

# Safety, tolerability and efficacy of lixisenatide as monotherapy in Japanese patients with type 2 diabetes mellitus: An open-label, multicenter study

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## Keywords

Glucagon-like peptide-1 receptor agonist, Japanese patients, Lixisenatide monotherapy

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## ABSTRACT

**Aim/Introduction:** To assess the overall safety of lixisenatide monotherapy in Japanese patients with type 2 diabetes mellitus.

**Materials and Methods:** Patients with type 2 diabetes mellitus, previously treated with  $\leq 1$  oral antidiabetic drug, were enrolled in an uncontrolled, open-label, single-arm study over 24 and 52 weeks. Any oral antidiabetic drug treatment was stopped at the start of the 6-week run-in period. From baseline, patients received once-daily lixisenatide monotherapy (10  $\mu\text{g}$  for 1 week, 15  $\mu\text{g}$  for 1 week, 20  $\mu\text{g}$  thereafter) for 52 weeks (first 140 patients enrolled) or 24 weeks (subsequently enrolled patients). The primary end-point was safety over 24 and 52 weeks. Secondary efficacy end-points included absolute change in glycated hemoglobin, fasting plasma glucose and bodyweight from baseline.

**Results:** Of 428 patients screened, 361 and 140 were treated for 24 and 52 weeks, respectively; 88.4 and 90.0% completed treatment. During the 24- and 52-week treatment periods, 268/361 (74.2%) and 117/140 (83.6%) patients, respectively, had treatment-emergent adverse events; the most frequently reported was nausea (33.2 and 31.4%, respectively). The risk of severe hypoglycemia was low; only one case was reported. Lixisenatide treatment resulted in a decrease in mean glycated hemoglobin A1c ( $-0.98$  and  $-0.86\%$ ), fasting plasma glucose ( $-1.05$  and  $-0.85$  mmol/L), and bodyweight ( $-1.33$  and  $-1.48$  kg) for the 24- and 52-week treatment periods, respectively.

**Conclusions:** Once-daily lixisenatide monotherapy was associated with a safety profile in line with the glucagon-like peptide-1 receptor agonist class, and improved glycemic control in Japanese patients with type 2 diabetes mellitus.

## INTRODUCTION

In the past two decades, the prevalence of diabetes mellitus has increased to epidemic proportions worldwide, with the number of affected individuals set to rise further, from an estimated 415 million in 2015 to 642 million in 2040<sup>1</sup>. In high-income countries, the majority (approximately 87–91%) of people who have

diabetes mellitus are estimated to have type 2 diabetes mellitus<sup>1</sup>. The 2012 Japanese National Health and Nutrition Survey showed that approximately 9.5 million people could be classed into the ‘strong suspicion of diabetes mellitus (glycated hemoglobin [HbA1c]:  $\geq 6.5\%$  [National Glycohemoglobin Standardization Program] or  $\geq 6.1\%$  [Japan Diabetes Society (JDS)])’ category, whereas for an estimated 11.0 million individuals, the possibility of having diabetes mellitus could not be denied (HbA1c  $\geq 6.0$  and  $< 6.5\%$  [National Glycohemoglobin Standardization Program] or  $\geq 5.6$  and  $< 6.1\%$  [JDS])<sup>2</sup>. Estimates from

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2013 suggest that 7.6% of the Japanese population have type 2 diabetes mellitus<sup>3</sup>. Hence, type 2 diabetes mellitus is considered a healthcare priority by the Japanese Ministry of Health, Labor and Welfare<sup>4</sup>.

Treatment of type 2 diabetes mellitus focuses on lowering blood glucose levels through exercise, diet, and medication if exercise and diet alone do not result in adequate improvement; the goal of type 2 diabetes mellitus therapy is prevention of microvascular complications and management of atherosclerotic cardiovascular disease with a patient-centered approach<sup>5,6</sup>. The JDS recommends HbA1c target levels below 7% for glycemic control to prevent complications in patients with type 2 diabetes mellitus<sup>7</sup>. Although there are numerous classes of glucose-lowering agents with beneficial treatment effects, common disadvantages noted in several classes include the risk of hypoglycemia (insulins, sulfonylureas [SUs], meglitinides and amylin mimetics [unless insulin dose is simultaneously reduced]), modest HbA1c efficacy (alpha-glucosidase inhibitors, bile acid sequestrants, dopamine-2-agonists and amylin mimetics), gastrointestinal side-effects (biguanides, alpha-glucosidase inhibitors, glucagon-like peptide-1 receptor agonists [GLP-1 RAs] and amylin mimetics), weight gain, (insulins, SUs, meglitinides and thiazolidinediones) and increased low-density lipoprotein (thiazolidinediones and sodium–glucose cotransporter 2 inhibitors)<sup>6,8</sup>.

GLP-1 RAs represent an incretin-based therapy that lowers plasma glucose, and has become an established treatment option for type 2 diabetes mellitus<sup>9</sup>. Benefits of GLP-1 RAs include reduction of HbA1c with a low risk of hypoglycemia, as well as additional effects that vary depending on the specific GLP-1 RA, including delay of gastric emptying, increased satiety and weight loss<sup>10</sup>. GLP-1 RA monotherapy is recommended by the JDS as a treatment option for patients with type 2 diabetes mellitus when initial diet, exercise and lifestyle changes do not result in adequate improvement<sup>7</sup>.

Lixisenatide (Lyxumia<sup>®</sup>, Adlyxin<sup>®</sup>; Sanofi, Paris, France) is a once-daily (QD), prandial, short-acting GLP-1 RA that has been evaluated extensively in the large, phase 3 GetGoal clinical trial program carried out in approximately 50 countries including Japan<sup>11–21</sup>. Treatment with lixisenatide monotherapy in patients with type 2 diabetes mellitus has shown improved glycemic control with reduced HbA1c, postprandial plasma glucose, fasting plasma glucose (FPG) and bodyweight, and has been shown to be well tolerated<sup>11–13</sup>. Lixisenatide has also shown improved glycemic control as an add-on treatment (including basal insulin with or without SU, metformin, metformin with or without SU, pioglitazone with or without metformin, and SU with or without metformin)<sup>12,14–19</sup>. More specifically, subanalyses of two randomized, placebo-controlled studies in patients with type 2 diabetes mellitus, GetGoal-S<sup>12</sup> (lixisenatide add-on to SU with or without metformin) and GetGoal-L-Asia (lixisenatide add-on to basal insulin with or without SU)<sup>14</sup>, showed that lixisenatide treatment provided glycemic control (decreased HbA1c, FPG and postprandial plasma

glucose), and was well tolerated in the Japanese subpopulation<sup>22,23</sup>.

Lixisenatide was approved in Japan in June 2013 for the treatment of adults with type 2 diabetes mellitus when the use of SU (with and without biguanide) or intermediate- or long-acting insulin (with and without SU), both in combination with diet and exercise, had not provided adequate glycemic control<sup>24,25</sup>. The purpose of the current study was to complement the lixisenatide development program in Japan by evaluating the safety of lixisenatide over 52 weeks in addition to the already existing efficacy evaluation of lixisenatide monotherapy treatment in patients with type 2 diabetes mellitus. The Japanese 'Guideline for Clinical Evaluation of Oral Hypoglycemic Agents' released in 2010 by the Japanese Ministry of Health, Labor and Welfare describes the required phase 1, 2 and 3 clinical studies. The current study aimed to satisfy the requirement for an open-label, long-term (1 year), phase 3 study to be carried out with the investigational drug as monotherapy treatment to evaluate its safety as a primary end-point, and efficacy as a secondary endpoint (section 3-1-2 of the guideline)<sup>26</sup>. Although the guideline specifies oral hypoglycemic agents, the corresponding question and answer document for the guideline indicates that the development of injectable medicinal products to treat diabetes mellitus (such as GLP-1 RAs) are also required to follow the guideline (except for insulin)<sup>27</sup>.

Thus, the primary objective of the present open-label study was to assess the overall safety of once-daily lixisenatide monotherapy over 24 and 52 weeks in Japanese patients with type 2 diabetes mellitus. Secondary objectives included assessment of the effects of lixisenatide on HbA1c reduction, FPG and bodyweight, as well as the proportion of patients requiring rescue therapy.

## METHODS

### Trial design

This was a multicenter, uncontrolled, open-label, single-arm, phase 3, 24- and 52-week study (NCT01960179) in Japanese outpatients with type 2 diabetes mellitus. The study was initiated on 16 November 2013, and the last patient completed the study on 12 March 2015; the study consisted of four periods: (i) a screening period of up to 2 weeks; (ii) a 6-week run-in period (for patients who were previously treated with an oral antidiabetic drug [OAD] or those who had not had at least 6 weeks of diet and lifestyle counseling); (iii) a 24- or 52-week open-label treatment period according to treatment group; and (iv) a 3-day post-treatment follow-up period (Figure 1). The first 140 enrolled patients (group 1) were treated with lixisenatide monotherapy for 52 weeks. The subsequent enrolled patients (group 2) were treated with lixisenatide monotherapy for 24 weeks.

The protocol, consent form, and written patient information were reviewed and approved by institutional review boards before the study initiation. The study was carried out in accordance with the recommendations of the Declaration of

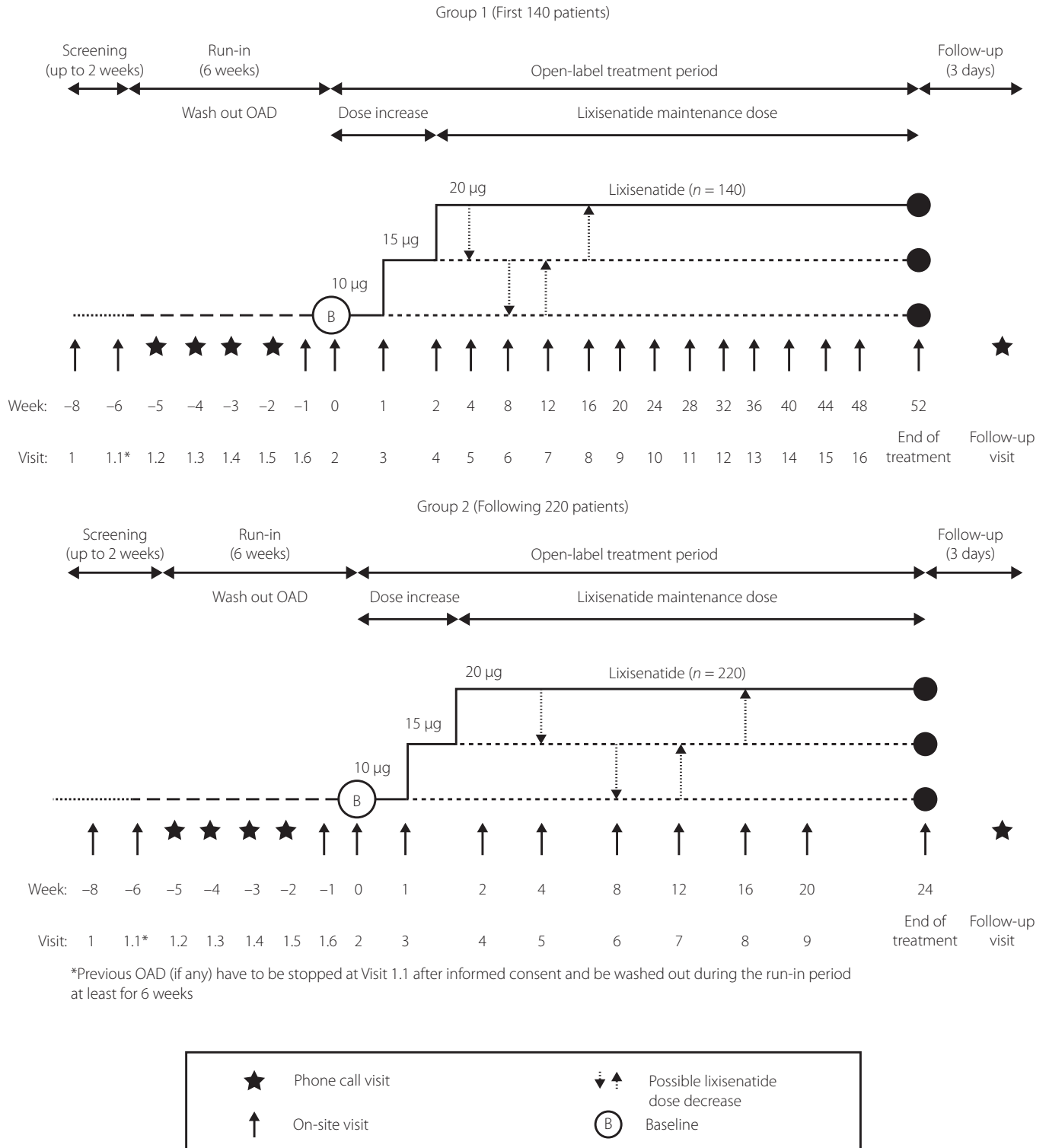


Figure 1 | Study design. OAD, oral antidiabetic drug.

Helsinki, Good Clinical Practice, and also complied with the laws, regulations and any applicable guidelines from Japan; for example, Japanese Ministry of Health, Labor and Welfare.

Adjudication committees, independent of the sponsor and the investigators, were responsible for reviewing and adjudicating the cardiovascular events (Cardiovascular Events Adjudication

Committee), allergic or allergic-like reactions (Allergic Reaction Assessment Committee) and pancreatic events (Pancreas Safety Assessment Committee).

### Trial population

Eligible patients were diagnosed with type 2 diabetes mellitus for at least 2 months, and were either naïve to antidiabetic drugs or had been treated with a stable dose of one OAD for at least 3 months before screening. The previous OAD (if any) had to be stopped at the first visit of the run-in period, and was to be washed out during the run-in period.

Key exclusion criteria at screening included patients aged <20 years, HbA1c <7 or >9.5% (if patients were not receiving an OAD treatment), or HbA1c <6.5 or >8.5% (if patients were treated with an OAD), FPG >13.9 mmol/L (>250 mg/dL), or if they had a weight change of >5 kg during the 3 months preceding the screening visit or initiation of weight loss drugs in the 3 months before screening. Patients were also excluded if they used more than one OAD or insulin within 3 months before screening (short-time use [ $\leq 10$  days] of insulin because of acute illness or surgery was allowed), thiazolidinediones within 6 months before screening, or if they previously used any GLP-1 RA.

Additional exclusion criteria included a history of gastrointestinal disease associated with prolonged nausea and vomiting, and uncontrolled gastroesophageal reflux disease (within 6 months before screening), and acute or chronic pancreatitis, pancreatectomy, stomach/gastric surgery, inflammatory bowel disease or history (including immediate family) of medullary thyroid cancer or genetic conditions that predispose to medullary thyroid cancer. Patients with severe renal impairment (estimated glomerular filtration rate of <30 mL/min/1.73 m<sup>2</sup>) and/or who were receiving dialysis treatment were also excluded. Laboratory findings requiring patient exclusion included amylase and/or lipase >3-fold the upper limit of the normal laboratory range (ULN), alanine aminotransferase >3-fold the ULN, total bilirubin >1.5-fold the ULN (except in the case of Gilbert's syndrome) and calcitonin  $\geq 5.9$  pmol/L ( $\geq 20$  pg/mL).

At the end of the run-in period, patients were excluded if at the last visit before treatment allocation HbA1c was <7 or >9.5%, or if amylase and/or lipase levels measured >3-fold the ULN.

### Interventions

All patients enrolled in the present open-label study were treated with lixisenatide, which they self-administered as a subcutaneous injection QD in the morning within 1 h before breakfast using a reusable self-injector device. Lifestyle and diet therapy provided before the time of screening were continued during the study in a similar manner. After baseline assessments on day 1 (week 0), lixisenatide treatment was initiated with 10  $\mu$ g QD injections for 1 week, then increased to 15  $\mu$ g QD injections for 1 week, followed by the maintenance dose of 20  $\mu$ g QD injections from week 2 (visit 4) onwards until the end of

the treatment period. If the target maintenance dose of 20  $\mu$ g QD was not tolerated, it could be reduced to 15  $\mu$ g and, if necessary, to 10  $\mu$ g. A further attempt at a dose increase took place within 4 weeks; if the patient could not reach or tolerate the target dose, they remained at 15 or 10  $\mu$ g QD.

Rescue therapy was initiated after three consecutive fasting self-monitored plasma glucose values above threshold values (which depended on the study period), and were confirmed by a central laboratory FPG value (and HbA1c after week 12) above threshold (Table S2). If reasonable explanations could not be found for insufficient glycemic control or if appropriate action failed to decrease FPG/HbA1c under threshold values, the patient could start rescue therapy according to investigator decision (no other incretin-based therapy was allowed).

### Study end-points

The primary end-point was safety over 24 and 52 weeks, and was assessed by treatment-emergent adverse events (TEAEs) and serious TEAEs (including symptomatic hypoglycemia), local tolerability at the injection site, allergic reactions (assessed by the Allergic Reaction Assessment Committee), pancreatic events (assessed by the Pancreas Safety Assessment Committee), cardiovascular events (assessed by the Cardiovascular Events Adjudication Committee), vital signs, 12-lead electrocardiogram, and laboratory safety parameters (hematology, clinical chemistry, lipid parameters, serum amylase and lipase, and serum calcitonin).

Symptomatic hypoglycemia was defined as an event with clinical symptoms that was considered to result from a hypoglycemic episode with either an accompanying plasma glucose <3.3 mmol/L (<60 mg/dL), or associated with prompt recovery after oral carbohydrate, intravenous glucose or glucagon administration if no plasma glucose measurement was available. Severe hypoglycemia was defined as an event with clinical symptoms that were considered to result from hypoglycemia in which the patient required the assistance of another person, because the patient could not treat themselves due to acute neurological impairment directly resulting from the hypoglycemic event, and one of the following: the event was associated with a plasma glucose level <2.0 mmol/L (36 mg/dL); if no plasma glucose measurement was available, then the event was associated with prompt recovery after oral carbohydrate, intravenous glucose or glucagon administration.

Secondary efficacy end-points were evaluated at week 24 (groups 1 and 2) and week 52 (group 1), and included the absolute change in HbA1c from baseline, percentage of patients achieving HbA1c <7 and  $\leq 6.5\%$ , absolute change in FPG from baseline, absolute change in bodyweight from baseline, and percentage of patients requiring rescue therapy.

### Statistical analysis

Following the 'Guideline for Clinical Evaluation of Oral Hypoglycemic Agents' in Japan, stating that at least 300 patients should be treated for 6 months or more and at least

100 patients should be treated for 52 weeks, 360 patients were considered as necessary to be enrolled for at least 2 weeks of treatment<sup>26</sup>. The safety population was defined as all patients enrolled (through the interactive web response system) who were exposed to at least one dose of lixisenatide. The efficacy population was the modified intention-to-treat population, defined as all randomized patients who were exposed to at least one dose of lixisenatide and had both a baseline, and at least one post-baseline, assessment of any efficacy end-points.

Analyses for the 24-week treatment period were combined for groups 1 and 2; analyses for the 52-week period were carried out for group 1. Continuous data were summarized by descriptive statistics. Categorical data were summarized with counts and percentages; missing data were not categorized. No formal statistical comparisons were carried out for efficacy variables; end-points were evaluated by descriptive statistics only.

## RESULTS

### Patient disposition and baseline characteristics

A total of 428 patients were screened, and 361 patients (groups 1 and 2 combined) were enrolled from 30 centers in Japan and treated with lixisenatide (Figure 2). In the 24-week treatment period (groups 1 and 2), 361 patients were enrolled and exposed to lixisenatide; 11.6% of patients permanently discontinued lixisenatide mainly due to an adverse event (9.7%), predominantly nausea. In the 52-week treatment period (group 1 only), 140 patients were enrolled and exposed to lixisenatide; 10.0% of patients permanently discontinued, again

mainly due to an adverse event (8.6%), predominantly nausea. Maintenance dose was reached during the dose-titration period, by 87.3 and 87.9% of patients in the 24- and 52-week treatment periods, respectively, with 77.0 and 78.6% of patients on the maintenance dose level at the end of the treatment periods. No patients were excluded from the modified intention-to-treat population. One patient, in the 24-week treatment period, was discontinued from the study due to simultaneous participation in another GLP-1 RA clinical trial.

The demographic and disease characteristics were generally typical of a population with type 2 diabetes mellitus (Table 1). The mean age of patients was 59 years, and approximately one-third of patients were aged  $\geq 65$  years at study entry. Unexpectedly, the majority of patients (approximately three-quarters) were men. The mean (standard deviation) baseline HbA1c was 7.81% (0.61) for the 24-week treatment group, and 7.78% (0.58) for the 52-week treatment group. At screening, 26.3% of patients in the 24-week treatment group and 8.6% of patients in the 52-week treatment group were on an OAD; the most common OAD was dipeptidyl peptidase-4 inhibitor.

### Primary end-points: Safety

An overview of primary safety end-points by treatment period (24 and 52 weeks) is shown in Table 2. On the whole, safety and tolerability data were consistent with the established safety profile of lixisenatide. During the 24- and 52-week treatment periods, 74.2 and 83.6% of patients reported at least one TEAE, which were mostly mild in severity. The most frequently

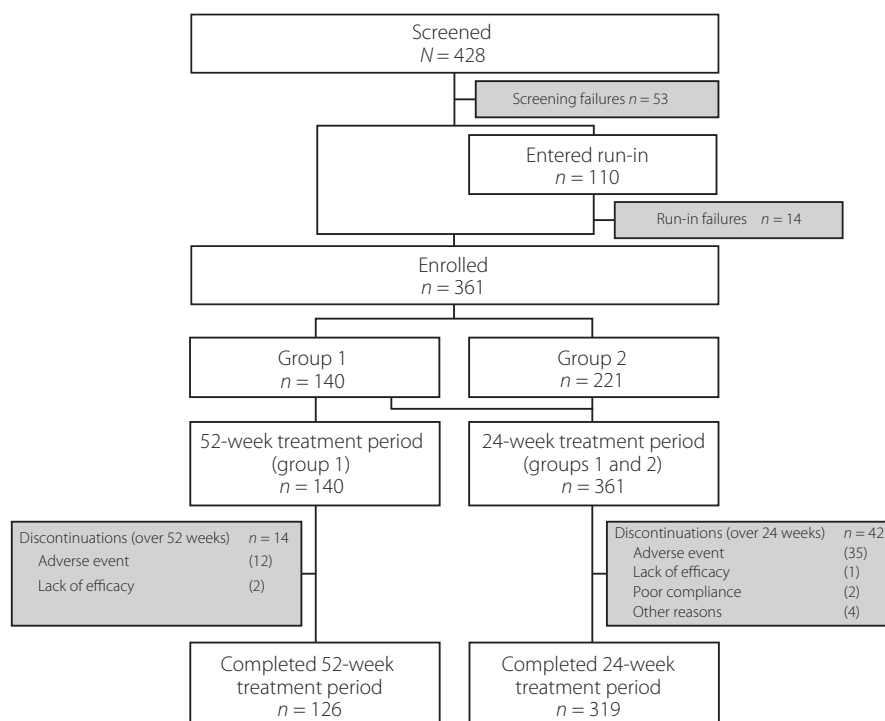


Figure 2 | Patient disposition.

**Table 1** | Baseline or screening demographics and disease characteristics – safety population

Parameter	24-week treatment (groups 1 and 2) (n = 361)	52-week treatment (group 1) (n = 140)
Age (years)	58.7 (10.2)	58.4 (10.6)
Age group, n (%)		
<65 years	240 (66.5)	93 (66.4)
≥65 years	121 (33.5)	47 (33.6)
Male, n (%)	276 (76.5)	105 (75.0)
Duration of type 2 diabetes mellitus at screening, years	5.83 (5.07)	5.71 (5.42)
Baseline weight (kg)	68.76 (12.75)	69.51 (13.37)
Baseline BMI (kg/m <sup>2</sup> )	25.11 (3.87)	25.32 (4.03)
Baseline HbA1c (%)	7.81 (0.61)	7.78 (0.58)
Baseline FPG (mmol/L)	8.42 (1.43)	8.31 (1.29)
Patients using OAD at screening <sup>†</sup> , n (%)	95 (26.3)	12 (8.6)
Biguanide	20 (21.1)	5 (41.7)
Thiazolidinedione	0	0
Alpha-glucosidase inhibitor	10 (10.5)	3 (25.0)
Glinide	3 (3.2)	0
Sulfonylurea	8 (8.4)	1 (8.3)
DPP-4 inhibitor	53 (55.8)	3 (25.0)
Other <sup>‡</sup>	1 (1.1)	0

Data are mean (standard deviation) unless otherwise stated. <sup>†</sup>Patients stopped oral antidiabetic drug (OAD) treatment at screening and participated in a 6-week run-in period before starting treatment. <sup>‡</sup>Included Tokaijo (herbal extract for diabetes). BMI, body mass index; DPP-4, dipeptidyl peptidase 4; FPG, fasting plasma glucose; HbA1c, glycated hemoglobin; SD, standard deviation.

**Table 2** | Treatment-emergent adverse event occurring in ≥5% of patients during the 24- and 52-week treatment periods – safety population

	24-week treatment (groups 1 and 2) (n = 361)	52-week treatment (group 1) (n = 140)
Patients with TEAEs		
Any TEAE	268 (74.2)	117 (83.6)
Any serious TEAE	7 (1.9)	7 (5.0)
Any TEAE leading to death	0	0
Any TEAE leading to permanent treatment discontinuation	34 (9.4)	11 (7.9)
AE by SOC/PT		
Infections and infestations		
Nasopharyngitis	60 (16.6)	44 (31.4)
Discontinuation due to nasopharyngitis	0	0
Gastrointestinal disorders		
Diarrhea	17 (4.7)	7 (5.0)
Discontinuation due to diarrhea	0	0
Constipation	28 (7.8)	8 (5.7)
Discontinuation due to constipation	0	0
Abdominal discomfort	25 (6.9)	8 (5.7)
Discontinuation due to abdominal discomfort	0	0
Nausea	120 (33.2)	44 (31.4)
Discontinuation due to nausea	21 (5.8)	5 (3.6)
Vomiting	29 (8.0)	16 (11.4)
Discontinuation due to vomiting	3 (0.8)	1 (0.7)
Symptomatic hypoglycemia		
Confirmed by blood glucose <3.3 mmol/L		
Patients with events, n (%)	3 (0.8)	1 (0.7)
No. events per 100 patient-years <sup>†</sup>	1.9	0.8

Data are n (%). <sup>†</sup>Calculated as (number of events × 100, divided by total exposure + 3 days in patient-years). AE, adverse event; PT, preferred term; SOC, system organ class; TEAE, treatment-emergent adverse event.



reported TEAEs ( $\geq 5\%$  of patients) during both treatment periods, were nausea (33.2 and 31.4%), nasopharyngitis (16.6 and 31.4%), vomiting (8.0 and 11.4%), constipation (7.8 and 5.7%), abdominal discomfort (6.9 and 5.7%), and diarrhea (4.7 and 5.0%) for 24 and 52 weeks, respectively (Table 2). Nausea, the most common TEAE, was mostly mild and occurred during the initial weeks of treatment (Figure S1), with some events leading to treatment discontinuation. TEAEs classed as being related to treatment with lixisenatide were reported for 54.8 and 55.0% of patients in the 24- and 52-week treatment periods, respectively. The most frequently reported TEAEs related to lixisenatide treatment during both treatment periods were nausea, vomiting, abdominal discomfort and constipation (data not shown).

The number of patients with serious TEAEs was low (24 weeks: 1.9%; 52 weeks: 5.0%). Of these, only one serious TEAE (hypoglycemic unconsciousness [classed as severe hypoglycemia]), reported by a patient during the first 24 weeks, was judged as being related to lixisenatide treatment. The hypoglycemic unconsciousness event (approximately 5 min in length) occurred during alcohol consumption after a skipped meal, with symptoms resolving without sequela on the same day. The lixisenatide dose was decreased in response to the event, and the patient completed the 52-week treatment period without further TEAEs or hypoglycemic events. No deaths were reported during the study. Less than 10% of patients during each treatment period permanently discontinued treatment as a result of a TEAE.

Injection-site reactions, which were generally mild, were reported for 5.8 and 5.7% of patients during the 24- and 52-week treatment periods, respectively. Of the adjudicated

allergic-like and allergic reactions (1.1% at 24 weeks and 3.6% at 52 weeks), none were considered to be related to lixisenatide treatment.

Overall, no clinically meaningful changes during the 24- and 52-week treatment periods were seen in the hematological parameters, lipid parameters, pancreatic enzymes (no reported cases of pancreatitis or pancreatic neoplasms), renal function tests, liver function tests, calcitonin and electrolytes. There were no clinically meaningful changes in mean or median blood pressure or heart rate from baseline to the end of the 24- and 52-week treatment periods. The number of patients with a change to a clinically significant abnormal electrocardiogram status during treatment was low, and any corresponding reported adverse events were non-serious and considered not related to lixisenatide treatment.

### Symptomatic hypoglycemic events

The incidence of symptomatic hypoglycemia, confirmed by blood glucose measurement of  $<3.3$  mmol/L ( $<60$  mg/dL), was low in both treatment periods; three out of 361 patients reported three events during the 24-week treatment period, and one out of 140 patients reported one event during the 52-week treatment period (Table 2). As noted above, there was one reported case of hypoglycemic unconsciousness (classed as severe hypoglycemia) that occurred in the first 24 weeks of the study; this was captured as an event in both the 24- and 52-week treatment groups.

### Secondary end-points: Efficacy

Secondary efficacy end-points by treatment period (24 and 52 weeks) are shown in Table 3. The change in HbA1c from

**Table 3** | Response to treatment at weeks 24 and 52 (observed cases; modified intention-to-treat population)

Efficacy end-point	Week 24 (groups 1 and 2)		Week 52 (group 1)	
	<i>n</i>		<i>n</i>	
HbA1c (%)				
Baseline	361	7.81 [7.74, 7.87], (0.61)	140	7.78 [7.68, 7.87], (0.58)
End of treatment period	320	6.81 [6.74, 6.88], (0.64)	124	6.90 [6.78, 7.03], (0.68)
Change from baseline	320	-0.98 [-1.06, -0.90], (0.73)	124	-0.86 [-0.99, -0.73], (0.74)
Percentage of patients reaching HbA1c target (%)				
$\leq 6.5\%$	320	37.5	124	30.6
$< 7.0\%$	320	67.5	124	62.1
FPG (mmol/L)				
Baseline	361	8.42 [8.27, 8.57], (1.43)	140	8.31 [8.09, 8.52], (1.29)
End of treatment period	323	7.37 [7.24, 7.50], (1.22)	123	7.48 [7.27, 7.70], (1.21)
Change from baseline	323	-1.05 [-1.20, -0.91], (1.31)	123	-0.85 [-1.07, -0.62], (1.26)
Bodyweight (kg)				
Baseline	361	68.76 [67.44, 70.08], (12.75)	140	69.51 [67.27, 71.74], (13.37)
End of treatment period	320	68.21 [66.79, 69.62], (12.87)	124	68.74 [66.36, 71.13], (13.42)
Change from baseline	320	-1.33 [-1.56, -1.09], (2.14)	124	-1.48 [-1.92, -1.04], (2.48)

Data are mean [95% confidence interval], (SD) unless stated otherwise. FPG; fasting plasma glucose; HbA1c; glycated hemoglobin; mITT, modified intention-to-treat; SD, standard deviation.

baseline was  $-0.98\%$  (95% confidence interval  $-1.06, -0.90$ ) and  $-0.86\%$  (95% confidence interval  $-0.99, -0.73$ ) for the 24- and 52-week treatment periods, respectively, showing maintenance of glycemic control over 52 weeks. The HbA1c targets of  $\leq 6.5$  and  $< 7\%$  were achieved by 37.5 and 67.5% of patients at 24 weeks, and 30.6 and 62.1% of patients at 52 weeks, respectively. Both FPG and bodyweight also decreased during the treatment periods, as shown in Table 3. No patients required rescue therapy during the first 24 weeks of treatment, and two out of 140 patients required rescue therapy in the 52-week treatment period.

## DISCUSSION

Lixisenatide monotherapy was not associated with any specific safety concerns, and was well tolerated in Japanese patients with type 2 diabetes mellitus over both the 24- and 52-week treatment periods. The safety profile was consistent with observations in previous studies<sup>13</sup>. Lixisenatide monotherapy improved glycemic control assessed by change in HbA1c, FPG and bodyweight over 24 weeks, and this was maintained in the patient cohorts up to 52 weeks.

The safety profile was typical of the GLP-1 RA class, and most TEAEs were mild in intensity. The most common TEAE in both treatment periods was nausea, which was predominantly mild, and occurred during the initial weeks of treatment. Of the reported serious TEAEs, only a single case of severe hypoglycemia was considered by the investigator to be related to lixisenatide treatment (a hypoglycemic unconsciousness event that occurred during alcohol consumption after a skipped meal). Discontinuations were low, with  $< 10\%$  occurring during 52 weeks of treatment despite lixisenatide being a once-daily injected drug; most patients (more than 75%) were able to tolerate the maintenance dose at trial completion. The results reported here are in line with what has been shown previously in a similar study of lixisenatide monotherapy in a smaller population of Japanese patients<sup>13</sup>. In that study, the most common TEAE reported for the two-step lixisenatide treatment for the 24-week period was nausea (36.4%), and other common TEAEs included vomiting (12.1%) and diarrhea (3.0%). The incidence of nausea in the present study was consistent with these previous findings in Japanese patients, which suggested that treatment with lixisenatide results in a higher incidence of nausea in Asian populations compared with predominately Western populations<sup>11,13</sup>. No severe hypoglycemia events were reported.

Overall, glycemic control was maintained over 52 weeks; treatment with lixisenatide monotherapy resulted in a decrease in HbA1c, with approximately two-thirds of patients achieving the target level of  $< 7\%$ , a decrease in FPG ( $-1.05$  and  $-0.85$  mmol/L), and a bodyweight reduction ( $-1.33$  and  $-1.48$  kg) for both 24- and 52-week treatment periods. Just two patients required rescue therapy in the second half of the 52-week treatment period. The aforementioned smaller-scale lixisenatide monotherapy study in Japan also showed a similar decrease in HbA1c ( $-0.99\%$ ) and FPG ( $-1.16$  mmol/L), with 34.8% of patients achieving the HbA1c target level of  $< 7\%$  at

24 weeks; however, a smaller reduction in bodyweight ( $-0.43$  kg) was observed<sup>13</sup>.

Other than lixisenatide, exenatide is the only other GLP-1 RA that is available in a short-acting formulation. Exenatide has shown glycemic control, and an adequate safety profile in Japanese patients with type 2 diabetes mellitus with both its short-acting<sup>28–30</sup> and long-acting<sup>31,32</sup> formulations; however, no monotherapy trials in Japanese patients have been reported to date. Similar efficacy and safety to that reported here for lixisenatide have also been shown for liraglutide, a long-acting GLP-1 RA. In a monotherapy study in Japanese patients with type 2 diabetes mellitus who were defined as overweight or obese, liraglutide treatment (0.9 mg/day) at 24 weeks resulted in a decrease in HbA1c from 7.7 to 6.9% and a weight change (standard deviation) of  $-0.3$  kg (1.9). Furthermore, 59.1% of patients achieved the HbA1c target level of  $< 7\%$ , and there were no reported cases of severe hypoglycemia<sup>33</sup>. In another Japanese cohort study, liraglutide monotherapy (0.9 mg/day) was an effective treatment for patients with type 2 diabetes mellitus inadequately controlled by diet therapy and/or OADs: 24-week treatment with liraglutide monotherapy resulted in a decrease in HbA1c from 8.87 to 6.99%, and a 0.92-kg weight reduction with 49.0% of patients reaching the American Diabetes Association target level of  $< 7\%$ <sup>34</sup>. In a 52-week extension, liraglutide monotherapy treatment (0.9 mg/day) resulted in a decrease in HbA1c (calculated based on the National Glycohemoglobin Standardization Program HbA1c definition) from 9.3 to 7.8%, and a 0.8-kg weight reduction with 22.1% of patients reaching the JDS target level of  $< 6.9\%$ <sup>35</sup>. Although gastrointestinal TEAEs were also common in the liraglutide studies, the incidences and ranking of the most common gastrointestinal events differed from the current lixisenatide study; in particular, incidences of nausea and vomiting differed the most. The most common gastrointestinal TEAEs for the liraglutide studies were diarrhea (6.3%) and constipation (5.6%) for the 24-week period, and diarrhea (9.7%), constipation (8.2%), stomach discomfort (5.2%) and nausea (5.2%) for the 52-week period<sup>34,35</sup>. The incidence of nausea with liraglutide treatment was lower in Japanese patients compared with other study populations, and has been suggested to be as a result of the lower liraglutide dose used in the Japanese studies<sup>36</sup>. No incidences of major hypoglycemia (defined as any hypoglycemic episode that required third-party assistance) were reported for either treatment period<sup>34,35</sup>. Importantly, it should be noted that comparisons between trials should be interpreted with caution.

A limitation of the current study was its single-arm, uncontrolled design, which provided no comparative data; however, the primary objective of this study was to provide complementary safety information in a descriptive manner up to 52 weeks. Another possible limitation was that some patients were using OADs at the time of screening. Patients with previous OAD use are expected to have a smaller HbA1c reduction compared with those who are OAD naïve; thus, lixisenatide monotherapy might show a greater HbA1c reduction in an OAD-naïve population compared with that reported for the present study.



However, a 6-week run-in for washout was implemented, and only a relatively small proportion of patients (26.3 and 8.6% for the 24- and 52-week treatment periods, respectively) were taking OADs at the time of screening and, hence, participated in the run-in. Thus, the treatment population was considered appropriate for the aim of the study, which was to determine the overall safety of lixisenatide monotherapy in Japanese patients with type 2 diabetes mellitus.

These data suggest that lixisenatide is a valuable monotherapy option for the initial treatment of type 2 diabetes mellitus owing to its demonstrated glycemic control, associated weight loss, good tolerability, low hypoglycemic risk and acceptable safety profile, in line with its GLP-1 RA class. These attributes suggest that lixisenatide might help patients overcome some barriers that are common during the initiation of other types of antidiabetic medication. On the whole, these results support the use of lixisenatide as an effective, well-tolerated, initial antidiabetic treatment for type 2 diabetes mellitus in Japanese patients.

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### DISCLOSURE

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**SUPPORTING INFORMATION**

Additional Supporting Information may be found in the online version of this article:

**Figure S1** | Kaplan–Meier plot of time to first onset of nausea during (a) 24-week treatment period, and (b) 52-week treatment period (safety population).

**Table S1** | List of principal investigator(s) and sub-investigator(s) per study site where patients were enrolled.

**Table S2** | Rescue therapy threshold values.