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CLINICAL TRIAL

Safety, tolerability and efficacy of lixisenatide in combination with oral antidiabetic treatment in Japanese patients with type 2 diabetes: An open-label, multicenter study

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ABSTRACT

Aim/Introduction: To assess the overall safety and efficacy of lixisenatide in combination with background oral antidiabetic drug treatment in Japanese patients with type 2 diabetes, as required by Japanese guidelines.

Materials and Methods: A phase 3, multicenter, uncontrolled, open-label, four-arm, parallel-group study of Japanese outpatients with type 2 diabetes was carried out; patients received once-daily lixisenatide in combination with biguanide, thiazolidinedione, alpha-glucosidase inhibitors or glinide (NCT01940965). The primary end-point was safety over 52 weeks; secondary end-points included absolute change from baseline in glycated hemoglobin A1c at weeks 24 and 52.

Results: A total of 294 patients were enrolled (biguanide, thiazolidinedione, alpha-glucosidase groups: 73 patients each; glinide group: 75 patients). Overall, 90.4% of patients in the biguanide group, 83.6% in the thiazolidinedione group, 83.6% in the alpha-glucosidase group and 85.3% in the glinide group reported one or more treatment-emergent adverse event, the most common of which were nasopharingitis, nausea and constipation. Symptomatic hypoglycemia was reported in 5.5, 0, 1.4, and 10.7% of patients in the biguanide, thiazolidinedione, alpha-glucosidase and glinide groups, respectively. No severe hypoglycemia was observed. Hemoglobin A1c decreased from baseline at weeks 24 and 52, with mean changes ranging from −0.98 to −1.22%, and from −0.80 to −1.08%, respectively, across all groups.

Conclusions: Lixisenatide treatment administered daily over 52 weeks was well tolerated and effective in improving glycemic control in Japanese patients with type 2 diabetes uncontrolled with existing oral antidiabetic drug therapies. The use of lixisenatide in combination with oral antidiabetic drugs is a valuable treatment option for Japanese patients with type 2 diabetes after failure of oral antidiabetic treatment alone.

INTRODUCTION

The worldwide prevalence of type 2 diabetes mellitus has substantially increased over the past two decades, and the number of patients with diabetes is projected to rise from an estimated 415 million in 2015 to 642 million in 2040[1,2]. According to the International Diabetes Federation, there were over 7.2 million people with diabetes in Japan in 2015[1]. A national survey carried out in Japan showed that the number of patients with 'suspicion of diabetes mellitus,' defined as glycated hemoglobin (HbA1c) ≥6.5% (National Glycohemoglobin Standardization Program) or ≥6.1% (Japanese Diabetes Society), was 9.5 million in 2012, whereas the number of patients with 'possibility of diabetes mellitus' (HbA1c ≥6.0 and <6.5% [National Glycohemoglobin Standardization Program] or ≥5.6 and <6.1% [Japanese Diabetes Society]) was 11.1 million[3].

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When exercise and diet alone are not sufficient to achieve glycemic control, the treatment of type 2 diabetes mellitus involves the addition of blood glucose-lowering agents, with the overall aim of maintaining quality of life, and preventing microvascular complications and atherosclerotic disease. The Japanese Diabetes Society recommends HbA1c target levels <7% for glycemic control to prevent complications in patients with type 2 diabetes mellitus[4].

There are several classes of antidiabetic drugs, including oral or injectable antidiabetic agents. Appropriate agents are selected according to the patient's condition; when HbA1c targets are not achieved, treatment is intensified by adding or switching to another agent from a different class. However, despite improvement in glucose-lowering agents, there is still a very sensitive equilibrium between achieving glycemic targets and avoiding contraindications or adverse effects, such as risk of hypoglycemia and weight gain[5]. Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) offer a valuable new therapeutic option for the treatment of type 2 diabetes mellitus[6]. GLP-1 RAs reduce blood glucose levels by glucose-dependent stimulation of insulin release and inhibition of glucagon secretion, which decreases prandial blood glucose excursions and hepatic glucose production. They provide a physiological blood glucose–insulin response associated with a low risk of hypoglycemia. GLP-1 RAs have additional effects, such as delay of gastric emptying, reduction of appetite and weight loss. GLP-1 RAs differ substantially in their duration of action, and can be classed as either short acting or long acting[7].

Lixisenatide (Lyxumia®, Japan and EU trade name; Adlyxin®, USA trade name) is a once-daily (QD), short-acting, selective GLP-1 RA. It is approved for use in Europe, the USA, and other countries with oral glucose-lowering agents and/or basal insulin (BI) in the treatment of adults with type 2 diabetes mellitus when the use of these agents with diet and exercise has provided inadequate glycemic control[8,9]. In Japan, lixisenatide is approved for use in patients with type 2 diabetes mellitus uncontrolled on sulfonylurea (SU), or an SU and a biguanide in combination with diet and exercise, or uncontrolled on BI (including concomitant use with an SU) in combination with diet and exercise.

The safety and efficacy of lixisenatide have been assessed in a large phase 3 program (GetGoal clinical trial program) carried out in approximately 50 countries, including Japan, with more than 5,900 adult patients with type 2 diabetes mellitus[10–22]. Over 7,800 patients have been exposed to lixisenatide, with more than 6,400 of these patients included in placebo-controlled studies[23]. Treatment with lixisenatide as monotherapy, as well as in combination with metformin, SU or BI (with or without oral antidiabetic drugs [OADs]) led to significant improvements in glycemic control, as assessed by reduction in HbA1c[10–22]. Efficacy and safety were also confirmed in Japanese patients[24,25].

The Japanese guideline for 'Clinical Evaluation Methods of Oral Hypoglycemic Agents,' released in 2010 by the Japanese Ministry of Health, Labor and Welfare, requires an open-label, long-term study to evaluate safety as a primary end-point and efficacy as a secondary end-point to be carried out in all groups of concomitant drugs that can, theoretically, be used with the investigational medicinal product and anticipated to be administered to patients in clinical practice[26]. Other agents for the treatment of diabetes, such as GLP-1 RAs, should also be investigated to follow the guidelines[27]. The objective of the present study was to assess the safety and efficacy of lixisenatide in combination with background oral antidiabetic treatment in Japanese patients with type 2 diabetes mellitus. Biguanides, thiazolidinediones (TZDs), alpha-glucosidase inhibitors (alpha-GIs) and glinides are the four OADs included as background treatment in the present study, and have been commonly used in Japan for the treatment of patients with type 2 diabetes mellitus[28]. SUs and dipeptidyl peptidase-4 inhibitors were not included as background treatment, as concomitant use of lixisenatide and SUs is already approved in Japan, whereas dipeptidyl peptidase-4 inhibitors affect the same incretin pathway as lixisenatide. The long-term effects of lixisenatide treatment combined with an OAD in Japanese patients with type 2 diabetes mellitus have not been reported previously.

METHODS

Study design

This was a phase 3, multicenter, uncontrolled, open-label, four-arm, parallel-group study carried out in outpatients with type 2 diabetes mellitus in Japan. The study comprised three periods: an up to 2-week screening period, followed by a 52-week open-label treatment period and a post-treatment follow-up period of 3 days (Figure 1). At baseline, patients were enrolled into one of the following four treatment groups based on their background OAD treatment: lixisenatide in combination with a biguanide, a TZD, an alpha-GI or a glinide.

The present study was designed and carried out in accordance with the guideline released by the Japanese Ministry of Health, Labor and Welfare. 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 Helsinki, Good Clinical Practice, and also complied with the laws, regulations and any applicable guidelines from Japan.

Patient population

Eligibility criteria included patients with type 2 diabetes mellitus diagnosed at least 1 year before screening and those treated with an OAD (a biguanide, a TZD, an alpha-GI or a glinide) at a stable dose for ≥3 months before screening.

Key exclusion criteria included: patients aged <20 years at screening; HbA1c <7 or >9.5% at screening; fasting plasma glucose (FPG) >13.9 mmol/L (>250 mg/dL) at screening; use of any glucose-lowering agent other than the permitted background treatment within 3 months before screening; previous

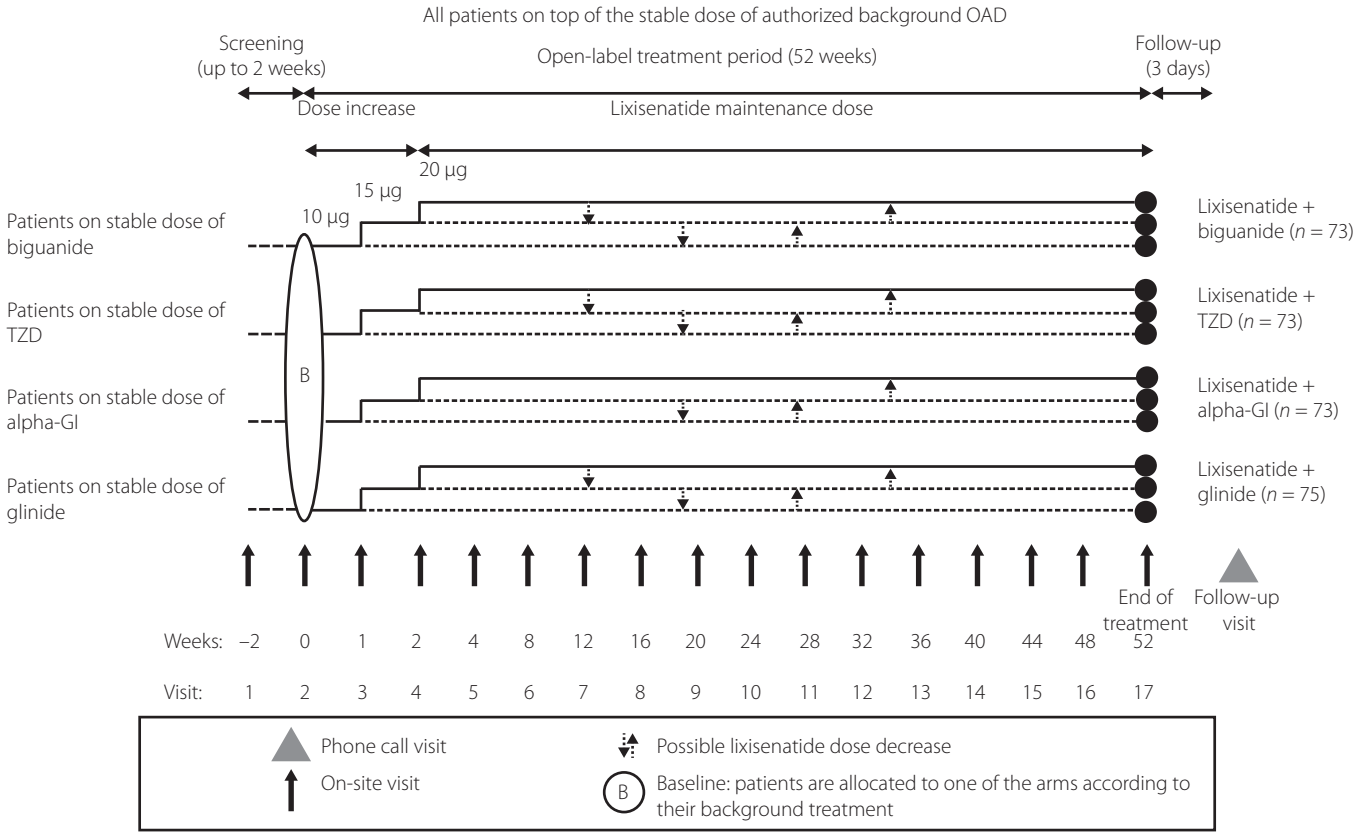

Figure 1 | Study design. Alpha-GI, alpha-glucosidase inhibitor; OAD, oral antidiabetic drug; TZD, thiazolidinedione.

treatment with lixisenatide or any other GLP-1 RA; weight change of >5 kg during the 3 months preceding the screening visit; history of metabolic acidosis, including diabetic ketoacidosis within 1 year before the screening visit; history of hypoglycemia unawareness; history of acute or chronic pancreatitis, pancreatectomy, stomach/gastric surgery or inflammatory bowel disease; amylase and/or lipase values >3-fold the upper limit of normal; clinically relevant history of gastrointestinal disease associated with prolonged nausea and vomiting; severe renal impairment and/or patients on dialysis; and personal or immediate family history of medullary thyroid cancer or genetic conditions that predispose to medullary thyroid cancer (e.g., multiple endocrine neoplasia syndromes).

Interventions

Patients self-administered lixisenatide QD by subcutaneous injection in the morning within 1 h (i.e., 0–60 min) before breakfast, using a specified reusable self-injector device. The starting dose of lixisenatide was 10 µg QD for 1 week. Patients then continued with 15 µg QD for 1 week, followed by 20 µg QD (maintenance dose) from week 2 (visit 4) up to the end of the treatment period. If the target dose of 20 µg was not tolerated, the dose of lixisenatide could be decreased to 15 µg, and then, if necessary, to 10 µg. Another attempt at dose increase was to take place within 4 weeks. If the patient could not reach or tolerate the target dose of 20 µg, he/she remained at the 15 or 10 µg dose. If the patient could not tolerate the 10 µg dose, the patient discontinued from the study.

Patients continued on the background OAD treatment they had been taking before the study at a stable dose of at least the usual maintenance dose described in the label instructions. The dose was reduced at baseline for patients treated with glinides if HbA1c at screening was ≥7% but <8%, or could be decreased during the treatment period, in the case of two or more symptomatic or one severe symptomatic hypoglycemic episodes.

Routine fasting self-monitored plasma glucose (SMPG) and central laboratory alerts on FPG (and HbA1c from week 12 onwards) were established to ensure that glycemic parameters remained under predefined thresholds values. If FPG/HbA1c remained above the prespecified threshold values, a rescue therapy could be initiated if no reasonable explanation for insufficient glycemic control could be found or efficiently tackled.

End-points

The primary end-point was safety over 52 weeks, as assessed by: treatment-emergent adverse events (TEAEs) and serious

TEAEs, including symptomatic hypoglycemia and severe hypoglycemia, local tolerability at the injection site, allergic reactions, pancreatic events, cardiovascular events, vital signs, 12-lead electrocardiogram, and laboratory data including hematology, serum chemistry, lipid parameters, serum amylase and lipase, and serum calcitonin.

Secondary end-points at weeks 24 and 52 included: absolute change in HbA1c from baseline; percentage of patients with HbA1c <7 and ≤6.5%; absolute change in FPG from baseline; absolute change in bodyweight from baseline; absolute change in seven-point SMPG profiles (for the overall average and at each time-point) from baseline; and the percentage of patients requiring rescue therapy.

An Allergic Reaction Assessment Committee, Pancreatic Safety Assessment Committee and Cardiovascular Events Adjudication Committee adjudicated possible allergic events, pancreatic events, and cardiovascular events, respectively.

TEAEs were defined as adverse events (AEs) that developed or worsened (according to the investigator's opinion), or became serious during the on-treatment period. Symptomatic hypoglycemia was defined as an event with clinical symptoms that was considered to result from a hypoglycemic episode and 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 of hypoglycemia in which the patient required the assistance of another person due to acute neurological impairment directly resulting from the hypoglycemic event, and 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.

Statistical analysis

In order to comply with the 'Guideline on Clinical Evaluation Methods for Oral Hypoglycemic Agents' in Japan[26], which requires at least 50 patients per background OAD group to be treated with lixisenatide plus one OAD for at least 1 year, a total of 292 patients were planned for enrollment. Taking into account a dropout rate of 30%, approximately 73 patients in each treatment arm were considered necessary to be enrolled.

The safety population was defined as all patients enrolled (through the interactive web response system) and exposed to at least one dose of lixisenatide, regardless of the amount of treatment administered. The efficacy population was the modified intention-to-treat population, which comprised all enrolled patients who were exposed to at least one dose of open-label lixisenatide, and had both a baseline assessment and at least one post-baseline assessment of any efficacy end-points, irrespective of compliance with the study protocol and procedures.

Continuous data were summarized by background OAD group and overall (when applicable) using descriptive statistics; categorical data were summarized by background OAD group and overall (when applicable) using counts and percentages; missing data were not categorized. No formal statistical comparisons were carried out, and end-points were evaluated by descriptive statistics only.

RESULTS

A total of 332 patients were screened, and 294 patients were enrolled to one of the four background OAD groups (73 patients each in the biguanide, TZD and alpha-GI groups; 75 patients in the glinide group; Figure 2). A total of 87.4% of patients completed the 52-week treatment period. Of the 294 enrolled and treated patients, 37 (12.6%) discontinued treatment with the study drug during the 52-week treatment period (3 patients [4.1%] in the biguanide group, 13 patients [17.8%] in the TZD group, 9 patients [12.3%] in the alpha-GI group and 12 patients [16.0%] in the glinide group). Most discontinuations occurred within the first 24 weeks of treatment (3 patients [4.1%] in the biguanide group, 12 patients [16.4%] in the TZD group, 8 patients [11.0%] in the alpha-GI group and 8 patients [10.7%] in the glinide group). The main reason for treatment discontinuation, during both treatment periods, was AEs for each of the background OAD groups. There was one death (1.4%) in the TZD group. Only one patient (in the biguanide group) had a treatment compliance of <80%, potentially impacting the efficacy analyses, but was not excluded from the modified intention-to-treat population.

Demographic and baseline characteristics were generally similar across all background OAD groups (Table 1). At the end of the titration period (corresponding to the period between week 0 and week 2), 84.0–90.4% of patients across the four background OAD groups were receiving the maintenance dose of 20 μg lixisenatide daily.

Primary safety end-point

The profile of TEAEs was generally similar across all background OAD groups (Table 2). A total of 90.4% of patients in the biguanide group, 83.6% in the TZD group, 83.6% in the alpha-GI group and 85.3% in the glinide group reported at least one TEAE; of these, 54.8, 57.5, 56.2 and 65.3% had TEAEs that were considered to be related to the study drug, respectively. TEAEs (listed in order of incidence) reported by ≥10% of patients in any background OAD group were: nausea, nasopharingitis, constipation, vomiting, diarrhea, back pain and hypoglycemia (Table 2). All patients with TEAEs of nausea or vomiting, except for one patient with a TEAE of nausea in the TZD group and two patients with a TEAE of vomiting in the alpha-GI group, had at least one event that was considered related to the study drug.

Nausea was the TEAE reported most frequently in all background OAD groups apart from the biguanide group (most frequent TEAE in this group was nasopharingitis), with patients reporting a first event primarily within the first 3 weeks of treatment. The percentage of patients with any event of nausea

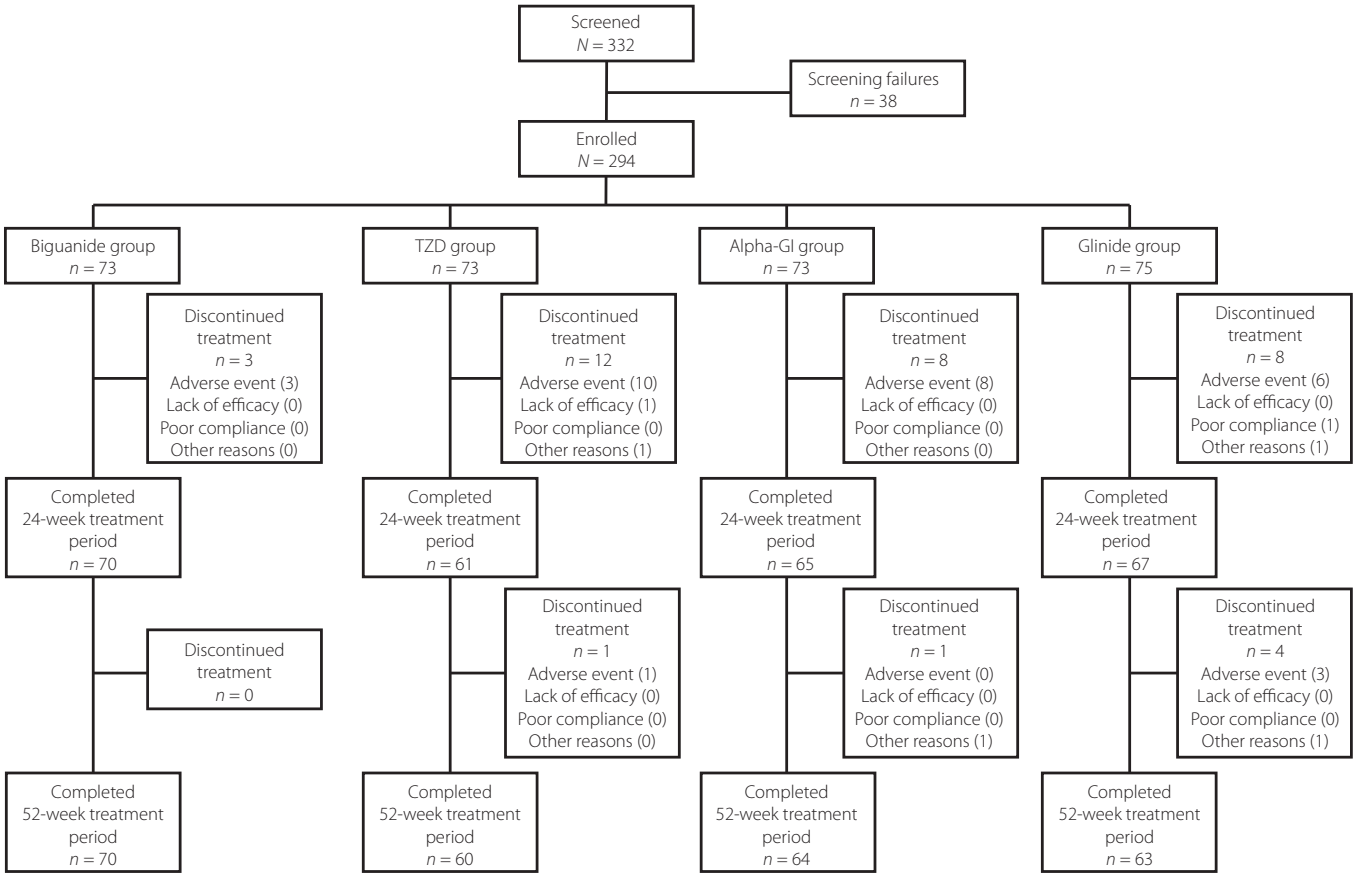

Figure 2 | Patient disposition. Alpha-GI, alpha-glucosidase inhibitor; TZD, thiazolidinedione.

Table 1 | Patient and disease characteristics at screening or baseline (safety population)

Characteristic	Biguanide (*n* = 73)	TZD (*n* = 73)	Alpha-GI (*n* = 73)	Glinide (*n* = 75)	All (*N* = 294)
Age (years)	56.2 (8.9)	57.8 (9.5)	58.1 (11.5)	60.7 (8.9)	58.2 (9.8)
Age group, *n* (%)					
<65 years	59 (80.8)	55 (75.3)	47 (64.4)	48 (64.0)	209 (71.1)
Male, *n* (%)	53 (72.6)	57 (78.1)	55 (75.3)	55 (73.3)	220 (74.8)
Baseline HbA1c (%)	7.93 (0.69)	7.91 (0.69)	7.88 (0.65)	8.19 (0.67)	7.98 (0.68)
Baseline BMI (kg/m^2)	27.18 (4.73)	27.03 (4.27)	25.19 (4.02)	24.99 (3.92)	26.09 (4.34)
Baseline FPG (mmol/L)	8.42 (1.53)	8.34 (1.38)	8.59 (1.72)	9.16 (1.52)	8.63 (1.57)
Baseline bodyweight (kg)	74.27 (14.20)	75.74 (15.86)	69.62 (15.33)	68.26 (14.30)	71.95 (15.18)
Duration of type 2 diabetes mellitus at screening (years)	8.43 (7.03)	8.07 (5.94)	7.80 (5.11)	10.41 (6.03)	8.69 (6.12)
Duration of background OAD (years)	6.04 (5.15)	5.73 (4.51)	5.32 (3.70)	6.87 (5.68)	6.00 (4.83)

Data are mean (SD) unless stated otherwise. Alpha-GI, alpha-glucosidase inhibitor; BMI, body mass index; FPG, fasting plasma glucose; HbA1c, glycated hemoglobin; OAD, oral antidiabetic drug; TZD, thiazolidinedione.

by weekly intervals peaked during the first 3 weeks of treatment, and decreased thereafter, remaining low from week 9 throughout the remaining treatment period (Figure S1a). For vomiting, patients in all background OAD groups reported a first event primarily within the first 7 weeks of treatment (Figure S1b). The percentage of patients with any event of vomiting by weekly intervals was higher during the first 7 weeks of treatment, and decreased thereafter, remaining low throughout the remaining treatment period.

Serious TEAEs were reported in eight patients: three (4.1%) patients in the biguanide group, two (2.7%) in the TZD group, none in the alpha-GI group and three (4.0%) in the glinide

Table 2 | Number of patients experiencing treatment-emergent adverse events during the on-treatment period (safety population)

	Biguanide (*n* = 73)	TZD (*n* = 73)	Alpha-GI (*n* = 73)	Glinide (*n* = 75)	All (*N* = 294)
Patients with TEAEs					
Patients with any TEAE	66 (90.4)	61 (83.6)	61 (83.6)	64 (85.3)	252 (85.7)
Patients with any serious TEAE	3 (4.1)	2 (2.7)	0	3 (4.0)	8 (2.7)
Patients with any TEAE leading to death	0	1 (1.4)	0	0	1 (0.3)
Patients with any TEAE leading to permanent treatment discontinuation	3 (4.1)	10 (13.7)	8 (11.0)	9 (12.0)	30 (10.2)
AE by SOC/PT (reported in ≥10% of patients in any one background OAD group)					
Infections and infestations					
Nasopharingitis	33 (45.2)	24 (32.9)	24 (32.9)	24 (32.0)	105 (35.7)
Discontinuation due to nasopharingitis	0	0	0	0	0
Gastrointestinal disorders					
Diarrhea	5 (6.8)	3 (4.1)	8 (11.0)	5 (6.7)	21 (7.1)
Discontinuation due to diarrhea	0	0	0	0	0
Constipation	5 (6.8)	4 (5.5)	6 (8.2)	12 (16.0)	27 (9.2)
Discontinuation due to constipation	0	1 (1.4)	0	1 (1.3)	2 (0.7)
Nausea	23 (31.5)	33 (45.2)	31 (42.5)	30 (40.0)	117 (39.8)
Discontinuation due to nausea	0	8 (11.0)	5 (6.8)	4 (5.3)	17 (5.8)
Vomiting	4 (5.5)	8 (11.0)	7 (9.6)	6 (8.0)	25 (8.5)
Discontinuation due to vomiting	1 (1.4)	0	0	0	1 (0.3)
Musculoskeletal and connective tissue disorders					
Back pain	8 (11.0)	3 (4.1)	5 (6.8)	1 (1.3)	17 (5.8)
Discontinuation due to back pain	0	0	0	0	0
Symptomatic hypoglycemia					
Any symptomatic hypoglycemia[†]					
Patients with events	4 (5.5)	0	1 (1.4)	8 (10.7)	13 (4.4)
No. events (*n*)	4	0	1	14	19
Confirmed by blood glucose <3.3 mmol/L					
Patients with events	2 (2.7)	0	1 (1.4)	6 (8.0)	9 (3.1)
No. events (*n*)	2	0	1	10	13

Data are *n* (%) unless stated otherwise. [†]Any symptomatic hypoglycemia was defined per protocol as an event with clinical symptoms that was considered to result from a hypoglycemic episode and 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. AE, adverse event; alpha-GI, alpha-glucosidase inhibitor; OAD, oral antidiabetic drug; PT, preferred term; SOC, system organ class; TEAE, treatment-emergent adverse event; TZD, thiazolidinedione.

group; no serious TEAEs were considered to be related to the study drug (Table 2). One fatal TEAE of gastric cancer was reported in the TZD group, and was adjudicated by the Cardiovascular Events Adjudication Committee as a non-cardiovascular death. The percentage of patients with TEAEs leading to permanent discontinuation of treatment with the study drug was three (4.1%) patients in the biguanide group, 10 (13.7%) in the TZD group, eight (11.0%) in the alpha-GI group and nine (12.0%) in the glinide group (Table 2).

The percentage of patients with injection-site reactions during the on-treatment period was seven (9.6%) in the biguanide group, five (6.8%) in the TZD group, three (4.1%) in the alpha-GI group and one (1.3%) in the glinide group; all injection-site reactions reported during the study were mild in intensity and none was serious. Of the adjudicated allergic reactions during the on-treatment period (4 in the biguanide group, 1 each in the TZD and alpha-GI groups, and none in the glinide group), none was considered related to lixisenatide treatment. No events were adjudicated as pancreatitis by the Pancreatic Safety Assessment Committee, and no events of pancreatic neoplasms were reported in the study.

There was a small decrease from baseline to end of treatment in blood pressure (both systolic and diastolic) in all four background OAD groups (range of mean changes at last on-treatment value across the groups: systolic −1.2 to −4.5 mmHg; diastolic −0.7 to −3.6 mmHg). There were no clinically meaningful changes from baseline to the end of treatment in heart rate in any of the background OAD groups. In general, no clinically meaningful changes from baseline to the end of treatment were observed in hematological parameters, lipid parameters, pancreatic enzymes, renal function tests, liver function tests, calcitonin and electrolytes in any of the background OAD groups. The percentage of patients with normal values at baseline who had abnormal 12-lead electrocardiograms during the

on-treatment period was similar across the four background OAD groups.

Symptomatic hypoglycemia

Symptomatic hypoglycemia during the on-treatment period was reported in four (5.5%) patients in the biguanide group, one (1.4%) in the alpha-GI group and eight (10.7%) in the glinide group. No patients reported symptomatic hypoglycemia in the TZD group during the on-treatment period (Table 2). There were no patients with protocol-defined severe symptomatic hypoglycemia during the on-treatment period.

Secondary efficacy end-points

HbA1c decreased from baseline at weeks 24 and 52, and the mean changes were similar across all background OAD groups (Table 3). The mean change in HbA1c from baseline at week 24 (observed cases [OC]) was −0.98% 95% confidence interval [CI]: 1.15, −0.81) in the biguanide group, −1.03% (95% CI: −1.18, −0.88) in the TZD group, −1.22% (95% CI: −1.38, −1.07) in the alpha-GI group and −1.17% (95% CI: −1.34, −0.99) in the glinide group. The mean change in HbA1c from baseline at week 52 (OC) was −0.80% (95% CI: −0.99, −0.61) in the biguanide group, −1.02% (95% CI: −1.18, −0.85) in the TZD group, −1.08% (95% CI: −1.26, −0.90) in the alpha-GI group and −0.99% (95% CI: −1.17, −0.80) in the glinide group. The mean change from baseline in HbA1c over time during the 52-week treatment period is shown in Figure S2. The profile of mean change in HbA1c from baseline by scheduled visit was similar across all background OAD groups; HbA1c decreased during the first 16 weeks of treatment, and thereafter remained relatively stable up to week 52 (Figure S2).

The percentage of patients with HbA1c values of <7.0 or ≤6.5% increased from baseline at weeks 24 and 52 in all four background OAD groups (Table 3). The percentage of patients

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

Efficacy end-point	Biguanide (*n* = 73)	TZD (*n* = 73)	Alpha-GI (*n* = 73)	Glinide (*n* = 75)
HbA1c (%)				
Baseline	7.93 (0.69)	7.91 (0.69)	7.88 (0.65)	8.19 (0.67)
Week 24	6.95 (0.71)	6.87 (0.74)	6.70 (0.55)	7.02 (0.67)
Change from baseline	−0.98 (0.70)	−1.03 (0.60)	−1.22 (0.62)	−1.17 (0.69)
Week 52	7.14 (0.79)	6.89 (0.68)	6.85 (0.70)	7.20 (0.68)
Change from baseline	−0.80 (0.79)	−1.02 (0.63)	−1.08 (0.73)	−0.99 (0.73)
HbA1c responders, *n* (%)				
<7%				
Week 24	39/70 (55.7)	41/64 (64.1)	46/65 (70.8)	34/66 (51.5)
Week 52	28/68 (41.2)	33/60 (55.0)	38/64 (59.4)	27/61 (44.3)
≤6.5%				
Week 24	25/70 (35.7)	22/64 (34.4)	28/65 (43.1)	17/66 (25.8)
Week 52	15/68 (22.1)	20/60 (33.3)	24/64 (37.5)	13/61 (21.3)
FPG (mmol/L)				
Baseline	8.42 (1.53)	8.34 (1.38)	8.59 (1.72)	9.16 (1.52)
Week 24	7.2 (1.3)	7.6 (1.4)	7.6 (1.4)	8.1 (1.8)
Change from baseline	−1.2 (1.5)	−0.7 (1.1)	−1.1 (1.5)	−1.0 (1.3)
Week 52	7.7 (1.2)	7.3 (1.2)	7.5 (1.7)	8.3 (1.6)
Change from baseline	−0.7 (1.4)	−0.9 (1.1)	−1.1 (1.7)	−0.9 (1.6)
Bodyweight (kg)				
Baseline	74.27 (14.20)	75.74 (15.86)	69.62 (15.33)	68.26 (14.30)
Week 24	72.8 (14.5)	75.7 (15.7)	69.4 (15.4)	67.6 (13.9)
Change from baseline	−1.6 (2.2)	−0.6 (2.4)	−1.9 (1.9)	−0.8 (2.3)
Week 52	72.6 (14.3)	75.1 (15.5)	69.4 (15.8)	67.5 (14.2)
Change from baseline	−1.6 (2.3)	−1.1 (3.2)	−2.0 (2.6)	−0.9 (2.6)
Average 7-point SMPG (mmol/L)				
Baseline	10.16 (1.94)	10.22 (2.05)	9.98 (1.72)	10.46 (1.84)
Week 24	8.2 (1.6)	8.2 (1.6)	8.2 (1.5)	8.2 (1.3)
Change from baseline	−2.0 (2.1)	−2.0 (1.9)	−1.9 (1.6)	−2.2 (1.9)
Week 52	8.4 (1.8)	8.3 (1.4)	8.2 (1.7)	8.4 (1.6)
Change from baseline	−1.8 (2.2)	−1.9 (2.0)	−1.8 (1.7)	−1.9 (1.9)

Data are mean (standard deviation) unless stated otherwise. FPG, fasting plasma glucose; HbA1c, glycated hemoglobin; LOCF, last observation carried forward; OC, observed case; SMPG, self-monitored plasma glucose.

with HbA1c values of <7.0% (OC) at week 24 and week 52, respectively, was 55.7 and 41.2% in the biguanide group, 64.1 and 55.0% in the TZD group, 70.8 and 59.4% in the alpha-GI group, and 51.5 and 44.3% in the glinide group. The percentage of patients achieving HbA1c values of ≤6.5% (OC) at week 24 and week 52, respectively, was 35.7 and 22.1% in the biguanide group, 34.4 and 33.3% in the TZD group, 43.1 and 37.5% in the alpha-GI group, and 25.8 and 21.3% in the glinide group.

FPG decreased from baseline at weeks 24 and 52, and the mean changes were similar across all background OAD groups (Table 3). The mean change in FPG from baseline at week 24 (OC) was between −0.7 and −1.2 mmol/L across the four background OAD groups. The mean change in FPG from baseline at week 52 (OC) ranged from −0.7 to −1.1 mmol/L.

Bodyweight decreased from baseline at weeks 24 and 52 (Table 3). The mean change in bodyweight from baseline at week 24 (OC) ranged from −0.6 to −1.9 kg. The mean change in bodyweight from baseline at week 52 (OC) was −0.9 to −2.0 kg.

Average seven-point SMPG decreased from baseline at weeks 24 and 52, and the mean changes were similar across all background OAD groups (Table 3). The mean change in average seven-point SMPG from baseline at week 24 (OC) ranged from −1.9 to −2.2 mmol/L across the four background OAD groups. The mean change in average seven-point SMPG from baseline at week 52 (OC) ranged from −1.8 to −1.9 mmol/L. In all groups, the greatest decreases were observed at 2 h post-breakfast and 2 h post-lunch.

At week 52, five patients required rescue therapy during the on-treatment period (two patients in both the biguanide and the glinide groups, and one patient in the TZD group).

DISCUSSION

Lixisenatide treatment administered daily over 52 weeks was well tolerated in Japanese patients with inadequately controlled type 2 diabetes mellitus, with a biguanide, TZD, alpha-GI or a glinide as background therapy. The safety profile of lixisenatide was generally similar across the four background OAD groups, and consistent with the known safety profile of this class of GLP-1 RAs. The safety data were also consistent with observations in previous international studies including Japanese patients[24,25], and Japan mono-country studies in which lixisenatide was investigated either as monotherapy, or in combination with BI with or without an SU[18,29,30].

Consistent with the mechanism of action of lixisenatide as a GLP-1 RA, nausea was the TEAE reported most frequently in the TZD, alpha-GI and glinide groups, and the second most frequently reported TEAE in the biguanide group; nasopharyngitis was the most frequently reported TEAE in the biguanide group. There was a low frequency of vomiting and diarrhea across all four background OAD groups. Gastrointestinal events generally occurred early on in treatment and decreased over the treatment period; this pattern is similar to what has been reported previously for lixisenatide treatment in Japanese patients[18,24]. TEAEs considered by the investigator as related to lixisenatide treatment that were reported most frequently across the four background OAD groups were nausea, constipation, vomiting and hypoglycemia. However, the possibility that the gastric cancer had developed before the initiation of the study cannot be ruled out.

Efficacy was a secondary end-point and was evaluated descriptively. Lixisenatide treatment, irrespective of background therapy, was effective in reducing HbA1c, FPG, bodyweight, and seven-point SMPG in patients with type 2 diabetes mellitus over the 24- and 52-week treatment periods. These results are consistent with a similar study in Japanese patients showing that liraglutide, a long-acting GLP-1 RA, was well tolerated and effective as combination therapy with an OAD (metformin, alpha-GI, TZD or glinide) in the treatment of type 2 diabetes mellitus[31].

Study limitations include the open-label trial design, and the fact that patients were not randomized (each treatment group was based on patients' existing background OAD therapy). However, despite these limitations, the overall safety and efficacy of lixisenatide were confirmed. Furthermore, the study design followed the guidance issued by the Japanese Ministry of Health, Labor and Welfare in 2010 to assess the long-term safety of antidiabetic agents in patients with insufficient glucose control.

Overall, lixisenatide treatment administered daily for 52 weeks in Japanese patients with type 2 diabetes mellitus treated with biguanide, alpha-GI, TZD or glinide as background therapy was well tolerated and efficient in improving glycemic control and decreasing bodyweight. These results support the use of lixisenatide in combination with OAD therapy as an effective and well tolerated treatment option for Japanese patients with type 2 diabetes mellitus after the failure of OAD treatment alone.

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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 Percent of (a) nausea and (b) vomiting by onset of any events at predefined time intervals up to week 24.
Figure S2 Mean change in glycated hemoglobin (HbA1c; %) from baseline by visit during the 52-week treatment period (modified intention-to-treat [mITT] population). Alpha-GI, alpha-glucosidase inhibitor; LOCF, last observation carried forward; SE, standard error; TZD, thiazolidinedione.
Table S1 List of principal investigator(s) and subinvestigator(s) per study site where patients were enrolled.