13.3† (*n*=262)	−3.1±10.2* (*n*=241)
Weight, mean±SD (kg)	92.5±14.6 (*n*=1410)	88.7±13.6 (*n*=1322)	84.8±12.9 (*n*=1262)
Mean±SD change from baseline	NA	−4.1±3.6* (*n*=1316)	−8.1±6.5* (*n*=1258)
BMI, mean±SD (kg/m²)	34.4±5.5 (*n*=1339)	33.0±5.2 (*n*=1248)	31.6±5.1 (*n*=1189)
Mean±SD change from baseline	NA	−1.5±1.4* (*n*=1245)	−2.9±2.4* (*n*=1187)
Waist circumference, mean±SD (cm)	103.4±11.9 (*n*=655)	99.1±11.9 (*n*=476)	96.6±11.7 (*n*=455)
Mean±SD change from baseline	NA	−3.2±4.0* (*n*=463)	−5.3±7.4* (*n*=437)
SBP, mean±SD (mmHg)	134.4±15.3 (*n*=1365)	126.5±9.4 (*n*=1261)	123.6±7.6 (*n*=1210)
Mean±SD change from baseline	NA	−7.9±12.9* (*n*=1222)	−10.7±15.0* (*n*=1172)
DBP, mean±SD (mmHg)	85.5±8.8 (*n*=1365)	82.3±5.5 (*n*=1261)	80.7±5.1 (*n*=1210)
Mean±SD change from baseline	NA	−3.2±7.9* (*n*=1222)	−5.0±8.9* (*n*=1172)

*P<0.0001 versus baseline. †Not significant versus baseline. BMI: Body mass index, DBP: Diastolic blood pressure, HDL-C: High-density lipoprotein cholesterol, LDL-C: Low-density lipoprotein cholesterol, NA: Not analyzed, SBP: Systolic blood pressure, SD: Standard deviation

Self-monitoring blood glucose

At baseline, the mean (standard deviation [SD]) number of times the SMBG done per day, per week, and per month was 1.0 (0.2), 1.6 (1.0), and 1.5 (0.9), respectively. At week 13, the mean (SD) number of times the SMBG was done per day, per week, and per month increased to 1.1 (0.3), 1.9 (1.1), and 2.1 (1.6), respectively. At week 26, the mean (SD) number of times the SMBG was done per day, per week, and per month was 1.1 (0.4), 2.0 (1.1), and 2.0 (1.5), respectively.

Change in concomitant medications
Diabetes medications

An overall decrease in the number of patients using concomitant medications for the treatment of T2D was observed between baseline and week 26. At all the study visits, metformin, sulfonylureas, and dipeptidyl dipeptidase-4 inhibitors were the most commonly used concomitant medications for T2D treatment. The number of patients taking each of these three classes of medication was lower at week 26 than at baseline, although no statistical analyses were performed [Table 6].

Antihypertensive and lipid-lowering treatments

At baseline, 766 (54.1%) patients were taking an antihypertensive, but this fell to 123 (9.3%) at week 13 and to 132 (10.5%) at week 26. Similarly, concomitant lipid-lowering treatments (statins, fibrates, and niacin) were being taken by 737 (52.0% [which comprised 90.5% statins, 28.2% fibrates, and 0.3% niacin]) patients at baseline, but only by 132 (10.0% [which comprised 79.5% statins, 53.8% fibrates, and 2.3% niacin]) patients at week 13, and 117 (9.3% [which comprised 76.9% statins, 35.0% fibrates, and 1.7% niacin]) at week 26.

DISCUSSION

In this observational study of patients with T2D treated in routine clinical practice in India, it is suggested that liraglutide was well tolerated, with a low incidence of reported AEs, and a low incidence of hypoglycemia. Treatment with liraglutide was found to be effective in the clinical practice setting, with mean reductions in HbA$_{1c}$ of 1.6%, and significant improvements in other measures of glycemic control from baseline to week 26.

In line with the previous studies, gastrointestinal AEs were the most commonly reported AEs.[2-7] However, although the pattern of AEs in LEAD-In was similar to that reported in the LEAD studies, as well as in other real-world studies in both India[20] and Europe,[21] the incidence of AEs was lower than would be expected from published data from other settings, and may not reflect the incidence rates in clinical practice in other countries. In a multinational RCT of liraglutide versus sitagliptin (both in combination with metformin), gastrointestinal side effects were reported in 43.1% (nausea: 27.5%; vomiting: 10.6%) of patients up to 1 year.[8] Results from a randomized study in China (liraglutide plus insulin vs. insulin alone) showed the incidence of AEs was 57.1%.[22] In the present study,

Table 6: Number of patients using concomitant diabetes medication from baseline to week 26			
Treatment	Baseline (*n*=1262)	Week 13 (*n*=1262)	Week 26 (*n*=1262)
Metformin			
n (%)	1095 (86.8)	1005 (79.6)	1034 (81.9)
Mean dose (mg)	1223.9	1232.6	1215.3
Sulfonylureas			
n (%)	779 (61.7)	655 (51.9)	674 (53.4)
Mean dose (mg)	9.7	11.0	8.9
Alpha-glucosidase inhibitors			
n (%)	108 (8.6)	75 (5.9)	87 (6.9)
Mean dose (mg)	59.6	61.6	56.6
Meglitinides			
n (%)	18 (1.4)	12 (1.0)	12 (1.0)
Mean dose (mg)	28.6	14.4	21.5
Thiazolidinediones			
n (%)	144 (11.4)	90 (7.1)	95 (7.5)
Mean dose (mg)	23.7	24.8	24.5
DPP-4 inhibitors			
n (%)	291 (23.1)	199 (15.8)	227 (18.0)
Mean dose (mg)	84.6	90.8	86.8
Exenatide			
n (%)	16 (1.3)	15 (1.2)	14 (1.1)
Mean dose (µg)	9.7	9.0	8.9
Premix insulin			
n (%)	114 (9.0)	61 (4.8)	72 (5.7)
Mean dose (IU)	37.1	39.5	39.6
Basal insulin			
n (%)	130 (10.3)	100 (7.9)	106 (8.4)
Mean dose (IU)	27.0	25.5	24.7
Bolus insulin			
n (%)	40 (3.2)	29 (2.3)	30 (2.4)
Mean dose (IU)	34.1	32.7	32.8

DPP-4: Dipeptidyl peptidase-4, IU: International units

just 1.2% (17 patients) reported at least one AE during scheduled visits.

It should be noted that although the importance of reporting AEs was emphasized to investigators at the start of the study, under-reporting is highly prevalent in India. Indeed, pharmacovigilance is a relatively new concept. Potential reasons for under-reporting include fear of personal liability and lack of resources or time.[23] In the present study, subjects were not explicitly told to report all AEs and were instructed on what side effects to expect; hence, some may have accepted nausea and vomiting as "expected" side effects and therefore not reported them. The absence of information on patients who discontinued liraglutide (*n* = 14) and were lost to follow-up (*n* = 129) may also partly explain the low numbers of AEs reported.

Of interest, it should be noted that the mean age of patients in the present study (46.8 ± 9.7 years) is lower than the mean ages of patients on liraglutide 1.8 mg in the LEAD studies (52–57.6 years). The mean duration of diabetes, however, at 7.2 ± 5.6 years, does fall within the range of mean durations seen in the LEAD studies (5.3–9.2 years).[2-7]

The effectiveness results from the current study were consistent with findings in the LEAD study program.[2-7] Furthermore, at week 26, significant benefits with regard to key cardiovascular risk factors that are commonly elevated in patients with T2D were observed; these included improvements in lipid levels, SBP, and body weight and are consistent with findings from the LEAD studies.[2-7] The number of patients taking concomitant antihypertensive and lipid-lowering medications appeared to decrease from baseline to week 26. Similarly, reductions in the number of patients taking other concomitant diabetes medications, including sulfonylureas, dipeptidyl peptidase-4 inhibitors, and exenatide were also observed. The reasons for changes in medication were not recorded but may reflect the attainment of relevant treatment goals; however, these results should be interpreted with caution. A possible reason for the decrease in the number of patients using lipid-lowering drugs throughout the trial may be the reduction seen in body weight. Patients who lose weight may believe that they no longer require lipid-lowering therapy. In India, patients frequently do not take their lipid-modifying medications as they cannot relate taking medication now with a cardiovascular benefit in the future. Patients are more likely to comply with

antihyperglycemia and antihypertensive medications than lipid-lowering medications as the results can be documented over a short period and patients can see the benefit. Therefore, it is possible that the reduction in the lipid-lowering medications during this trial may reflect a compliance issue, rather than that physicians withdrew them as a treatment.

There are a number of limitations to this study. The timings of the visits were "approximate," with no strict limits imposed. Furthermore, and in line with the nature of many observational trials conducted in real-world clinical practice, there was no obligation to collect all requested data, and the data collected were not extensively monitored. Therefore, not all analyses that might be desired were possible. In addition, many patients may have entered this study at a time when they were experiencing poor glycemic control, and hence some of the effects observed could be due to regression toward the mean. Thus, all observed changes from baseline are to be interpreted with caution; the changes could be due to a variety of factors and physician bias cannot be ruled out. In LEAD-In, there was no comparator drug; instead, subjects acted as their own controls with comparison pre- and post-treatment with liraglutide for 26 weeks, according to the selected end-points. Like all observational studies, the study is limited by the unblinded nature of the design. Furthermore, a major limitation of observational studies is that the patients are aware that they are being observed and modify their behavior accordingly.

Conclusions

LEAD-In shows that treatment with liraglutide is well tolerated and effective in the management of patients with T2D under standard clinical practice conditions in India, albeit with the caveat of the high prevalence of under-reporting of AEs in this country.

Conflicts of interest
Shahid Akhtar and Raman Shetty are employees of Novo Nordisk Pharma Gulf FZ-LLC. No other conflicts of interest to declare.

References

1. Inzucchi SE, Bergenstal RM, Buse JB, Diamant M, Ferrannini E, Nauck M, *et al.* Management of hyperglycemia in type 2 diabetes, 2015: A patient-centered approach: Update to a position statement of the American Diabetes Association and the European Association for the Study of Diabetes. Diabetes Care 2015;38:140-9.
2. Marre M, Shaw J, Brändle M, Bebakar WM, Kamaruddin NA, Strand J, *et al.* Liraglutide, a once-daily human GLP-1 analogue, added to a sulphonylurea over 26 weeks produces greater improvements in glycaemic and weight control compared with adding rosiglitazone or placebo in subjects with type 2 diabetes (LEAD-1 SU). Diabet Med 2009;26:268-78.
3. Nauck M, Frid A, Hermansen K, Shah NS, Tankova T, Mitha IH, *et al.* Efficacy and safety comparison of liraglutide, glimepiride, and placebo, all in combination with metformin, in type 2 diabetes: The LEAD (liraglutide effect and action in diabetes)-2 study. Diabetes Care 2009;32:84-90.
4. Garber A, Henry R, Ratner R, Garcia-Hernandez PA, Rodriguez-Pattzi H, Olvera-Alvarez I, *et al.* Liraglutide versus glimepiride monotherapy for type 2 diabetes (LEAD-3 Mono): A randomised, 52-week, phase III, double-blind, parallel-treatment trial. Lancet 2009;373:473-81.
5. Zinman B, Gerich J, Buse JB, Lewin A, Schwartz S, Raskin P, *et al.* Efficacy and safety of the human glucagon-like peptide-1 analog liraglutide in combination with metformin and thiazolidinedione in patients with type 2 diabetes (LEAD-4 Met TZD). Diabetes Care 2009;32:1224-30.
6. Russell-Jones D, Vaag A, Schmitz O, Sethi BK, Lalic N, Antic S, *et al.* Liraglutide vs insulin glargine and placebo in combination with metformin and sulfonylurea therapy in type 2 diabetes mellitus (LEAD-5 met SU): A randomised controlled trial. Diabetologia 2009;52:2046-55.
7. Buse JB, Rosenstock J, Sesti G, Schmidt WE, Montanya E, Brett JH, *et al.* Liraglutide once a day versus exenatide twice a day for type 2 diabetes: A 26-week randomised, parallel-group, multinational, open-label trial (LEAD-6). Lancet 2009;374:39-47.
8. Pratley R, Nauck M, Bailey T, Montanya E, Cuddihy R, Filetti S, *et al.* One year of liraglutide treatment offers sustained and more effective glycaemic control and weight reduction compared with sitagliptin, both in combination with metformin, in patients with type 2 diabetes: A randomised, parallel-group, open-label trial. Int J Clin Pract 2011;65:397-407.
9. Denker PS, Dimarco PE. Exenatide (exendin-4)-induced pancreatitis: A case report. Diabetes Care 2006;29:471.
10. Cure P, Pileggi A, Alejandro R. Exenatide and rare adverse events. N Engl J Med 2008;358:1969-70.
11. Zhou J, Martin RJ, Tulley RT, Raggio AM, McCutcheon KL, Shen L, *et al.* Dietary resistant starch upregulates total GLP-1 and PYY in a sustained day-long manner through fermentation in rodents. Am J Physiol Endocrinol Metab 2008;295:E1160-6.
12. Jura N, Archer H, Bar-Sagi D. Chronic pancreatitis, pancreatic adenocarcinoma and the black box in-between. Cell Res 2005;15:72-7.
13. Parnaud G, Bosco D, Berney T, Pattou F, Kerr-Conte J, Donath MY, *et al.* Proliferation of sorted human and rat beta cells. Diabetologia 2008;51:91-100.

14. Victoza® Summary of Product Characteristics. Available from: https://www.medicines.org.uk/EMC/medicine/21986/SPC/Victoza+6+mg+ml+solution+for+injection+in+pre-filled+pen/. [Last accessed on 2015 Nov 19].

15. Jensen TM, Saha K, Steinberg WM. Is there a link between liraglutide and pancreatitis? A *post hoc* review of pooled and patient-level data from completed liraglutide type 2 diabetes clinical trials. Diabetes Care 2015;38:1058-66.

16. Egan AG, Blind E, Dunder K, de Graeff PA, Hummer BT, Bourcier T, *et al.* Pancreatic safety of incretin-based drugs – FDA and EMA assessment. N Engl J Med 2014;370:794-7.

17. Saunders C, Byrne CD, Guthrie B, Lindsay RS, McKnight JA, Philip S, *et al.* External validity of randomized controlled trials of glycaemic control and vascular disease: How representative are participants? Diabet Med 2013;30:300-8.

18. World Medical Association Declaration of Helsinki. Recommendations guiding physicians in biomedical research involving human subjects. JAMA 1997;277:925-6.

19. American Diabetes Association. Executive summary: Standards of medical care in diabetes – 2014. Diabetes Care 2014;37 Suppl 1:S5-13.

20. Kaur P, Mishra SK, Mithal A, Saxena M, Makkar A, Sharma P. Clinical experience with liraglutide in 196 patients with type 2 diabetes from a tertiary care center in India. Indian J Endocrinol Metab 2014;18:77-82.

21. Mulligan CM, Harper R, Harding J, McIlwaine W, Petruckevitch A, McLaughlin DM. A retrospective audit of type 2 diabetes patients prescribed liraglutide in real-life clinical practice. Diabetes Ther 2013;4:147-51.

22. Li CJ, Li J, Zhang QM, Lv L, Chen R, Lv CF, *et al.* Efficacy and safety comparison between liraglutide as add-on therapy to insulin and insulin dose-increase in Chinese subjects with poorly controlled type 2 diabetes and abdominal obesity. Cardiovasc Diabetol 2012;11:142.

23. Prakasam A, Nidamanuri A, Kumar S. Knowledge, perception and practice of pharmacovigilance among community pharmacists in South India. Pharm Pract (Granada) 2012;10:222-6.