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ORIGINAL RESEARCH

The Durable Safety and Effectiveness of Lixisenatide in Japanese People with Type 2 Diabetes: The Post-Marketing Surveillance PRANDIAL Study

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ABSTRACT

Introduction: Real-world evidence on lixisenatide in Japanese people with type 2 diabetes (T2D) is lacking. Therefore, the 3-year post-marketing PRANDIAL study was conducted to evaluate the safety (primary objective) and effectiveness (secondary objective) of lixisenatide in Japanese people with T2D during routine clinical practice.

Methods: This prospective, observational, multicenter, open-label study was conducted in Japanese individuals with T2D who initiated lixisenatide treatment between March 2014 and June 2017. Using electronic case report forms, investigators collected baseline demographic and clinical information and data on medications, safety and effectiveness up to 3 years after initiation of lixisenatide.

Results: Overall, 3046 participants were analyzed; their mean ± standard deviation (SD) age was 58.9 ± 13.1 years, and 53.7% were male. Mean ± SD duration of T2D was 12.8 ± 8.6 years, and baseline glycated hemoglobin (HbA1c) was 8.7% ± 1.7%. Most participants (93.9%) were receiving concomitant antidiabetic medications when they initiated lixisenatide. Median (range) lixisenatide treatment duration was 382 (1–1096) days. Adverse drug reactions (ADRs) were reported in 604 participants (19.8%) and serious ADRs in 22 (0.7%). The most common ADR was nausea (9.0%). Of ADRs of special interest, hypoglycemia occurred in 2.9% of participants, injection site reactions in 0.9%, and hypoglycemic unconsciousness in 0.03%. Baseline characteristics associated with an increased risk of ADRs ($p < 0.05$) were history of treatment for cardiovascular disease, hepatic dysfunction, and other complications. Effectiveness was analyzed in 2675 participants; HbA1c, fasting plasma glucose, postprandial glucose, and body weight all decreased significantly at last observation (all $p < 0.0001$ vs. baseline).

Conclusions: Lixisenatide was well tolerated, with no unexpected ADRs or new safety signals identified, and showed effective glycemic control and weight reduction up to 3 years, supporting the use of lixisenatide as a safe and

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effective treatment option for T2D in routine clinical practice in Japan.

PLAIN LANGUAGE SUMMARY

Glucagon-like peptide-1 receptor agonists (GLP-1RAs) are antidiabetic drugs that lower blood glucose levels by stimulating the release of insulin and suppressing glucagon, the key hormones involved in controlling blood glucose levels in the body. The selective GLP-1RA lixisenatide was approved for the management of adults with type 2 diabetes (T2D) in Japan based on data from randomized clinical trials. However, these studies may not be representative of the safety and effectiveness of the drug when used in routine clinical practice. Therefore, we conducted the 3-year post-marketing PRANDIAL study to assess the safety and effectiveness of lixisenatide in 3046 Japanese individuals with T2D who started the drug between March 2014 and June 2017. Adverse drug reactions (adverse events for which lixisenatide causality could not be excluded) occurred in 19.8% of participants, with the most common adverse drug reaction being nausea. Hypoglycemia (abnormally low blood glucose levels) was reported in 2.9%. Individuals with a history of treatment for cardiovascular disease, hepatic dysfunction, and other complications had an increased risk of adverse drug reactions. Lixisenatide provided significant improvements in blood glucose control, with significant decreases in glycated hemoglobin (a marker of blood glucose control), fasting plasma glucose, and postprandial glucose levels from baseline, as well as significant reductions in body weight. In this real-world post-marketing surveillance study, lixisenatide was well tolerated, raising no new safety concerns, and provided durable effective blood glucose control and weight reduction. These results support the use of lixisenatide in Japanese individuals with T2D in routine clinical practice.

Keywords: Japan; Lixisenatide; Post-marketing surveillance; PRANDIAL study; Type 2 diabetes

Key Summary Points

Why carry out this study?

Type 2 diabetes (T2D) is a growing health problem and one of the most common aging-associated diseases in Japan because of the rapidly aging population

Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) have shown greater efficacy in Asian versus non-Asian populations with T2D, and their use is steadily increasing in Japan

The GLP-1 RA lixisenatide was approved in Japan in 2013, but real-world evidence on the safety and effectiveness of its use in Japanese people with T2D is lacking

What was learned from the study?

This prospective, observational, multicenter, open-label post-marketing surveillance study was conducted in more than 3000 Japanese people with T2D who started treatment with lixisenatide and were followed up for 3 years

Lixisenatide was well tolerated; the most common adverse drug reaction was nausea, and no new safety signals were identified

Lixisenatide significantly reduced a range of glycemic parameters (glycated hemoglobin, fasting plasma glucose, postprandial glucose) and body weight, supporting real-word effectiveness in Japanese individuals with T2D

INTRODUCTION

Type 2 diabetes (T2D) is an increasingly prevalent major health problem in Japan due to the rapidly aging population [1, 2]. Differences in the pathophysiology of T2D in Asian and Western populations influence appropriate

therapeutic approaches in these populations [3, 4]. In Japanese people, T2D is characterized by rapid deterioration of pancreatic β-cell functional capacity, which leads to a prominent defect in insulin secretion (as opposed to insulin resistance that develops in Western populations) and pronounced postprandial plasma glucose (PPG) excursions [5–7].

First-line treatment of T2D generally involves lifestyle modifications and oral antidiabetic drugs (OADs) as appropriate [8], but addition of an injectable agent to OADs is one of the pharmacologic options that may be used to achieve glycemic control [9]. Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) provide a valuable non-insulin-based option, with their benefits including a low risk of hypoglycemia and the potential for weight loss [8–10].

Glucagon-like peptide-1 (GLP-1) is an incretin hormone that is secreted postprandially by the intestine, leading to stimulation of insulin release and the suppression of glucagon; however, endogenous GLP-1 levels are low, and meal-induced secretion of GLP-1 is negligible in Japanese people [4, 11]. GLP-1RAs have shown greater efficacy in Asian versus non-Asian populations with T2D [12], and their use is steadily increasing in Japan [13].

Lixisenatide, a selective GLP-1 RA administered once daily by subcutaneous (SC) injection, has been assessed extensively in the large multinational phase 3 GetGoal clinical trial program [14–24]. Consistent with findings from the overall GetGoal study populations, add-on lixisenatide safely improved glycemic control in Japanese subpopulations inadequately controlled on a sulfonylurea ± metformin or basal insulin [25–27]. Lixisenatide was also well tolerated and effectively improved glycemic control when added to OADs (i.e., biguanides, thiazolidinediones, α-glucosidase inhibitors, or glinides) and as monotherapy in studies of Japanese people with T2D [28–30]. Lixisenatide was observed to have greater benefits in terms of PPG control in Japanese versus Caucasian populations, which may be attributable to differences in disease characteristics between ethnicities, including low endogenous GLP-1 production in Japanese individuals [11].

In Japan, lixisenatide was approved in 2013 for the treatment of adults with uncontrolled T2D despite treatment with a sulfonylurea with or without biguanide, or basal insulin with or without a sulfonylurea [31], and in 2016 the indication was expanded to any eligible patient with T2D [32]. However, real-world evidence on the safety and effectiveness of its use in Japanese people with T2D is lacking. Here, we report the results of PRANDIAL (Post-maRketing surveillANce in patients with type 2 DIAbetes mellitus to evaluate the long-term safety and effectiveness of Lixisenatide), a 3-year post-marketing surveillance (PMS) study of lixisenatide in Japanese individuals with T2D.

METHODS

Study Design and Participants

A multicenter, observational, longitudinal, prospective, single-arm cohort study was conducted in the post-marketing period to evaluate the safety and effectiveness of lixisenatide for treatment of T2D in routine clinical practice in Japan. Such PMS studies are a mandatory requirement of the Japanese Pharmaceutical Medical and Devices Agency (PMDA). Eligible participants were identified at 516 medical institutions (mainly endocrinology and diabetes centers) throughout Japan. Individuals who initiated treatment with lixisenatide at these centers were prospectively registered in the study between March 6, 2014, and June 29, 2017. The package insert for lixisenatide recommends that lixisenatide should be administered once daily at a dose of 20 μg before breakfast [32]. All treatment decisions were at the prescribing physician's discretion.

The study was conducted in accordance with the Japanese Ministerial Ordinance on Good Post-Marketing Study Practice (Ministry of Health, Labour and Welfare Ordinance No. 171, December 20, 2004) and the ethical guidelines for medical and health research involving human subjects. Under these Japanese regulations, this study was conducted without the review or approval by the ethics committee of the participating medical institutions or for

collection of informed consent from study participants. All data were collected anonymously to protect personal information; the study sponsor had no access to individual participant medical records.

Data Collection

Investigators collected baseline demographic and clinical history information, data on medications, laboratory test results, and safety and effectiveness data using electronic case report forms (CRFs). Data were collected for 3 years after initiation of lixisenatide treatment, or until lixisenatide discontinuation or patient withdrawal, up to the last day of follow-up, which was August 1, 2020. If treatment was discontinued during the observation period for any reason, safety and effectiveness were evaluated up to the point of discontinuation and imputed using the last observation carried forward (LOCF) approach.

Outcomes and Measures

The primary endpoint of the study was lixisenatide's safety based on the incidence of adverse drug reactions (ADRs) and serious ADRs. ADRs were classified according to the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use Medical Dictionary for Regulatory Activities, Japanese edition (MedDRA/J), version 23.1. ADRs were defined as adverse events for which a causal relationship with lixisenatide could not be excluded, and serious ADRs were life-threatening or important medical events, fatal ADRs, or those resulting in hospitalization or congenital defect, or requiring intervention. Secondary endpoints were the occurrence of any unexpected ADRs, which were not listed in the approved prescribing information, and ADRs of special interest defined in the lixisenatide risk management plan in Japan as: (1) important identified risks, i.e., hypoglycemia, gastrointestinal disorders, systemic hypersensitivity reactions (including anaphylaxis and angioedema), injection site reactions, and acute pancreatitis; (2) other important potential risks, i.e., acute kidney injury, intestinal obstruction, medullary thyroid cancer, pancreatic carcinoma, immunogenicity/neutralizing activity (effect of anti-lixisenatide antibody production), rapid hyperglycemia, and diabetic ketoacidosis due to discontinuation of insulin when starting lixisenatide); and (3) important missing information, i.e., cardiovascular (CV) events (CV death, non-fatal myocardial infarction or stroke, hospitalization for unstable angina, heart failure, or other CV events). The International Hypoglycaemia Study Group proposed that the three glucose levels be adopted by the diabetes community to address the issue of hypoglycemic risk in clinical trials [33]. The severity of hypoglycemia in this study was finally evaluated by the safety department with reference to the severity described by the investigators in the CRF.

ADRs were assessed in the safety population and in subpopulations of participants in older age groups (i.e., $\geq$ 65 and $\geq$ 75 years), as well as in those with renal dysfunction (most commonly presenting as chronic kidney disease, nephrolithiasis, or renal cysts) or hepatic dysfunction (most commonly presenting as of fatty liver, abnormal liver function, or cholelithiasis), and by baseline characteristics, including gender, age, duration of T2D, alcohol use, smoking, medical history (i.e., renal, hepatic, CV disease), diabetic complications, and previous T2D treatment.

Effectiveness endpoints included changes in parameters of glycemic control (i.e., glycated hemoglobin [HbA1c], fasting plasma glucose [FPG], and PPG) and changes in body weight from baseline over 3 years. The proportion of participants achieving an HbA1c $<$ 7% at LOCF was also assessed.

Statistical Analysis

The target sample size was $\geq$ 3000 in the safety analysis set; therefore, we aimed to register 3600 participants overall to account for an expected dropout rate of 20%. Registration of 3000 participants was required to observe CV events in approximately 200 individuals, assuming that the incidence of CV events would be similar to

that observed in the Japan Diabetes Complications study (approximately 20 per 1000 person-years) [33]. The sample size was chosen to meet the study objective of identifying CV events to provide missing information to the PMDA in accordance with the lixisenatide risk management plan.

The effectiveness analysis set comprised all study participants with T2D who received lixisenatide in accordance with the approved product label (SC injection, 10–20 μg administered before breakfast) for whom effectiveness data were available. Categorical and continuous variables were summarized as percentages and descriptive statistics (mean ± standard deviation [SD]), respectively. Paired *t*-tests were used to test for changes in continuous variables from baseline. All tests were conducted with a significance level of 5%. Missing data were managed using the LOCF approach.

Univariate analysis of the incidence of ADRs according to baseline characteristics was conducted using the Fisher's exact test for nominal variables and the Cochran-Armitage test for ordinal variables. Multivariable logistic regression analysis was employed to determine the relationship between baseline characteristics and the incidence of ADRs as follows: first, baseline characteristics for which a univariate analysis indicated significant differences in the incidence of ADRs (i.e., $p < 0.05$ by Chi-squared test) were included in the multivariable logistic regression analysis. These factors included age, gender, duration of diabetes, concomitant medications, comorbidities, body weight/body mass index (BMI), and HbA1c measured at baseline. This multivariable logistic regression analysis was then carried out using a stepwise method for selecting predictor variables, which were considered significant at the 20% level (i.e., $p < 0.20$).

RESULTS

Study Participants

A total of 3177 participants were registered at 516 sites, and CRFs were collected for 3090 participants (Fig. 1). The safety analysis set included 3046 participants. The main reason for exclusion was failure to start lixisenatide administration within 15 days of registration ($n = 27$). The effectiveness analysis set included 2675 participants. Exclusion from the effectiveness analysis set was mainly because effectiveness data were unavailable ($n = 255$) and/or because lixisenatide was not administered at the recommended dosage according to the product label ($n = 113$). Deviations from the recommended dosage were mainly that lixisenatide was administered twice daily or at a daily dose of > 20 μg.

A summary of the baseline characteristics of the safety analysis set are shown in Table 1. The mean ± SD age was 58.9 ± 13.1 years, 53.7% of participants were male, and the mean ± SD BMI was 28.6 ± 5.6 kg/m^2. The mean ± SD duration of T2D was 12.8 ± 8.6 years, with a mean ± SD baseline HbA1c level of 8.7% ± 1.7%. Hepatic dysfunction was present in 19.4% of participants in the safety analysis set, and 6.9% had renal dysfunction.

Overall, 93.9% of participants in the safety analysis set were receiving concomitant antidiabetic medications at the start of lixisenatide therapy (Table 2). Basal insulin (59.2%) was the most commonly administered concomitant antidiabetic medication, followed by biguanides (44.5%) and sulfonylureas (21.8%).

The duration of lixisenatide treatment ranged from 1 to 1096 days (median 382 days; mean ± SD 521.8 ± 424.9 days). Overall, 1489 participants (48.9%) received lixisenatide for < 1 year; 1557 (51.1%) received lixisenatide for ≥ 1 year, 1086 (35.7%) received lixisenatide for ≥ 2 years, and 577 (18.9%) received lixisenatide for ≥ 3 years. The median dose of lixisenatide was 17.8 μg/day (mean ± SD; 15.9 ± 4.2 μg/day). Three thousand participants (98.5%) took lixisenatide once daily, and 2684 participants (88.1% of the total cohort) administered lixisenatide before breakfast. The other participants took lixisenatide at other times of the day ($n = 316$) or twice daily ($n = 46$), in the morning and evening; 45 participants had no data available on timing of administration.

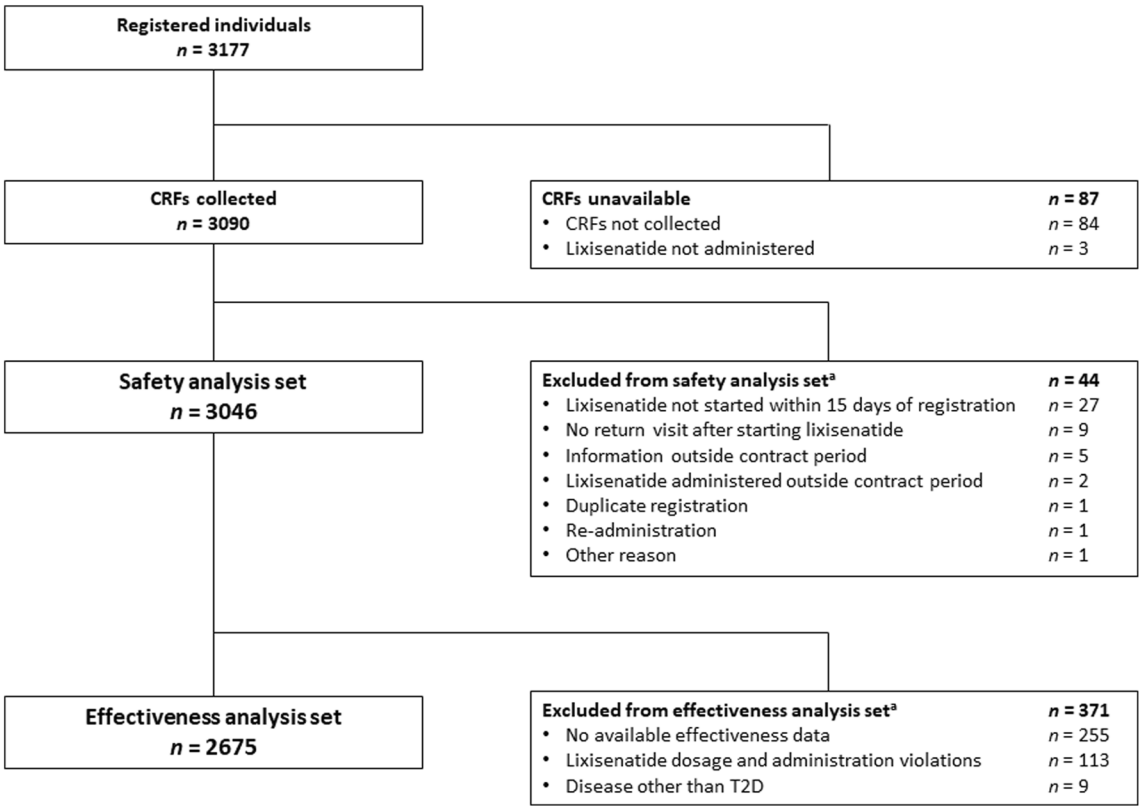


Fig. 1 Study participant disposition. *T2D* type 2 diabetes. [a]Multiple reasons were possible

Safety

Overall

Over the 3-year observation period, ADRs were reported in 604 participants (19.8%) in the safety analysis set, including serious ADRs in 22 participants (0.7%; Table 3). The most common ADRs were nausea, which occurred in 9.0% of participants, followed by hypoglycemia (2.9%), vomiting (1.9%), decreased appetite (1.5%), abdominal discomfort (1.1%), and constipation (0.9%).

The overall incidence of gastrointestinal ADRs was 3.8% during the first week of lixisenatide, which tended to be higher than that during subsequent follow-up (data not shown). Gastrointestinal ADRs reported in the first week were nausea (2.6%), vomiting (0.7%), abdominal discomfort (0.5%), and abdominal distension (0.2%).

Serious ADRs

Serious ADRs are listed in Table 3, the most common being serious hypoglycemia and serious hyperglycemia, each of which occurred in three participants (0.1%), followed by inadequate T2D control and increased blood glucose levels, each of which occurred in two participants (0.1%). Serious gastrointestinal-related ADRs included constipation ($n = 1$), vomiting ($n = 1$), and two cases of pancreatitis (one acute and one chronic) (Table 3).

ADRs of Special Interest

ADRs of special interest included gastrointestinal ADRs, reported in 13.4% of participants, hypoglycemia in 2.8%, injection site reactions in 0.9%, acute (or chronic) pancreatitis in 0.1%, and acute kidney injury, pancreatic carcinoma, and hypoglycemic unconsciousness, each of which occurred in 0.03% of participants (Table 4). The two pancreatitis events developed > 10 months after starting lixisenatide

Table 1 Demographics and baseline characteristics of the safety analysis set ($N = 3046$)

Characteristic	$N = 3046$
Age	$n = 3036$
Mean ± SD, years	58.9 ± 13.1
< 65 years, *n* (%)	1882 (61.8)
≥ 65 years, *n* (%)	1154 (37.9)
≥ 75 years, *n* (%)	345 (11.3)
Gender, *n* (%)	
Male	1637 (53.7)
Female	1409 (46.3)
Mean duration of T2D ± SD, years	$n = 1991$
	12.8 ± 8.6
Mean body weight ± SD, kg	$n = 2660$
	75.5 ± 17.4
Mean BMI ± SD, kg/m^2	$n = 2566$
	28.6 ± 5.6
Mean HbA1c ± SD, %	$n = 2863$
	8.7 ± 1.7
Mean FPG ± SD, mg/dl	$n = 1104$
	169.4 ± 71.7
Diabetic complications, *n* (%)	
Retinopathy	173 (5.7)
Nephropathy	345 (11.3)
Neuropathy	190 (6.2)
Other complications, *n* (%)	
Hepatic dysfunction	592 (19.4)
Renal dysfunction	210 (6.9)
CVD and CeVd	1640 (53.8)

BMI body mass index, *CeVD* cerebrovascular disease, *CVD* cardiovascular disease, *FPG* fasting plasma glucose, *HbA1c* glycated hemoglobin, *SD* standard deviation, *T2D* type 2 diabetes

Table 2 Concomitant antidiabetic therapies used during lixisenatide therapy in the safety analysis set ($N = 3046$)

Concomitant agents, *n* (%)	Start of lixisenatide therapy	> 1 year after the start of lixisenatide therapy
None	186 (6.1)	45 (1.5)
Any oral antidiabetic drug	2086 (68.5)	1044 (34.3)
Biguanide	1354 (44.5)	704 (23.1)
Sulfonylurea	664 (21.8)	296 (9.7)
SGLT2 inhibitor	336 (11.0)	179 (5.9)
α-Glucosidase inhibitor	288 (9.5)	140 (4.6)
Insulin sensitizer (thiazolidinedione)	198 (6.5)	92 (3.0)
Rapid-acting insulin secretagogue	145 (4.8)	65 (2.1)
DPP-4 inhibitor	165 (5.4)	49 (1.6)
Mixed insulin	85 (2.8)	37 (1.2)
Basal insulin	1802 (59.2)	838 (27.5)
Rapid insulin	3 (0.1)	0

DPP-4 dipeptidyl peptidase-4, *SGLT2* sodium-glucose cotransporter-2

treatment—acute pancreatitis after 524 days and chronic pancreatitis after 332 days. Both patients were hospitalized and lixisenatide was discontinued, after which the pancreatitis improved (chronic) or resolved (acute).

There were no reports of systemic hypersensitivity reactions, intestinal obstruction, medullary thyroid cancer, immunogenicity/neutralizing activity, rapid hyperglycemia, or diabetic ketoacidosis as a result of insulin discontinuation when starting lixisenatide therapy, or lixisenatide-related CV events (Table 4). CV events with no causal relationship to lixisenatide occurred in 46 participants (1.5%).

Subgroup Analyses

The incidence of ADRs in older participants was significantly higher than in younger participants, occurring in 23.4% of those aged ≥ 65 years versus 17.4% of those aged < 65 years ($p < 0.0001$) and in 27.0% of

Table 3 ADRs that occurred in ≥ 0.5% of the population or as serious ADRs in the safety analysis set (N = 3046)

Type of ADR, *n* (%)	All ADRs	Serious ADRs
Any ADR	604 (19.83)	22 (0.72)
Abdominal discomfort	34 (1.12)	0
Abdominal distension	18 (0.59)	0
Constipation	26 (0.85)	1 (0.03)
Diarrhea	18 (0.59)	0
Nausea	275 (9.03)	0
Pancreatitis acute	1 (0.03)	1 (0.03)
Pancreatitis chronic	1 (0.03)	1 (0.03)
Vomiting	59 (1.94)	1 (0.03)
Decreased appetite	45 (1.48)	1 (0.3)
Gastroenteritis	1 (0.03)	1 (0.03)
Diabetic ketoacidosis	1 (0.03)	1 (0.03)
Hyperglycemia	14 (0.46)	3 (0.1)
Hypoglycemia	88 (2.89)	3 (0.1)
Hypoglycemic unconsciousness	1 (0.03)	1 (0.03)
Inadequate diabetes control	2 (0.07)	2 (0.07)
Blood glucose increased	12 (0.39)	2 (0.07)
Diabetic nephropathy	1 (0.03)	1 (0.03)
Renal impairment	1 (0.03)	1 (0.03)
Cholecystitis acute	1 (0.03)	1 (0.03)
Drug-induced liver injury	1 (0.03)	1 (0.03)
Cholangiocarcinoma	1 (0.03)	1 (0.03)
Pancreatic carcinoma	1 (0.03)	1 (0.03)
Femoral neck fracture	1 (0.03)	1 (0.03)

ADR adverse drug reaction

Table 4 ADRs of special interest in the safety analysis set (N = 3046)

Type of ADR, *n* (%)	All ADRs	Serious ADRs
Important identified risk(s)		
Hypoglycemia/hypoglycemic unconsciousness	89 (2.92)	4 (0.13)
Gastrointestinal disorders	408 (13.39)	3 (0.10)
Anaphylaxis, systemic hypersensitivity	0	0
Injection site reactions	27 (0.89)	0
Pancreatitis acute/pancreatitis chronic	2 (0.07)	2 (0.07)
Important potential risk(s)		
Acute kidney injury	1 (0.03)	1 (0.03)
Intestinal obstruction	0	0
Medullary thyroid cancer	0	0
Pancreatic carcinoma	1 (0.03)	1 (0.03)
Immunogenicity/neutralizing activity	0	0
Rapid hyperglycemia and diabetic ketoacidosis	0	0
Important missing information		
Cardiovascular events	0	0

ADR adverse drug reaction

those aged ≥ 75 years versus 18.8% of those aged < 75 years (p = 0.0005) (Table S1 in the Supplementary Material). The incidence of nausea in particular tended to be higher in elderly participants (11.5%) compared with those aged < 65 years (7.6%). Serious ADRs occurred in 10 out of 1154 participants aged ≥ 65 years (0.9%) and in four out of 345 participants aged ≥ 75 years (1.2%).

The incidence of ADRs was significantly higher among participants with renal dysfunction (defined according to the treating physician per local institution criteria) than in those with normal renal function (25.2% vs. 19.4%; $p < 0.05$). The most common ADRs among participants with renal dysfunction were nausea (12.9%) and decreased appetite (3.8%). There

were no serious ADRs in the subgroup of participants with renal dysfunction.

Similarly, the incidence of ADRs was also significantly higher in the subgroup of participants with hepatic dysfunction compared with those with normal hepatic function (26.2% vs. 18.3%; $p < 0.0001$) (Table S1 in the Supplementary Material). The most common ADRs among participants with hepatic dysfunction were nausea (11.2%) and hypoglycemia (5.1%). Ten serious ADRs occurred in 8 out of 592 participants with hepatic dysfunction (1.6%). One of these events was drug-induced liver injury, two were infections (pancreatitis in one and cystitis in another), one was a femoral neck fracture, and the other six were diabetes-related (hypoglycemia [$n = 2$], diabetes mellitus inadequate control [$n = 1$], diabetic ketoacidosis [$n = 1$], diabetic nephropathy [$n = 1$], and blood glucose increased [$n = 1$]).

Multivariable logistic regression analysis identified the following baseline participant characteristics as being significantly associated with an increased risk of ADRs ($p < 0.05$): history of treatment for CV disease (odds ratio [OR], 1.45; 95% confidence interval [CI], 1.08–1.93), hepatic dysfunction (OR, 1.37; 95% CI, 1.09–1.71), and other complications (i.e., kidney disease, CV disease, diabetic nephropathy; OR, 1.74; 95% CI, 1.40–2.16) (Table S1 in the Supplementary Material).

Concomitant therapy at the start of lixisenatide with a rapid-acting insulin secretagogue was associated with an increased risk of ADRs (OR, 1.58; 95% CI, 1.01–2.49), but the risk of ADRs was reduced in participants receiving a biguanide (OR, 0.82; 95% CI, 0.67–1.00) or sulfonylurea (OR, 0.72; 95% CI, 0.57–0.91) at the start of lixisenatide therapy ($p < 0.05$) (Table S1 in the Supplementary Material).

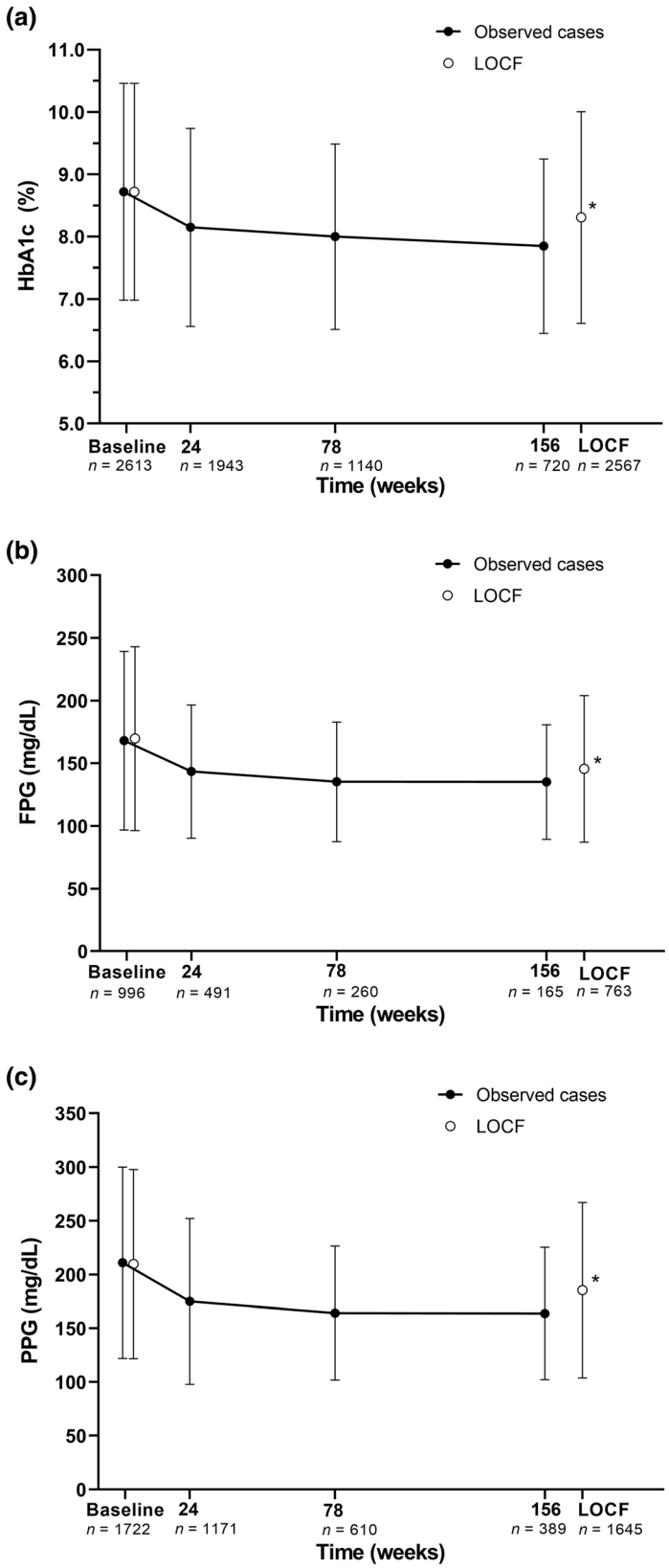
Effectiveness

Of 2675 participants in the effectiveness analysis set, HbA1c, FPG, and PPG were all significantly reduced at LOCF ($p < 0.0001$ vs. baseline for all parameters). Figure 2a–c shows changes in these parameters at the predefined evaluation points of 24, 78, and 156 weeks. HbA1c levels (mean ± SD) decreased from 8.72 ± 1.74% at baseline to 8.31 ± 1.70% at LOCF (mean ± SD change − 0.41 ± 0.85%). Approximately one-fifth of participants (564/2675; 21.1%) achieved an HbA1c of < 7% at LOCF. Mean ± SD FPG levels decreased from 169.7 ± 73.4 mg/dl at baseline to 145.5 ± 58.4 mg/dl at LOCF (mean ± SD change − 24.3 ± 85.1 mg/dl) and mean ± SD PPG levels decreased from 209.7 ± 88.1 mg/dl to 185.3 ± 81.7 mg/dl (mean ± SD change − 24.3 ± 104.9 mg/dl). Table S2 in the Supplementary Material shows changes in laboratory and clinical values during the study, including body weight, which decreased significantly from 75.8 ± 17.6 kg at baseline to 73.5 ± 17.1 kg at LOCF (mean ± SD change − 2.3 ± 4.8 kg; $p < 0.0001$ vs. baseline).

Similar significant changes in HbA1c, FPG, PPG, and body weight were also observed in subgroups of participants who were receiving concomitant basal insulin, biguanide, or sulfonylurea treatment when lixisenatide was initiated (data not shown).

DISCUSSION

This 3-year PMS study provides real-world evidence of the durable safety and effectiveness of lixisenatide in Japanese individuals with T2D. Consistent with its mechanism of action as a GLP-1 RA, the most commonly reported ADRs with lixisenatide were gastrointestinal adverse events, primarily nausea (occurring in 9.0% of participants in the safety analysis set). The incidence of vomiting was relatively low (1.9% of the safety analysis set). These observations are in line with those of clinical studies conducted with lixisenatide in Japan [28–30] and in Japanese subpopulations from international studies [25, 27], although these studies reported a relatively high incidence of nausea (up to approximately 44%). It is possible that reporting bias as well as the potential impact of some participants receiving an inadequate (lower than recommended) dose of lixisenatide may have contributed to the differences in the incidence of nausea between the current PMS study and previous clinical studies (i.e., some adverse


(a)
Observed cases
LOCF
HbA1c (%)
11.0
10.0
9.0
8.0
7.0
6.0
5.0
*
Baseline n = 2613
24 n = 1943
78 n = 1140
156 n = 720
LOCF n = 2567
Time (weeks)
(b)
Observed cases
LOCF
FPG (mg/dL)
300
250
200
150
100
50
0
*
Baseline n = 996
24 n = 491
78 n = 260
156 n = 165
LOCF n = 763
Time (weeks)
(c)
Observed cases
LOCF
PPG (mg/dL)
350
300
250
200
150
100
50
0
*
Baseline n = 1722
24 n = 1171
78 n = 610
156 n = 389
LOCF n = 1645
Time (weeks)

◀**Fig. 2** Mean ± SD values for (**a**) HbA1c, (**b**) FPG, and (**c**) PPG at baseline (i.e., prior to lixisenatide), at each follow-up time point, and at LOCF. *FPG* fasting plasma glucose, *HbA1c* glycated hemoglobin, *LOCF* last observation carried forward, *PPG* postprandial plasma glucose, *SD* standard deviation. $^{*}p < 0.0001$ vs. baseline by paired *t*-test

events and ADRs may have been under-reported during the PMS study).

Gastrointestinal ADRs were rarely serious; there was one case of vomiting, one of constipation, and one each of acute and chronic pancreatitis. Concerns have been raised regarding the potential for lixisenatide to cause pancreatic disease, including pancreatic cancer [34, 35]. There were no reports of pancreatitis in individuals receiving lixisenatide in the majority of clinical trials [15–20, 22–24] or in previous real-world, 6-month observational studies of lixisenatide use in Europe [36–38]. The two participants with pancreatitis in the current PRANDIAL study showed improvement or recovery after lixisenatide discontinuation. In addition to these two participants, there was one case of pancreatic carcinoma. However, the possibility that these conditions had started to develop or were present before the initiation of lixisenatide treatment cannot be ruled out. Although a causal relationship has not been established, monitoring for signs and symptoms of pancreatitis is recommended during lixisenatide therapy [39].

Hypoglycemia occurred in a small proportion (2.9%) of participants in the safety analysis set. Hypoglycemia is more likely to develop if lixisenatide is used in combination with medications that directly lower blood glucose [39]. When starting treatment with lixisenatide, 59.2% of participants in this study were receiving basal insulin and 21.8% were receiving sulfonylurea therapy, which have been shown to significantly increase the risk of hypoglycemia [40, 41], so episodes of symptomatic hypoglycemia may be expected in these individuals. Nevertheless, the incidence of serious hypoglycemia in the safety analysis set was very low (0.1%). This finding is consistent with previous European real-world studies of lixisenatide, in which serious or severe hypoglycemia events were also rare [36–38]. A conservative approach to limit the risk of hypoglycemia is to reduce the dose of sulfonylurea, or any other medication that directly lowers blood glucose, when adding lixisenatide to an antidiabetic regimen containing such agents [39].

In addition to gastrointestinal events and hypoglycemia, other ADRs that may potentially occur with lixisenatide include immunogenic reactions, whereby production of anti-lixisenatide antibodies contribute to hypersensitivity and injection site reactions [39]. There was no measured case of immunogenicity/neutralization (effect of anti-lixisenatide antibody production) in the current PMS study, no reports of hypersensitivity reaction, and a low rate of injection site reactions.

Apart from gastrointestinal events, hypoglycemia, injection site reactions, acute pancreatitis, acute kidney injury, and pancreatic carcinoma, there were no reports of other ADRs of special interest, including intestinal obstruction, medullary thyroid cancer, systemic hypersensitivity reactions including anaphylaxis and angioedema, immunogenicity/neutralizing activity, rapid hyperglycemia, and diabetic ketoacidosis after discontinuing insulin and switching to lixisenatide, or lixisenatide-related CV events. CV events with no causal relationship to lixisenatide occurred in 1.5% of participants, which is consistent with available epidemiology data and reflective of a lower rate of CV events in general among Japanese people with T2D compared with that observed in Western populations [42].

The PMS study population was indicative of the real-world setting, facilitating assessment of safety in the older individuals with T2D as well as those with renal or hepatic dysfunction. The incidence of ADRs was significantly higher in participants aged ≥ 65 years and ≥ 75 years versus younger subgroups and in participants with hepatic or renal dysfunction versus those with normal hepatic or renal function. These subgroups are generally more prone to adverse events as a result of multiple factors, including the need for polypharmacy [43–45]. Multivariable analysis identified treatment for CV disease, hepatic dysfunction, and other complications as being independent risk factors

for ADRs during lixisenatide therapy. Although lixisenatide is removed by the kidneys and hepatic impairment is unlikely to affect its pharmacokinetic profile [39], people with liver disease often have other serious comorbidities [44], thereby increasing the likelihood of ADRs in general. Although renal impairment was not identified in the multivariable analysis, it is recommended that people with renal impairment should be monitored closely for an increased risk of adverse events during lixisenatide treatment, particularly gastrointestinal events and worsening renal function [39].

Sulfonylureas have historically been the most commonly used OAD in Japan, but the use of other OADs is growing [3, 46]. Dipeptidyl peptidase-4 (DPP-4) inhibitors, which act on the same incretin hormone pathway as GLP-1 RAs (DPP-4 inactivates endogenous GLP-1), are now preferentially prescribed as first-line medication [46–48]. However, the low use of DPP4 inhibitors in the current PMS study (5% of participants) suggests that GLP-1 RAs and DPP-4 inhibitors are generally not administered together; rather, when targets are not achieved with a DPP-4 inhibitor, treatment is intensified by adding another antidiabetic agent that acts on a different pathway.

Although the primary focus of the current PMS study was safety, the effectiveness of lixisenatide in Japanese people with T2D was also evaluated. Consistent with previous randomized controlled trials and a meta-analysis in Japanese T2D study populations [25–30], as well as previous European real-world studies of individuals with T2D [36–38], the current study observed significant improvements in glycemic control (HbA1c, FPG, and PPG) during treatment with lixisenatide for up to 3 years. The proportion of participants who achieved the target HbA1c of < 7%, as recommended by the Japan Diabetes Society to prevent complications of T2D [8], was lower in the current PMS study (21%) than in previous clinical trials of lixisenatide as monotherapy or in combination with OAD in Japan (up to approximately 60%) [28, 29]. However, the proportion of participants achieving an HbA1c of < 7% with lixisenatide in previous European real-world studies was also lower than randomized clinical trials, ranging from 19 to 39% [36–38]. It is possible that poorer adherence to treatment as well as inadequate dosing in everyday clinical practice versus the clinical trial setting may have contributed to the lower proportion of participants achieving an HbA1c < 7% in real-world studies compared with the randomized controlled trials [49]. The phase 2 and 3 studies with lixisenatide used a starting dose of 10 μg once daily, increased to 15 μg after 1 week and 20 μg after 2 weeks, for optimal risk/benefit and patient convenience, but our results show that the average dose of lixisenatide during routine clinical practice in Japan is lower than this (median 17.8 μg/day and mean 15.9 μg/day), which suggests that some patients do not increase the lixisenatide dose from 15 to 20 μg.

In the current PMS study, lixisenatide showed a pronounced effect on PPG, control of which is particularly important in Asian populations, and is likely to be an important goal for individuals who do not achieve HbA1c targets [50, 51]. Lixisenatide was also associated with a beneficial effect on body weight (2 kg reduction from baseline). This is in line with randomized controlled trials in Japanese people with T2D [25–30] and real-world studies in European populations [36–38], in whom lixisenatide had beneficial or neutral effects on body weight, and is consistent with the hypothesis that lixisenatide mitigates body weight gain caused by basal insulin and/or sulfonylurea treatment [26]. Mean baseline BMI in the current PMS study (29 kg/m^2) was higher than in previous clinical trials conducted in Japan (approximately 25–26 kg/m^2), in which more modest effects of lixisenatide on body weight were observed [25, 27–30]. Overweight and obesity are increasing in prevalence among people with T2D in Japan [52], and concerns over weight gain, as well as glycemic control, may have driven prescribing decisions, with lixisenatide being preferentially prescribed for overweight/obese individuals with T2D in the current PMS study.

The strengths of this study include the large number of participants enrolled and its long duration of follow-up. The limitations of this study include its non-interventional, single-arm, observational design with no control

group and the fact that it was conducted in routine clinical practice; therefore, safety and effectiveness data may be affected by factors other than lixisenatide (e.g., concomitant antidiabetic medications, concurrent diseases). Furthermore, adherence to lixisenatide treatment was not formally assessed. Safety data were collected using electronic CRFs, which could have led to an underestimation of the number of ADRs if some ADRs had not been captured in the CRFs.

CONCLUSIONS

The results of this 3-year PMS study support the use of lixisenatide as a safe and effective option for the treatment of T2D in routine clinical practice in Japan. The ADRs observed over this time period were consistent with its known safety profile, and no new safety signals were observed. Lixisenatide showed durable improvements in glycemic control (median follow-up of 382 days), with significant improvements from baseline in HbA1c, FPG, and PPG observed. In addition to these improvements in glycemic control, lixisenatide also provided beneficial effects on body weight in this population of Japanese people with T2D.

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Compliance with Ethics Guidelines. The study was conducted in accordance with the Japanese Ministerial Ordinance on Good Post-Marketing Study Practice (Ministry of Health, Labour and Welfare Ordinance No. 171, December 20, 2004) and the ethical guidelines for medical and health research involving human subjects. Under these Japanese regulations, this study was conducted without the review or approval by the ethics committee of the participating medical institutions or for collection of informed consent from study

participants. All data were collected anonymously to protect personal information; the study sponsor had no access to individual participant medical records.

Data Availability. The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

REFERENCES

1. Charvat H, Goto A, Goto M, et al. Impact of population aging on trends in diabetes prevalence: a meta-regression analysis of 160,000 Japanese adults. J Diabetes Investig. 2015;6(5):533–42.

2. Goto A, Noda M, Inoue M, Goto M, Charvat H. Increasing number of people with diabetes in Japan: is this trend real? Intern Med. 2016;55(14):1827–30.

3. Seino Y, Kuwata H, Yabe D. Incretin-based drugs for type 2 diabetes: focus on East Asian perspectives. J Diabetes Investig. 2016;7(Suppl 1):102–9.

4. Yabe D, Seino Y, Fukushima M, Seino S. β cell dysfunction versus insulin resistance in the pathogenesis of type 2 diabetes in East Asians. Curr Diab Rep. 2015;15(6):602.

5. Inaishi J, Saisho Y. Ethnic similarities and differences in the relationship between beta cell mass and diabetes. J Clin Med. 2017;6(12):113.

6. Ma RC, Chan JC. Type 2 diabetes in East Asians: similarities and differences with populations in Europe and the United States. Ann N Y Acad Sci. 2013;1281:64–91.

7. Moller JB, Dalla Man C, Overgaard RV, et al. Ethnic differences in insulin sensitivity, beta-cell function, and hepatic extraction between Japanese and Caucasians: a minimal model analysis. J Clin Endocrinol Metab. 2014;99(11):4273–80.

8. Araki E, Goto A, Kondo T, et al. Japanese clinical practice guideline for diabetes 2019. Diabetol Int. 2020;11(3):165–223.

9. American Diabetes Association. 9. Pharmacologic approaches to glycemic treatment: *Standards of Medical Care in Diabetes—2021*. Diabetes Care. 2021;44(Suppl 1):S111–S24.

10. Levin PA, Nguyen H, Wittbrodt ET, Kim SC. Glucagon-like peptide-1 receptor agonists: a systematic review of comparative effectiveness research. Diabetes Metab Syndr Obes. 2017;10:123–39.

11. Seino Y, Takami A, Boka G, Niemoeller E, Raccah D, on behalf of the PDY6797 Investigators. Pharmacodynamics of the glucagon-like peptide-1 receptor agonist lixisenatide in Japanese and Caucasian patients with type 2 diabetes mellitus poorly controlled on sulphonylureas with/without metformin. Diabetes Obes Metab. 2014;16(8):739–47.

12. Kim YG, Hahn S, Oh TJ, Park KS, Cho YM. Differences in the HbA1c-lowering efficacy of glucagon-like peptide-1 analogues between Asians and non-Asians: a systematic review and meta-analysis. Diabetes Obes Metab. 2014;16(10):900–9.

13. Japanese Diabetes Clinical Data Management Study Group. Fundamental statistics on diabetes in Japan 2019. 2020. http://jddm.jp/. Accessed May 13, 2021.

14. Rosenstock J, Guerci B, Hanefeld M, et al. Prandial options to advance basal insulin glargine therapy: testing lixisenatide plus basal insulin versus insulin glulisine either as basal-plus or basal-bolus in type 2 diabetes: the GetGoal Duo-2 trial. Diabetes Care. 2016;39(8):1318–28.

15. Rosenstock J, Raccah D, Koranyi L, et al. Efficacy and safety of lixisenatide once daily versus exenatide twice daily in type 2 diabetes inadequately controlled on metformin: a 24-week, randomized, open-label, active-controlled study (GetGoal-X). Diabetes Care. 2013;36(10):2945–51.

16. Fonseca VA, Alvarado-Ruiz R, Raccah D, et al. Efficacy and safety of the once-daily GLP-1 receptor agonist lixisenatide in monotherapy: a randomized, double-blind, placebo-controlled trial in patients with type 2 diabetes (GetGoal-Mono). Diabetes Care. 2012;35(6):1225–31.

17. Bolli GB, Munteanu M, Dotsenko S, et al. Efficacy and safety of lixisenatide once daily vs. placebo in people with Type 2 diabetes insufficiently controlled on metformin (GetGoal-F1). Diabetes Med. 2014;31(2):176–84.

18. Ahrén B, Leguizamo Dimas A, Miossec P, Saubadu S, Aronson R. Efficacy and safety of lixisenatide once-daily morning or evening injections in type 2 diabetes inadequately controlled on metformin (GetGoal-M). Diabetes Care. 2013;36(9):2543–50.

19. Yu Pan C, Han P, Liu X, et al. Lixisenatide treatment improves glycaemic control in Asian patients with type 2 diabetes mellitus inadequately controlled on metformin with or without sulfonylurea: a randomized, double-blind, placebo-controlled, 24-week trial (GetGoal-M-Asia). Diabetes Metab Res Rev. 2014;30(8):726–35.

20. Pinget M, Goldenberg R, Niemoeller E, Muehlen-Bartmer I, Guo H, Aronson R. Efficacy and safety of lixisenatide once daily versus placebo in type 2 diabetes insufficiently controlled on pioglitazone (GetGoal-P). Diabetes Obes Metab. 2013;15(11):1000–7.

21. Rosenstock J, Hanefeld M, Shamanna P, et al. Beneficial effects of once-daily lixisenatide on overall and postprandial glycemic levels without significant excess of hypoglycemia in type 2 diabetes inadequately controlled on a sulfonylurea with or without metformin (GetGoal-S). J Diabetes Complicat. 2014;28(3):386–92.

22. Riddle MC, Forst T, Aronson R, et al. Adding once-daily lixisenatide for type 2 diabetes inadequately controlled with newly initiated and continuously titrated basal insulin glargine: a 24-week, randomized, placebo-controlled study (GetGoal-Duo 1). Diabetes Care. 2013;36(9):2497–503.

23. Riddle MC, Aronson R, Home P, et al. Adding once-daily lixisenatide for type 2 diabetes inadequately controlled by established basal insulin: a 24-week, randomized, placebo-controlled comparison (GetGoal-L). Diabetes Care. 2013;36(9):2489–96.

24. Seino Y, Min KW, Niemoeller E, Takami A, on behalf of the EFC10887 GETGOAL-L Asia Study Investigators. Randomized, double-blind, placebo-controlled trial of the once-daily GLP-1 receptor agonist lixisenatide in Asian patients with type 2 diabetes insufficiently controlled on basal insulin with or without a sulfonylurea (GetGoal-L-Asia). Diabetes Obes Metab. 2012;14(10):910–7.

25. Onishi Y, Niemoeller E, Ikeda Y, Takagi H, Yabe D, Seino Y. Efficacy and safety of lixisenatide in Japanese patients with type 2 diabetes mellitus inadequately controlled by sulfonylurea with or without metformin: subanalysis of GetGoal-S. J Diabetes Investig. 2015;6(2):201–9.

26. Seino H, Onishi Y, Naito Y, Komatsu M. Lixisenatide improves glycemic outcomes of Japanese patients with type 2 diabetes: a meta-analysis. Diabetol Metab Syndr. 2016;8:36.

27. Seino Y, Ikeda Y, Niemoeller E, et al. Efficacy and safety of lixisenatide in Japanese patients with type 2 diabetes insufficiently controlled with basal insulin ± sulfonylurea: a subanalysis of the GetGoal-L-Asia study. Horm Metab Res. 2015;47(12):895–900.

28. Seino Y, Stjepanovic A, Takami A, Takagi H, on behalf of the study investigators. Safety, tolerability and efficacy of lixisenatide in combination with oral antidiabetic treatment in Japanese patients with type 2 diabetes: An open-label, multicenter study. J Diabetes Investig. 2018;9(1):127–36.

29. Seino Y, Terauchi Y, Wang X, Watanabe D, Niemoeller E, on behalf of the study investigators. Safety, tolerability and efficacy of lixisenatide as monotherapy in Japanese patients with type 2 diabetes mellitus: an open-label, multicenter study. J Diabetes Investig. 2018;9(1):108–18.

30. Seino Y, Yabe D, Takami A, Niemoeller E, Takagi H. Long-term safety of once-daily lixisenatide in Japanese patients with type 2 diabetes mellitus: GetGoal-Mono-Japan. J Diabetes Complicat. 2015;29(8):1304–9.

31. Sanofi Diabetes. Lyxumia® is first diabetes therapy of its class approved in Japan for use in combination with basal insulin. 2013. https://www.prnewswire.com/in/news-releases/lyxumia-is-first-diabetes-therapy-of-its-class-approved-in-japan-for-use-in-combination-with-basal-insulin-213472681.html. Accessed May 13, 2021.

32. Sanofi. Lyxumia prescribing information (in Japanese). 2021. https://www.info.pmda.go.jp/go/pack/2499415G1024_1_08/?view=frame&style=XML&lang=ja. Accessed September, 13, 2021.

33. Tanaka S, Tanaka S, Iimuro S, et al. Cohort profile: The Japan diabetes complications study: a long-term follow-up of a randomised lifestyle intervention study of type 2 diabetes. Int J Epidemiol. 2014;43(4):1054–62.

34. Egan AG, Blind E, Dunder K, et al. Pancreatic safety of incretin-based drugs–FDA and EMA assessment. N Engl J Med. 2014;370(9):794–7.

35. Nauck MA, Quast DR, Wefers J, Meier JJ. GLP-1 receptor agonists in the treatment of type 2 diabetes - state-of-the-art. Mol Metab. 2021;46:101102.

36. Brath H, Abrahamian H, Karuza T, Mihaljevic R, Pfohl M. Austrian experience with lixisenatide under real-life conditions: a prospective observational study. Diabetes Ther. 2019;10(2):451–62.

37. Temelkova N, Vladeva S, Delchev A, et al. Real-world effectiveness and safety of lixisenatide as add-on to oral antidiabetic drugs as part of routine clinical practice in Bulgaria: LIXODAR study. Diabetes Ther. 2019;10(3):981–93.

38. Haluzík M, Adamíková A, Běhunčík M, Macko M, Štěpánova R. Effectiveness and safety of lixisenatide for treatment of diabetes in the real world: data from the monitoring registry in a real-life cohort in the Czech and Slovak Republic. Vnitr Lek. 2018;64(4):357–66.

39. Leon N, LaCoursiere R, Yarosh D, Patel RS. Lixisenatide (Adlyxin): a once-daily incretin mimetic injection for type-2 diabetes. P T. 2017;42(11):676–711.

40. Bodmer M, Meier C, Krähenbühl S, Jick SS, Meier CR. Metformin, sulfonylureas, or other antidiabetes drugs and the risk of lactic acidosis or hypoglycemia: a nested case-control analysis. Diabetes Care. 2008;31(11):2086–91.

41. Watada H, Takami A, Spranger R, Amano A, Hashimoto Y, Niemoeller E. Efficacy and safety of 1:1 fixed-ratio combination of insulin glargine and lixisenatide versus lixisenatide in Japanese patients with type 2 diabetes inadequately controlled on oral antidiabetic drugs: the LixiLan JP-O1 randomized clinical trial. Diabetes Care. 2020;43(6):1249–57.

42. Fujihara K, Sone H. Cardiovascular disease in Japanese patients with type 2 diabetes mellitus. Ann Vasc Dis. 2018;11(1):2–14.

43. Offurum A, Wagner LA, Gooden T. Adverse safety events in patients with chronic kidney disease (CKD). Expert Opin Drug Saf. 2016;15(12):1597–607.

44. Papazafiropoulou A, Melidonis A. Antidiabetic agents in patients with hepatic impairment. World J Meta-Anal. 2019;7(8):380–8.

45. Peron EP, Ogbonna KC, Donohoe KL. Antidiabetic medications and polypharmacy. Clin Geriatr Med. 2015;31(1):17–27, vii.

46. Kohro T, Yamazaki T, Sato H, et al. Trends in antidiabetic prescription patterns in Japan from 2005 to 2011: impact of the introduction of dipeptidyl peptidase-4 inhibitors. Int Heart J. 2013;54(2):93–7.

47. Morita Y, Murayama H, Odawara M, Bauer M. Treatment patterns of drug-naive patients with type 2 diabetes mellitus: a retrospective cohort study using a Japanese hospital database. Diabetol Metab Syndr. 2019;11:90.

48. Nishimura R, Kato H, Kisanuki K, *et al.* Treatment patterns, persistence and adherence rates in patients with type 2 diabetes mellitus in Japan: a claims-based cohort study. BMJ Open. 2019;9(3):e025806.

49. Carls GS, Tuttle E, Tan RD, et al. Understanding the gap between efficacy in randomized controlled trials and effectiveness in real-world use of GLP-1 RA and DPP-4 therapies in patients with type 2 diabetes. Diabetes Care. 2017;40(11):1469–78.

50. Chan WB, Luk A, Chow WS, Yeung VTF. What next after basal insulin? Treatment intensification with lixisenatide in Asian patients with type 2 diabetes mellitus. J Diabetes. 2017;9(6):562–74.

51. Wang JS, Tu ST, Lee IT, et al. Contribution of postprandial glucose to excess hyperglycaemia in Asian type 2 diabetic patients using continuous glucose monitoring. Diabetes Metab Res Rev. 2011;27(1):79–84.

52. Miyazawa I, Kadota A, Miura K, et al. Twelve-year trends of increasing overweight and obesity in patients with diabetes: the Shiga Diabetes Clinical Survey. Endocr J. 2018;65(5):527–36.