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Long-term safety of once-daily lixisenatide in Japanese patients with type 2 diabetes mellitus: GetGoal-Mono-Japan

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ABSTRACT

Aims: This 76-week, open-label, parallel-group study assessed the long-term safety of once-daily lixisenatide monotherapy in Japanese patients with type 2 diabetes mellitus.
Methods: Patients were randomized to receive lixisenatide in a 2-step or a 1-step dose-increase regimen. The primary objective was to assess the safety of lixisenatide at week 24 by a descriptive comparison of the 2- and 1-step groups.
Results: As expected with treatment with a glucagon-like peptide-1 agonist, nausea was the most common treatment-emergent adverse event (2-step group: $n = 12/33$ [36.4%] vs 1-step group: $n = 18/36$ [50.0%] up to week 24). In total, 5/33 patients (15.2%; 2-step group) and 2/36 patients (5.6%; 1-step group) prematurely discontinued treatment up to week 24, mainly due to adverse events. Serious treatment-emergent adverse events occurred in 2/33 patients (6.1%; 2-step group) versus 0/36 patients (0%; 1-step group) up to week 24. Symptomatic hypoglycemia occurred in 2/33 patients (6.1%; 2-step group) versus 1/36 patients (2.8%; 1-step group) up to week 24, with no severe events reported. Glycated hemoglobin, fasting plasma glucose, and body weight were reduced from baseline at weeks 24 and 76.
Conclusion: In Japanese patients with type 2 diabetes mellitus, once-daily lixisenatide monotherapy was well tolerated, with less nausea with the 2-step regimen.

1. Introduction

The prevalence of diabetes is increasing both globally and in Japan. A total of 7.1 million people (7.5% of the population) were reported to have diabetes in Japan in 2012, which is estimated to increase to 10.2 million (12.0% of the population) by 2030 (International Diabetes Federation, 2013). This increase in Japan is attributed to rising obesity levels and a more sedentary lifestyle (Kawamori, 2002).

In addition to lifestyle interventions, patients with type 2 diabetes mellitus (T2DM) often require glucose-lowering agent(s) to maintain glycemic control. However, a number of treatment options currently available are associated with hypoglycemia (e.g. sulfonylureas, insulin, and meglitinides) and/or weight gain (e.g. sulfonylureas, insulin, meglitinides, and thiazolidinediones), which may play a major role in drug selection (Inzucchi et al., 2012; van Dieren et al., 2012). Glucagon-like peptide-1 (GLP-1) receptor agonists are glucose-lowering agents that stimulate insulin secretion in a glucose-dependent manner, suppress glucagon release, and delay gastric emptying, with a beneficial effect on body weight and a low risk of hypoglycemia (Drucker & Nauck, 2006; Meier, 2012; Shin, 2012). It has been suggested that these agents may also preserve β-cell function (Seino, Fukushima, & Yabe, 2010; Seino, Rasmussen, Clauson, & Kaku, 2012) and prevent diabetes-related complications (Seino & Yabe, 2013). GLP-1 receptor agonists may be particularly effective in Asian and Japanese patients, as there is evidence to suggest an underlying GLP-1 insufficiency in this patient population (Seino, Fukushima, & Yabe, 2010; Yabe et al., 2010; Yabe et al., 2012). Furthermore, β-cell dysfunction is considered to be the primary cause of T2DM in Japanese patients (Namba et al., 2013), which may be confounded by the GLP-1

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deficiency reported in these patients, as GLP-1 is associated with β-cell protection (Yabe & Seino, 2011).

Lixisenatide is a once-daily prandial GLP-1 receptor agonist for the treatment of T2DM, and has been approved in Japan for the treatment of T2DM insufficiently controlled on diet and exercise in combination with sulfonylurea with or without biguanide, or with basal insulin with or without sulfonylurea (Sanofi, 2013). Lixisenatide has been extensively evaluated in the phase III 'GetGoal' clinical trials program, in which it was shown to be efficacious and well tolerated in patients with T2DM (Ahren et al., 2013; Fonseca et al., 2012; Pinget et al., 2013; Riddle, Aronson, et al., 2013; Riddle, Forst, et al., 2013; Rosenstock et al., 2013; Seino, Min, Niemoeller, Takami, & Investigators, 2012). Lixisenatide improves glycemic control and has distinct effects on postprandial plasma glucose owing to a delay in gastric emptying (Horowitz et al., 2013; Lorenz et al., 2013). The effects of lixisenatide in Japanese and other Asian patients were reported in a 24-week, randomized controlled trial evaluating once-daily treatment of lixisenatide in combination with basal insulin with or without sulfonylurea (GetGoal-L-Asia study) (Seino, Min, Niemoeller, Takami, & Investigators, 2012). In contrast to other GLP-1 receptor agonists (Inagaki et al., 2011; Kaku et al., 2011; Onishi et al., 2012; Seino et al., 2011), the long-term effects of lixisenatide treatment in Japanese patients have not been reported previously. The GetGoal-Mono-Japan trial reports the long-term safety for lixisenatide when used as a monotherapy in Japanese patients with T2DM.

2. Materials and methods

2.1. Study design

This 76-week, randomized, open-label, parallel-group, multicenter study was conducted in nine centers in Japan. The study consisted of a screening period of up to 2 weeks, a 1-week run-in period, and a 52-week treatment period. Patients who completed the 52-week phase entered a 24-week extension phase and continued the same treatment. Patients were randomized in a 1:1 ratio to a 2-step (10 μg once daily for 1 week, 15 μg once daily for 1 week, then the maintenance dose of 20 μg once daily; $n = 33$) or a 1-step dose-increase regimen (10 μg once daily for 2 weeks, then 20 μg once daily; $n = 36$) of lixisenatide, administered subcutaneously once daily within 1 h before breakfast. Patients were stratified by screening values of glycated hemoglobin (HbA_{1c}; <8.0%, ≥8.0%) and prior use of an oral antidiabetic drug (OAD) within 3 months before screening. The study was approved by the institutional review boards or ethics committees of the participating centers, and was conducted in accordance with the principles of the Declaration of Helsinki and Good Clinical Practice guidelines. All participants provided written informed consent. An external and independent Data Monitoring Committee supervised conduct of the study. Possible allergic events were adjudicated by an external Allergic Reaction Assessment Committee (ARAC).

2.2. Participants

Main entry criteria included patients in Japan with T2DM diagnosed at least 2 months before the screening visit, not treated with an OAD in the 3 months before screening, except treatment with sulfonylureas or α-glucosidase inhibitors at a stable dose, which had to be stopped before starting the single-blind, run-in phase. Exclusion criteria included insulin use within 3 months prior to screening visit; fasting plasma glucose (FPG) at screening >13.9 mmol/L (250 mg/dL); history of unexplained pancreatitis, chronic pancreatitis, pancreatectomy, stomach/gastric surgery or inflammatory bowel disease; amylase and/or lipase values of more than three times the normal laboratory range; history of metabolic acidosis, including diabetic ketoacidosis within 1 year prior to screening; end-stage renal disease and/or patients on dialysis; history of gastrointestinal disease associated with prolonged nausea and vomiting within 6 months prior to screening.

2.3. Safety and efficacy measurements

The primary objective of the study was to assess the safety of once-daily lixisenatide treatment up to week 24 by a descriptive comparison of a 2- and 1-step dose regimen. Primary safety assessments during the 24-week on-treatment period included: adverse events (AEs), primarily treatment-emergent AEs (TEAEs) and serious TEAEs, symptomatic hypoglycemia and severe symptomatic hypoglycemia, local tolerability at injection site, allergic reactions, suspected pancreatitis, vital signs (systolic/diastolic blood pressure [SBP/DBP]), serum amylase, lipase and calcitonin, hematology, and serum chemistry. Symptomatic hypoglycemia was defined per protocol as an event with clinical symptoms that were considered to result from a hypoglycemic episode, with 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 symptomatic hypoglycemia was defined as an event with clinical symptoms that was considered to result from hypoglycemia in which the patient required the assistance of another person, and which was associated either with a plasma glucose level of <2.0 mmol/L (36 mg/dL) or, if no plasma glucose measurement was available, with prompt recovery with oral carbohydrate, intravenous glucose, or glucagon injection.

The secondary objective of the study was to assess the overall safety of once-daily lixisenatide treatment up to week 76 for the pooled data from the 2- and 1-step dose regimens, and efficacy at weeks 24, 52, and 76, as assessed by change in HbA_{1c}, FPG, and body weight. HbA_{1c} values were expressed as the National Glycohemoglobin Standardization Program values, as recommended by the Japan Diabetes Society (Kashiwagi et al., 2012).

2.4. Statistical analyses

The evaluation of AEs, clinical laboratory data, vital signs and electrocardiogram data was descriptive. Analysis of primary safety variables with 24-week data was performed for the 2- and 1-step groups. Secondary analyses and assessment were performed on the pooled data of the 2- and 1-step dose regimens based on the safety data (combined group). The efficacy analysis was performed using descriptive statistics and here the results at baseline, at week 24 and at week 76 time points are reported on observed cases in the modified intent-to-treat population, which comprised all randomized patients who received at least one dose of study drug and who had both a baseline assessment and at least one post-baseline assessment of any efficacy variable. The safety population comprised all randomized patients exposed to at least one dose of study drug.

3. Results

3.1. Patients

A total of 75 patients were screened, of whom 69 patients were randomized to one of the two dose-increase regimens (Fig. 1). During the 24-week treatment period, 7/69 patients (10.1%) discontinued from the study ($n = 5/33$ [15.2%] in the 2-step group and $n = 2/36$ [5.6%] in the 1-step group), the main reason being AEs. During the whole 76-week study period, 22/69 patients (31.9%) in the combined group discontinued study treatment, mainly due to AEs.

Patient demographic and baseline characteristics were well matched between the two treatment groups in this generally non-obese population (Table 1).

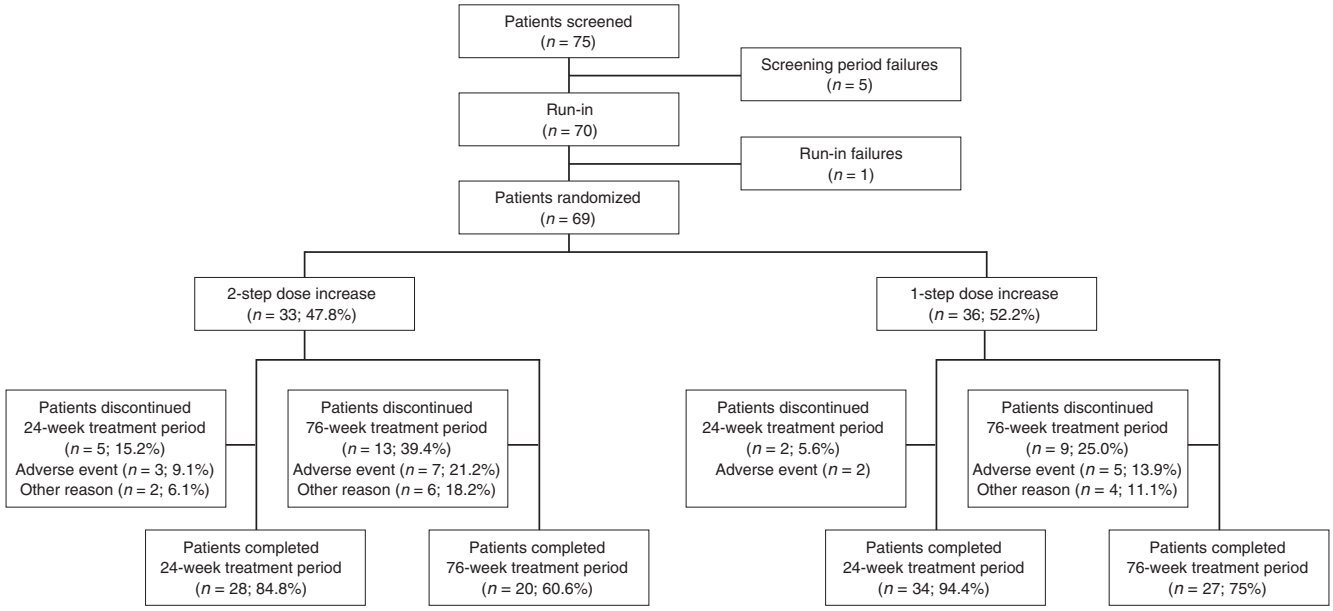

Fig. 1. Patient disposition.

3.2. Safety and tolerability

The proportion of patients with TEAEs was comparable between the groups (Table 2). Up to week 24, serious TEAEs occurred in 2/33 patients (6.1%) in the 2-step group (one patient had gastroenteritis and one patient had a skin laceration) and none of the patients in the 1-step group. Over the entire 76-week trial period, four serious TEAEs occurred in 3/69 patients (4.3%) in the combined group (gastroenteritis, cataract, intervertebral disc protrusion, and skin laceration). No deaths occurred during the study. TEAEs leading to treatment discontinuation were reported for 3/33 patients (9.1%) in the 2-step group, 4/36 patients (11.1%) in the 1-step group up to week 24 and 10/69 patients (14.5%) in the combined group up to week 76 (Table 2), with the majority of events being due to gastrointestinal disorders ($n = 4/69$, 5.8%), primarily nausea ($n = 3/69$, 4.3%). In addition, nausea was the most frequently reported TEAE ($n = 12/33$ [36.4%] in the 2-step group compared with $n = 18/36$ [50.0%] in the 1-step group up to week 24; $n = 30/69$ [43.5%] in the combined group up to week 76; Table 2).

Nausea was reported more frequently during the first 3 weeks of treatment, with a relatively low occurrence from week 4 onwards (Fig. 2). The majority of the events of nausea were mild ($n = 24/69$ [34.8%]), with 6/69 patients (8.7%) in the combined group having events reported as moderate in intensity during the 76-week on-treatment period. No severe events were reported. The majority of patients recovered without the need to administer corrective treatment.

Vomiting was reported in 4/33 patients (12.1%) in the 2-step group and in 1/36 patients (2.8%) in the 1-step group up to week 24. No further patients reported vomiting during the remainder of the 76-week treatment period (combined group: $n = 5/69$ [7.2%] at week 76). Diarrhea was reported in 1/33 patients (3%) in the 2-step group and in 3/36 patients (8.3%) in the 1-step group up to week 24, with no additional events reported during the remainder of the 76-week trial period (combined group: $n = 4/69$ [5.8%] at week 76; Table 2).

Symptomatic hypoglycemia (as defined in the protocol) occurred in 2/33 patients (6.1%) in the 2-step group compared with 1/36 patients (2.8%) in the 1-step group up to week 24 and 5/69 patients (7.2%) in the combined group up to week 76 (Table 2), with no events considered to be severe according to the protocol-defined criteria.

Other safety assessments are also summarized in Table 2. Injection-site reactions were reported for 3/33 patients (9.1%) in the 2-step group and 4/36 patients (11.1%) in the 1-step group during the

Table 1
Baseline characteristics (safety population).

	2-step regimen ($n = 33$)	1-step regimen ($n = 36$)	Combined ($n = 69$)
Male, n (%)	30 (90.9)	28 (77.8)	58 (84.1)
Median age, years (range)	58.0 (40–73)	61.0 (41–76)	61.0 (40–76)
Median diabetes duration, years (range)	6.4 (0.6–29.5)	7.6 (0.6–36.5)	7.3 (0.6–36.5)
Mean HbA_{1c} at screening, % (SD)	8.3 (0.9)	8.2 (0.7)	8.3 (0.8)
Randomized strata of screening HbA_{1c}, n (%)			
<8	14 (42.4)	17 (47.2)	31 (44.9)
≥8	19 (57.6)	19 (52.8)	38 (55.1)
Mean BMI, kg/m^2 (SD)	25.2 (5.3)	24.8 (3.7)	25.0 (4.5)
Mean FPG, mmol/L (SD)	9.9 (1.9)	9.2 (1.9)	9.5 (1.9)
Mean SBP, mmHg (SD)	126.4 (12.6)	127.9 (14.8)	127.2 (13.7)
Mean DBP, mmHg (SD)	77.6 (9.0)	76.9 (9.3)	77.2 (9.1)
OAD use at screening, *n* (%)	16 (48.5)	18 (50.0)	34 (49.3)
Sulfonylurea	14 (42.4)	17 (47.2)	31 (44.9)
α-Glucosidase inhibitor	2 (6.1)	1 (2.8)	3 (4.3)

Abbreviations: BMI, body mass index; DBP, diastolic blood pressure; FPG, fasting plasma glucose; HbA_{1c}, glycated hemoglobin; OAD, oral antidiabetic agent; SBP, systolic blood pressure; SD, standard deviation.

Table 2
Summary of outcome measures and safety assessments (safety population).

Time period	Week 24	Week 24	Week 76
n (%)	2-step regimen ($n = 33$)	1-step regimen ($n = 36$)	Combined ($n = 69$)
Patients with any TEAE	27 (81.8)	32 (88.9)	63 (91.3)
Patients with any serious TEAE	2 (6.1)	0	3 (4.3)
Patients with any TEAE leading to death	0	0	0
Patients with any TEAE leading to permanent treatment discontinuation	3 (9.1)	4 (11.1)	10 (14.5)
Patients with any gastrointestinal TEAEs	21 (63.6)	28 (77.8)	51 (73.9)
Nausea	12 (36.4)	18 (50.0)	30 (43.5)
Vomiting	4 (12.1)	1 (2.8)	5 (7.2)
Diarrhea	1 (3.0)	3 (8.3)	4 (5.8)
Patients with symptomatic hypoglycemia[a]	2 (6.1)	1 (2.8)	5 (7.2)
Patients experiencing injection-site reactions			
Any injection-site reaction	3 (9.1)	4 (11.1)	7 (10.1)
Blood pressure, mean change from baseline (SD)			
SBP, mmHg	−1.9 (12.4)	−2.7 (10.8)	0.1 (12.3)
DBP, mmHg	−0.1 (9.5)	0.2 (9.3)	0.2 (9.6)

Abbreviations: ARAC, Allergic Reaction Assessment Committee; DBP diastolic blood pressure; SBP, systolic blood pressure; SD, standard deviation; TEAE, treatment-emergent adverse event.
n subset of total number of patients who met criterion in question at least once during treatment.
[a] According to the protocol definition.

24-week treatment period. None were severe in intensity or led to discontinuation of treatment (Table 2). No additional patients had injection-site reactions during the remainder of the 76-week treatment period. Allergic reaction positively adjudicated by the ARAC occurred in 1/33 patients (3.0%) in the 2-step group (asthma) and 2/36 patients (5.6%) in the 1-step group (one event of rhinitis allergic and one of urticaria). The urticaria event reported in the 1-step group was adjudicated as possibly related to study treatment by the ARAC and led to treatment discontinuation. An additional two patients had a TEAE of allergic reaction positively adjudicated by the ARAC up to week 76 in the combined group (one additional event of rhinitis allergic and one of urticaria), neither of which were considered to be related to treatment. No patient had a TEAE of increased blood calcitonin levels ≥20 ng/L. No event of pancreatitis was reported during the study, and no patient had lipase or amylase values of more than two times the normal laboratory range. Additionally, SBP and DBP remained stable throughout the entire treatment period (Table 2).

3.3. Efficacy

Mean HbA_{1c} was reduced from baseline at week 24 for both the 2- and the 1-step regimen (mean change from baseline: −0.99% [95% confidence interval (CI) −1.45 to −0.52] for the 2-step group vs −0.74% [95% CI −1.02 to −0.46] for the 1-step group). For patients who stayed on-treatment, this reduction was maintained in the combined group at week 76 (−0.72% [95% CI −1.15 to −0.30]) (Fig. 3). A total of 17.4% of patients in the 2-step group compared with 15.2% in the 1-step group achieved HbA_{1c} of ≤6.5% at week 24. In addition, 34.8% (2-step group) versus 33.3% (1-step group) achieved HbA_{1c} of <7.0%. Based on observed cases, this effect was also maintained throughout the 76-week study period (HbA_{1c} ≤6.5 and <7%: 18.2 and 27.3%, respectively, in the combined group at week 76).

At week 24, the mean changes from baseline in FPG were −1.16 and −0.56 mmol/L for the 2- and 1-step regimens, respectively. In the combined group, the mean change in FPG was −0.46 mmol/L at week 76.

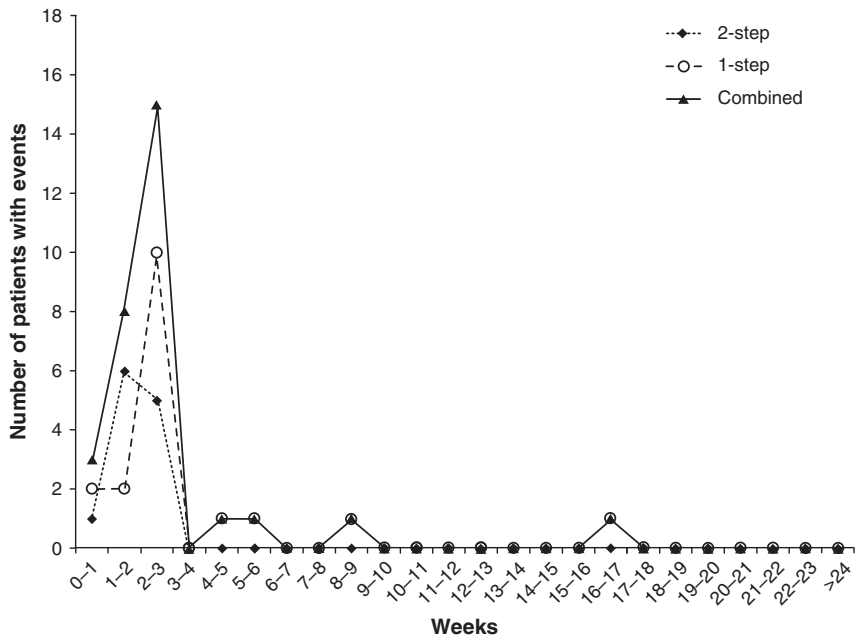

Fig. 2. Nausea events over time. Number of patients with events for the 2-step, 1-step, and combined groups by visit.

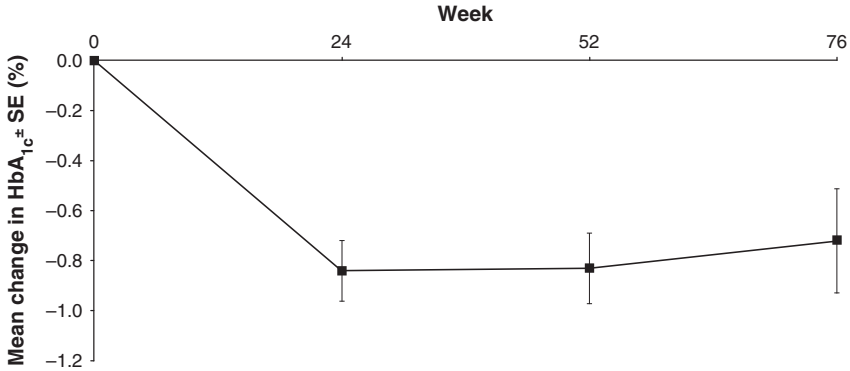

Fig. 3. Mean change in key efficacy variables (observed cases). Mean change in glycated hemoglobin (HbA_{1c}; %) ± standard error (SE) from baseline by visit for combined group*. *Analysis excluded measurements obtained after the introduction of rescue medication and/or after treatment cessation plus 3 days.

Body weight was reduced from baseline at week 24 by −0.43 kg in the 2-step group compared with −1.08 kg in the 1-step group. Body weight further decreased to −1.58 kg in the combined group at week 76.

4. Discussion

This open-label study in Japanese patients with T2DM demonstrated that long-term treatment with once-daily lixisenatide monotherapy was well tolerated. Safety and tolerability were maintained during the entire 76-week study, and the frequency of serious TEAEs was low (4.3%). The incidences of TEAEs and AEs leading to permanent discontinuation of study treatment were generally similar for both the 2- and the 1-step dose regimens during the 24-week treatment period.

As observed with other GLP-1 receptor agonists, the most frequently reported AEs in this study were gastrointestinal in nature, predominantly nausea, with lower levels of vomiting and diarrhea. Nausea was reported in fewer patients in the 2-step group compared with the 1-step group. Events generally occurred early on in treatment and decreased over the treatment period. In the present study, the combined nausea frequency throughout the 76-week study period (43.5%) was higher than that observed with lixisenatide monotherapy in a 12-week study in predominantly Caucasian patients (GetGoal-Mono study: 22.2%) (Fonseca et al., 2012), but was consistent with the nausea levels reported with lixisenatide treatment in combination with basal insulin in a 24-week study in an exclusively Asian population (GetGoal-L-Asia trial: 39.6%) (Seino, Min, Niemoeller, Takami, & Investigators, 2012). In both the GetGoal-Mono and the GetGoal-L-Asia studies, nausea generally occurred during the initial weeks of treatment and decreased over the treatment period, which is consistent with what was observed in the current study.

A meta-analysis of clinical trials of GLP-1 receptor agonists highlighted the differences in risk of gastrointestinal AEs between Asian and non-Asian patients, with a higher observed incidence of nausea and vomiting in Asian patients, but a lower incidence of diarrhea (Kim et al., 2014). However, the authors suggested that the observed differences by study could be also explained by the tendency towards lower body mass indexes in Asian populations compared with non-Asian cohorts (Kim et al., 2014).

The incidence of nausea seen with lixisenatide monotherapy in this study (36.4% in the 2-step group and 50.0% in the 1-step group at 24 weeks, 43.5% for the combined group at week 76) appears similar to that seen in a 24-week study of exenatide 10 μg twice daily (with sulfonylurea alone or combined with a biguanide or thiazolidinedione) in Japanese patients (36.1%) (Kadowaki et al., 2011). Vomiting was reported in 16.7% of patients at week 24 in the exenatide study (Kadowaki et al., 2011); and in 7.2% of patients at week 76 in this study (combined lixisenatide group). In a 24-week study of liraglutide once daily (as monotherapy) and a 26-week study of exenatide once weekly (on a background of biguanide ± sulfonylurea ± thiazolidinedione), both in Japanese patients, the incidence of nausea was 4.5% and 12.6%, respectively (Inagaki et al., 2012; Seino, Rasmussen, Nishida, & Kaku, 2010). However, such comparisons must be interpreted carefully owing to differences in the study designs, populations, and background medications. Furthermore, the reported frequency of nausea can vary, even for trials using the same GLP-1 receptor agonist (Buse et al., 2013; Drucker et al., 2008).

In GetGoal-Mono-Japan, the incidence of symptomatic hypoglycemia was low, with events reported in only 2/33 patients (6.1%) in the 2-step group and 1/36 patients (2.8%) in the 1-step group at 24 weeks. In a 24-week 2010 study by Seino et al. where liraglutide monotherapy was evaluated, 8.2% and 13.4% of patients experienced minor hypoglycemia (defined as self-treatment by the patient) and symptoms of hypoglycemia, respectively (Seino, Rasmussen, Nishida, & Kaku, 2010). However, the different definitions for hypoglycemia used in GetGoal-Mono-Japan and the study by Seino, Rasmussen, Nishida, and Kaku (2010) should be noted. The current study used the same definitions for symptomatic hypoglycemia as used in the entire development program for lixisenatide (blood glucose <3.3 mmol/L [60 mg/dL] and/or prompt recovery with oral carbohydrate, glucagon, or intravenous glucose).

Evidence from this long-term safety study supports the use of a 2-step dose-increase regimen during the initiation of lixisenatide treatment in Japanese patients, as patients in the 2-step group had a lower incidence of nausea compared with the 1-step group. Minor reductions in SBP were observed during the trial, and at the end of the study blood pressure remained stable, though the significance of these changes could not be assessed in the descriptive analysis presented here. Laboratory assessments did not reveal any abnormal findings. Finally, no safety signal specific to patients in Japan was observed.

HbA_{1c} levels decreased primarily during the initial weeks of treatment up to week 24 (−0.99% [2-step group] and −0.74% [1-step group]), and were maintained during the entire 76-week study period (−0.72%). Similar reductions were observed in the GetGoal-L-Asia study at week 24 (least squares [LS] mean change: −0.77%) (Seino, Min, Niemoeller, Takami, & Investigators, 2012). Lixisenatide treatment was associated with improvements in FPG levels at week 24 and at the end of the 76-week study period. This magnitude of reduction in FPG (−1.16 and −0.56 mmol/L at week 24) was consistent with that observed in the GetGoal-Mono and GetGoal-L-Asia trials (LS mean change: −0.66 mmol/L [2-step group] and −0.87 mmol/L [1-step group] for GetGoal-Mono versus −0.42 mmol/L for GetGoal-L-Asia). Characteristically of an Asian population, most patients in the present study were non-obese, but nevertheless there was a modest reduction in body weight at week 24, which was more marked at the end of the whole study period (−1.58 kg). The findings of the present

study in Japanese patients are consistent with those of the predominantly Caucasian population in the previous 12-week GetGoal-Mono study. In that trial, lixisenatide administered as monotherapy significantly improved glycemic control, and was safe and well tolerated (Fonseca et al., 2012).

A limitation of the current trial was its open-label design with no placebo comparator arm. However, the design was considered appropriate given that the objective of the study was to assess long-term safety and tolerability.

5. Conclusions

The current study shows that lixisenatide monotherapy administered once daily in Japanese patients with T2DM was well tolerated, with less nausea with the 2-step regimen. Furthermore, lixisenatide treatment was associated with beneficial effects on HbA_{1c}, FPG, and body weight. This suggests a role for once-daily lixisenatide administration in a 2-step dose-increase regimen as a favorable treatment option for Japanese patients with T2DM.

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Yutaka Seino, Daisuke Yabe, Akane Takami, and Elisabeth Niemoeller were involved in the protocol development, medical supervision and study reporting; Hiroki Takagi performed the statistical analyses for the study.

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