ORIGINAL ARTICLE

Efficacy and safety of lixisenatide in Japanese patients with type 2 diabetes mellitus inadequately controlled by sulfonylurea with or without metformin: Subanalysis of GetGoal-S

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ABSTRACT

Aims/Introduction: This was a subanalysis of Japanese patients included in the glucagon-like peptide-1 receptor agonist AVE0010 in patients with type 2 diabetes mellitus for glycemic control and safety evaluation (GetGoal-S) study – a 24-week, randomized, placebo-controlled study of lixisenatide in patients with type 2 diabetes mellitus inadequately controlled by sulfonylurea with or without metformin.

Materials and Methods: In GetGoal-S, 127 Japanese patients received the once-daily prandial glucagon-like peptide-1 receptor agonist lixisenatide 20 μg/day or a matching placebo. The primary outcome was change in glycated hemoglobin.

Results: At week 24, lixisenatide significantly reduced mean glycated hemoglobin (least squares mean difference vs the placebo −1.1% [12 mmol/mol, $P < 0.0001$]), and significantly more lixisenatide patients reached glycated hemoglobin targets of <7% (53 mmol/mol) and ≤6.5% (48 mmol/mol) vs the placebo. Lixisenatide produced statistically significant reductions in 2-h postprandial plasma glucose (least squares mean difference vs the placebo −8.51 mmol/L, $P < 0.0001$) and glucose excursion vs the placebo, and significantly reduced fasting plasma glucose (least squares mean difference vs the placebo −0.65 mmol/L, $P = 0.0454$). Bodyweight decreased with both lixisenatide and the placebo (least squares mean change −1.12 kg for lixisenatide, −1.02 kg for placebo). The overall incidence of adverse events was similar for lixisenatide and the placebo (84.2 and 82.4%, respectively), the most frequent being gastrointestinal disorders (52.6% for lixisenatide vs 29.4% for placebo). The incidence of symptomatic hypoglycemia was higher with lixisenatide vs the placebo (17.1 and 9.8%, respectively), with no cases of severe symptomatic hypoglycemia in either group.

Conclusions: In the Japanese subpopulation of the GetGoal-S study, lixisenatide produced a significant and clinically relevant improvement in glycated hemoglobin, with a pronounced improvement in postprandial plasma glucose, and a good safety and tolerability profile.

INTRODUCTION

Following a similar trend to Western countries, the prevalence of type 2 diabetes mellitus is increasing in Japan, and this nation is now one of the most affected by the worldwide diabetes epidemic[1]. In 2013, an estimated 7.6% of the population of Japan had type 2 diabetes mellitus and 12.6% had impaired glucose tolerance[2,3]. This high prevalence of type 2 diabetes mellitus is associated with a significant economic burden, with

diabetes accounting for 8% of the total Japanese national healthcare budget in 2010[4].

For many years, sulfonylureas (SUs) have been the most widely prescribed first-line therapy for type 2 diabetes mellitus in Japan; the use of new drugs, combination therapies and insulin is, however, increasing[5]. Both SUs and insulin are associated with the risk of weight gain and hypoglycemia. Glucagon-like peptide-1 (GLP-1) receptor agonists are a relatively recent addition to the treatment options for type 2 diabetes mellitus, and are highly effective in reducing glycated hemoglobin (HbA$_{1c}$), with low risks of hypoglycemia and bodyweight gain[6].

Lixisenatide is a once-daily short-acting or prandial GLP-1 receptor agonist for the treatment of type 2 diabetes mellitus[7]. Lixisenatide has been evaluated in a series of phase III, randomized, placebo-controlled trials known as the GetGoal program (GLP-1 receptor agonist AVE0010 in patients with type 2 diabetes mellitus for glycemic control and safety evaluation) as monotherapy[8], in combination with commonly used oral antidiabetic drugs[9–13], and as an add-on to basal insulin[14–16] in a total of more than 5,000 patients with type 2 diabetes mellitus globally. One of these trials, GetGoal-S, was a randomized, placebo-controlled, multinational study that evaluated the use of lixisenatide in patients with type 2 diabetes mellitus inadequately controlled by SU with or without metformin[11]. Lixisenatide is approved in several countries, including Japan, for the treatment of adults with type 2 diabetes mellitus, and could have particular efficacy in Japanese patients owing to potential differences in the pathophysiology of diabetes in this population[14,17,18]. Here, we report the results from an analysis assessing the efficacy and safety of lixisenatide in patients with type 2 diabetes mellitus inadequately controlled by SU with or without metformin that was carried out in a population of Japanese patients from the GetGoal-S study.

MATERIALS AND METHODS
Study Design
GetGoal-S (NCT00713830) was a phase III, randomized, double-blind, placebo-controlled, two-arm, parallel-group, multicenter trial carried out in 859 patients (127 of whom were Japanese) with type 2 diabetes mellitus insufficiently controlled by SU with or without metformin. The study consisted of up to 2 weeks' screening and a 1-week, single-blind, run-in period followed by a 24-week main treatment period, plus a variable controlled extension period of at least 52 weeks, mainly for safety purposes (not reported here). The study was approved by the local institutional review boards or ethics committees, and was carried out in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines. All subjects provided written informed consent to participate in the study. An independent data monitoring committee supervised the conduct of the study, and any possible allergic events were adjudicated by the external allergic reaction assessment committee.

Male and female participants with type 2 diabetes mellitus currently receiving SU with or without metformin and with a HbA$_{1c}$ level of 7–10% (53–86 mmol/mol), inclusive, were included in the study. Type 2 diabetes mellitus was diagnosed according to the diagnostic criteria of the World Health Organization, which is in line with those of the Japan Diabetes Society (JDS)[19]. The main exclusion criteria were: use of oral or injectable glucose-lowering agents other than SU or metformin within 3 months before the time of screening; fasting plasma glucose (FPG) level at screening of >250 mg/dL (13.9 mmol/L); and a history of unexplained pancreatitis, chronic pancreatitis, pancreatectomy, stomach/gastric surgery, inflammatory bowel disease, or end-stage renal disease (defined by serum creatinine clearance of <15 mL/min) and/or dialysis[11].

Eligible patients were randomized in a 2:1 ratio to receive lixisenatide once daily or a matching placebo in a two-step dose-increase regimen (10 μg once daily for 1 week, 15 μg once daily for 1 week, then 20 μg once daily). Randomization was stratified by HbA$_{1c}$ at screening (<8.0%, ≥8.0% [<64, ≥64 mmol/mol]) and metformin use at screening (yes/no). As recommended by the JDS, HbA$_{1c}$ values were expressed as the national glycohemoglobin standardization program values[20]. During the present study, HbA$_{1c}$ was blinded and investigators were alerted when FPG or HbA$_{1c}$ exceeded predefined thresholds for rescue (see Supplementary Table S1).

Treatment
During treatment, lixisenatide or a placebo was given subcutaneously within 1 h before the morning meal. In patients with HbA$_{1c}$ <8.0% (<64 mmol/mol), the SU dose was decreased by 25–50% at the randomization visit to prevent hypoglycemia, then gradually increased to the dose received at screening between weeks 4 and 12, according to fasting self-monitored plasma glucose measurements. Patients with HbA$_{1c}$ ≥8.0% (≥64 mmol/mol) continued on their established doses of SU. If metformin was prescribed, the dose was kept stable throughout the entire study. Rescue therapy was initiated based on routine fasting self-monitored plasma-calibrated glucose and central laboratory alerts set up on FPG (and HbA$_{1c}$ after week 12). Both treatment groups received lifestyle and dietary counseling at screening and then every 3 months thereafter.

Efficacy and Safety Outcomes
The primary efficacy end-point of the GetGoal-S was absolute change in HbA$_{1c}$ from baseline to week 24 for the modified intent-to-treat population, which consisted of all randomized patients who received at least one dose of double-blind investigational product, and had both a baseline and at least one post-baseline assessment of any primary or secondary efficacy parameter. Secondary efficacy measures included the percentage of patients reaching HbA$_{1c}$ <7.0% (53 mmol/mol) or ≤6.5% (48 mmol/mol) at week 24, changes in FPG and bodyweight from baseline to week 24, and the percentage of patients requiring rescue medication during the 24-week treatment period. In addition, at selected sites including those in Japan, all randomized patients underwent a standardized 600-kcal liquid

breakfast meal challenge test (400 mL of Ensure Plus® [Abbott Nutrition, Columbus, OH, USA], composed of 53.8% carbohydrate, 16.7% protein and 29.5% fat) 30 min after drug administration at baseline and week 24 for assessment of the secondary efficacy measure of 2-h postprandial plasma glucose (PPG). The 2-h glucose excursion was calculated as 2-h PPG – plasma glucose levels 30 min before the meal test before study drug administration. Changes from baseline to week 24 in 2-h postprandial glucagon, insulin, proinsulin and C-peptide were collected after a standardized meal in a subset of patients in selected centers.

The GetGoal-S safety population comprised all randomized patients exposed to at least one dose of double-blind investigational product. Safety and tolerability were assessed by review of adverse events (AEs) and treatment-emergent AEs, symptomatic and severe hypoglycemia, and clinical laboratory data. Potential allergic or allergic-like reactions were assessed by a blinded allergic reaction assessment committee.

Statistical Analysis

The primary efficacy end-point of the GetGoal-S study was analyzed using an analysis of covariance model, with treatment group, randomization strata and country (for overall population) as fixed effects, and baseline HbA_{1c} as a covariate.

Continuous secondary efficacy variables were also evaluated by analysis of covariance; categorical secondary efficacy variables were analyzed using a Cochran–Mantel–Haenszel method that was stratified on randomization strata. Differences between lixisenatide and the placebo and two-sided 95% confidence intervals (CIs) and P-values were estimated within the framework of analysis of covariance. Statistical analysis was carried out using the Statistical Analysis System software (SAS Institute Inc., Cary, NC, USA) version 9.2. For this subanalysis, no adjustment for multiplicity was carried out.

RESULTS

Demographic and Clinical Characteristics

A total of 127 Japanese patients were randomized in the GetGoal-S study, of whom 114 patients completed the 24-week treatment period (Figure S1). The discontinuation rate was 13.2% ($n = 10$) in the lixisenatide group and 5.9% ($n = 3$) in the placebo group. At baseline, demographic and clinical characteristics were generally similar between the two treatment groups (Table 1). In the lixisenatide group, measurements of body mass index were slightly lower, and slightly fewer patients were receiving metformin compared with the placebo group (Table 1). Baseline HbA_{1c} levels were also slightly lower in the lixisenatide group (8.4% [68 mmol/mol]) compared with the placebo group (8.6% [70 mmol/mol]). The most commonly used SU was glimepiride in both treatment groups.

Efficacy

At week 24, lixisenatide significantly reduced mean HbA_{1c} (Figure 1), with a least squares (LS) mean difference vs the

Table 1 | Demographic and baseline characteristics (safety population)

	Lixisenatide ($n = 76$)	Placebo ($n = 51$)
Male (%)	48 (63.2)	35 (68.6)
Mean age, years (SD)	59.3 (10.3)	59.2 (12.1)
Mean diabetes duration, years (SD)	12.0 (7.8)	12.4 (8.7)
Mean weight, kg (SD)	65.3 (11.5)	69.9 (16.6)
Mean BMI, kg/m² (SD)	24.9 (3.2)	26.2 (4.4)
Mean HbA_{1c}, % (SD) [mmol/mol]	8.4 (0.9) [68]	8.6 (0.8) [70]
Mean FPG, mmol/L (SD)	9.1 (2.0)	9.4 (2.2)
Mean 2-h PPG, mmol/L (SD)	17.8 (4.3)	17.8 (3.6)
MET use at screening, n (%)	47 (61.8)	36 (70.6)
SU use at screening, n (%)		
Glimepiride	54 (71.1)	38 (74.5)
Glibenclamide	17 (22.4)	12 (23.5)
Gliclazide LM	3 (3.9)	0 (0.0)
Gliclazide	2 (2.6)	1 (2.0)

BMI, body mass index; FPG, fasting plasma glucose; HbA_{1c}, glycated hemoglobin; LM, libération modifiée (modified release); MET, metformin; PPG, postprandial plasma glucose; SD, standard deviation; SU, sulfonylurea.

placebo of −1.1% (12 mmol/mol; 95% CI −1.407 to −0.803), $P < 0.0001$. With lixisenatide treatment, mean (standard error [SE]) HbA_{1c} was reduced from 8.4% (0.12%) at baseline to 7.5% (0.10%) at week 8, 7.3% (0.10%) at week 12, and 7.5% (0.12%) at week 24; mean (SE) HbA_{1c} did not reduce with the placebo, and was 8.6% (0.11%) at baseline, 8.6% (0.13%) at week 8, 8.7% (0.15%) at week 12, and 8.6% (0.17%) at week 24. Significantly more patients in the lixisenatide group reached HbA_{1c} targets of <7.0% (53 mmol/mol) and ≤6.5% (48 mmol/mol) vs those in the placebo group (Figure 1). Lixisenatide also led to significant reductions in 2-h PPG and glucose excursion at week 24 (LS mean difference in 2-h PPG vs the placebo of −8.51 mmol/L [95% CI −10.128 to −6.895], $P < 0.0001$, and LS mean difference in glucose excursion vs the placebo of −7.98 mmol/L [95% CI −9.480 to −6.485], $P < 0.0001$; Figure 2). Lixisenatide provided a significant reduction in FPG from baseline to week 24 compared with the placebo (LS mean difference vs placebo of −0.65 mmol/L [95% CI −1.287 to −0.014], $P = 0.0454$).

Improvements in glycemic control with lixisenatide were associated with significant reductions in parameters of postprandial insulin secretion (LS mean difference in 2-h postprandial plasma insulin vs the placebo [$n = 113$] of −81.50 pmol/L [95% CI −117.934 to −45.072], $P < 0.0001$, LS mean difference in 2-h postprandial proinsulin vs the placebo [$n = 103$] of −10.64 pmol/L [95% CI −19.968 to −1.317], $P = 0.0257$, and LS mean difference in 2-h postprandial C-peptide vs the placebo [$n = 112$] of −0.44 nmol/L [95% CI −0.671 to −0.203], $P = 0.0003$). Levels of 2-h postprandial glucagon were also signfiicantly lower with lixisenatide vs the placebo ($n = 110$; LS
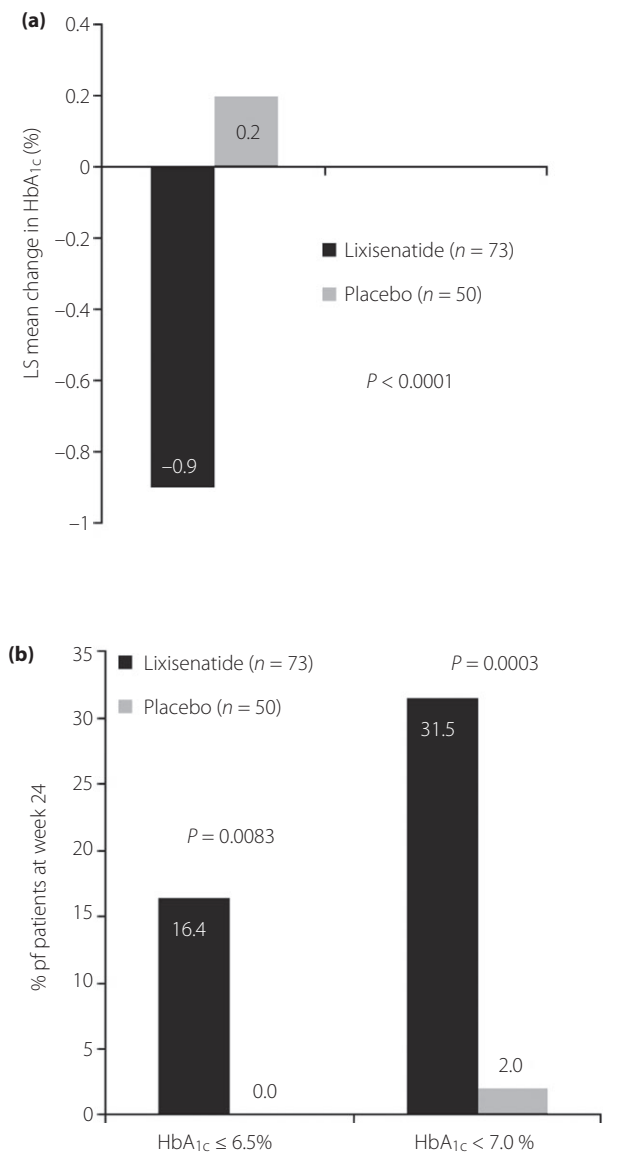
Figure 1 | Glycated hemoglobin (HbA$_{1c}$) at week 24. (a) Least squares (LS) mean change in HbA$_{1c}$. (b) Proportion of patients achieving HbA$_{1c}$ targets. Data are for the modified intent-to-treat population (last observation carried forward), $n = 73$ and $n = 50$ for lixisenatide and the placebo, respectively. HbA$_{1c}$ −0.9% = 10 mmol/mol; HbA$_{1c}$ 0.2% = 2 mmol/mol; HbA$_{1c}$ ≤6.5% = 48 mmol/mol; HbA$_{1c}$ <7% = 53 mmol/mol.
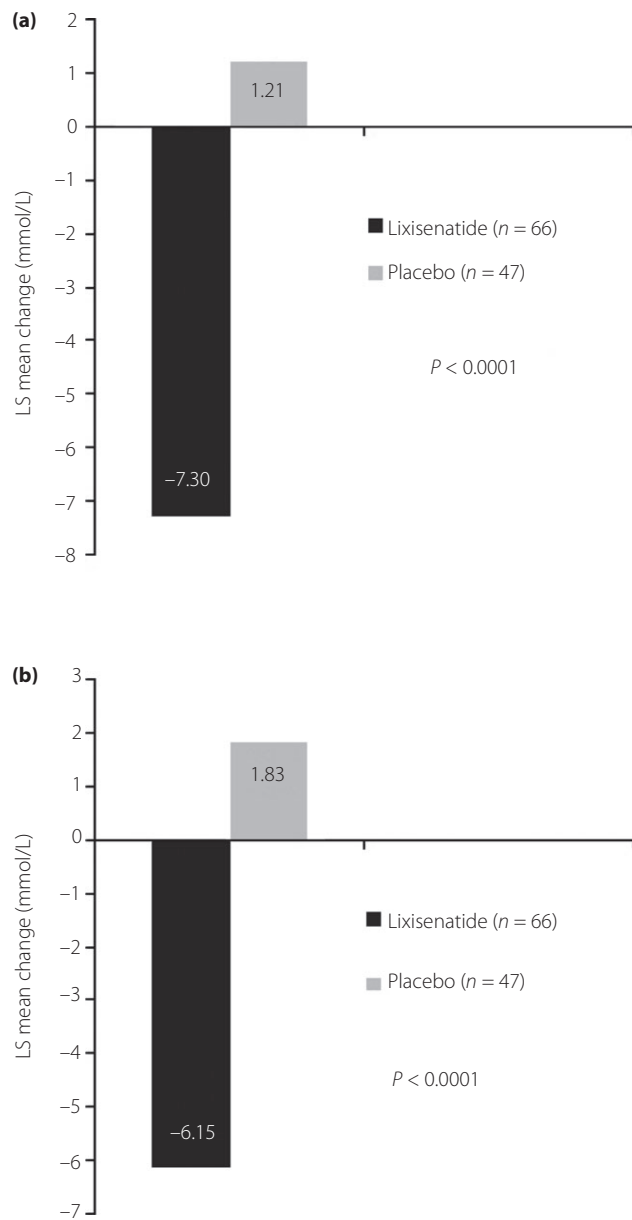

Figure 2 | Postprandial plasma glucose at week 24. (a) Least squares (LS) mean change in 2-h postprandial plasma glucose. (b) LS mean change in glucose excursion. *Data are for the modified intent-to-treat population (last observation carried forward), $n = 66$ and $n = 47$ for lixisenatide and placebo, respectively. *Based on 127 patients undergoing a standardized breakfast meal test at selected sites. Glucose excursion = 2-h postprandial plasma glucose − plasma glucose 30 min before the meal test before study drug administration.

mean difference of −17.84 ng/L [95% CI −25.207 to −10.465], $P < 0.0001$).

Bodyweight decreased with both lixisenatide and the placebo (−1.12 kg for lixisenatide and −1.02 kg for placebo), with a LS mean difference vs the placebo of −0.11 kg (95% CI −0.798 to 0.586, $P = 0.7628$). The proportion of patients requiring rescue therapy was significantly lower in the lixisenatide group compared with the placebo group (2.6 vs 15.7%, $P = 0.0158$).

Safety and Tolerability

The overall incidence of AEs during the 24-week treatment period was similar in the lixisenatide (84.2%) and placebo treatment groups (82.4%; Table 2); however, fewer serious AEs were reported for lixisenatide than for the placebo ($n = 3$ [3.9%] vs $n = 4$ [7.8%], respectively). AEs leading to discontinuation were

Table 2 | Adverse events over the 24-week main treatment period (safety population)

	Lixisenatide (n = 76)	Placebo (n = 51)
Any AE	64 (84.2)	42 (82.4)
Serious AE	3 (3.9)	4 (7.8)
Any AE leading to discontinuation	10 (13.2)	2 (3.9)
GI disorders (all)	40 (52.6)	15 (29.4)
Nausea	19 (25.0)	1 (2.0)
Nausea leading to discontinuation	6 (7.9)	0 (0.0)
Vomiting	4 (5.3)	2 (3.9)
Diarrhea	9 (11.8)	4 (7.8)
Symptomatic hypoglycemia*	13 (17.1)	5 (9.8)
Severe symptomatic hypoglycemia†	0 (0.0)	0 (0.0)
Lipase increased	0 (0.0)	1 (2.0)

Data are n (%). *Symptomatic hypoglycemia is an event with clinical symptoms considered to result from a hypoglycemic episode (e.g., sweating, palpitations, hunger, restlessness, anxiety, fatigue, irritability, headache, loss of concentration, somnolence, psychiatric or visual disorders, transient sensory or motor defects, confusion, convulsions, or coma), with an accompanying plasma glucose <60 mg/dL (3.3 mmol/L) or associated with prompt recovery after oral carbohydrate administration, intravenous glucose, or glucagon injection if no plasma glucose measurement was available. †Severe symptomatic hypoglycemia is symptomatic hypoglycemia requiring the assistance of another person, because the patient could not treat him/herself because of acute neurological impairment, and which was associated either with a plasma glucose level <36 mg/dL (2.0 mmol/L) or, if no plasma glucose measurement was available, a prompt recovery with carbohydrate, intravenous glucose or glucagon administration. AE, adverse event; GI, gastrointestinal.

more frequent in the lixisenatide group (n = 10, 13.2%) compared with the placebo group (n = 2, 3.9%; Table 2). The most frequent AEs were gastrointestinal disorders (52.6 vs 29.4% in the lixisenatide and placebo groups, respectively), with the most frequent being nausea (25.0 vs 2.0% for lixisenatide and placebo, respectively; Table 2), which was mostly reported during the initial weeks of treatment, was generally mild-to-moderate and transient in nature.

The incidence of symptomatic hypoglycemia in the lixisenatide group was 17.1% compared with 9.8% in the placebo group, with no cases of severe symptomatic hypoglycemia in either group (Table 2).

No allergic reactions were reported during the 24-week, main double-blind treatment period. As per specified protocol recommendations, events potentially qualifying as pancreatitis were reported separately. One patient (2.0%) in the placebo group reported an event (lipase increase) compared with none in the lixisenatide group for the whole period.

DISCUSSION
In the present analysis of Japanese patients with type 2 diabetes mellitus inadequately controlled by SU with or without metformin, lixisenatide 20 μg once daily significantly reduced HbA$_{1c}$, mostly through a significant reduction in PPG and glucose excursions. The current analysis showed a major improvement in glycemic control, as assessed by change in HbA$_{1c}$ (LS mean difference vs placebo −1.1% [12 mmol/mol]; 95% CI −1.407 to −0.803, P < 0.0001), PPG parameters (2-h PPG [LS mean difference vs placebo −8.51 mmol/L, P < 0.0001] and glucose excursion [LS mean difference vs placebo −7.98 mmol/L, P < 0.0001]) and FPG (LS mean difference vs placebo −0.65 mmol/L, P = 0.0454), in line with the overall study results[11]. Additionally, the reductions in mean HbA$_{1c}$ levels from baseline to week 8, 12 and 24 showed the quick and durable efficacy of lixisenatide compared with the placebo.

In a 24-week study of short-acting exenatide added to SU-based oral therapy in Japanese patients[21], twice-daily exenatide 10 μg was associated with a significant reduction in HbA$_{1c}$ vs the placebo (−1.62 vs −0.28%, P < 0.001) and FPG (−1.61 vs 0.42 mmol/L, P = 0.0002 vs placebo) with a treatment difference comparable with that achieved in the present study with lixisenatide[21]. The long-acting GLP-1 receptor agonist liraglutide 0.9 mg/day also showed substantial improvements in HbA$_{1c}$ in Japanese patients when added to SU therapy, with a treatment difference over the placebo of −1.3% (P < 0.0001 vs placebo) over 24 weeks[22]. The reduction in FPG with liraglutide vs placebo (−1.80 mmol/L, P < 0.0001)[22] was greater than the smaller, though significant, reduction in FPG with lixisenatide in the current study, or with exenatide as previously reported[21]. This is despite similar reductions in HbA$_{1c}$ in the three studies, and suggests that there are different mechanisms underlying glycemic control with the long- vs short-acting agents.

Of note in this analysis was the pronounced reduction in PPG seen with lixisenatide vs placebo. Indeed, only modest reductions in PPG have been reported in studies of long-acting GLP-1 receptor agonists, which have minimal impact on gastric emptying due to tachyphylaxis with continuous GLP-1 receptor activation[23]. Conversely, short-acting GLP-1 receptor agonists lead to a substantial and maintained delay in gastric emptying, with the consequence of pronounced PPG reduction, making them an effective prandial therapy[24], and a complementary therapy for use with basal insulin, which predominantly lowers FPG. The beneficial efficacy of lixisenatide in reducing PPG compared favorably with a long-acting GLP-1 receptor agonist in a head-to-head study. A recent 28-day, randomized, open-label, parallel-group, multicenter study carried out in seven German centers found that once-daily prandial lixisenatide reduced PPG significantly more than the long-acting GLP-1 receptor agonist liraglutide at the 1.8 mg/day dose (mean change in area under the curve$_{(0.30–4.30 h)}$ −12.6 vs −4.0 h/mmol/L, respectively, P < 0.0001)[25]. Indeed, the placebo-subtracted PPG reduction in this Japanese population was substantial: −8.51 mmol/L.

The reduction in 2-h PPG levels seen in the present study is consistent with previous studies in mixed populations, in whom lixisenatide has shown profound effects on PPG as

monotherapy[8], as add-on to oral antidiabetic drugs[9,11], and in combination with basal insulin[15,16]. In an analysis of lixisenatide in a mixed Asian population (including Japanese patients) in combination with basal insulin with or without SU (GetGoal-L-Asia)[14], comparable results with our analysis were reported, with significant reductions in both HbA$_{1c}$ vs the placebo (−0.88%) and 2-h PPG vs the placebo (−7.83 mmol/L)[14]. It has been previously reported that GLP-1 receptor agonists exert a greater effect on glycemic control in Asian patients compared with non-Asian patients[26]. The improvements in glucose control observed in Japanese patients can be explained by two factors: (i) limited meal-induced enhancement of GLP-1 secretion[17,18]; and (ii) a pathophysiology of impaired glucose tolerance characterized by impaired early phase insulin secretion and insulin resistance[27,28]. Lixisenatide has been shown to restore first-phase insulin secretion in patients with type 2 diabetes mellitus, making it pertinent for use in a Japanese population[29].

In addition, other possible predictive factors of efficacy with GLP-1 receptor agonists include baseline HbA$_{1c}$, residual β-cell function and sex[30–34]. Although not evaluated here, it would be of interest to evaluate these possible predictors in Japanese and Asian patients treated with lixisenatide in the future.

In contrast to the overall GetGoal-S population, in which there was a significant treatment difference in bodyweight of 0.84 kg vs the placebo[11], no significant difference in bodyweight reduction was reported in this Japanese subpopulation. The study of liraglutide added to SU in Japanese patients also failed to show a reduction in bodyweight despite significant reductions in other populations[22]. This could be attributed to the fact that Asian populations typically have lower bodyweight than Western patients and, as such, are less likely to see large bodyweight reductions. This is supported by the GetGoal-L-Asia study[14], in which a small reduction in bodyweight was reported over time in an Asian population with relatively low mean body mass index[14].

In the present Japanese population, lixisenatide was generally well tolerated, with nausea being the most commonly reported gastrointestinal event (25.0%), similar to the incidence with lixisenatide in the overall study population (25.3%) of GetGoal-S[11]. The incidence of symptomatic hypoglycemia was higher in the lixisenatide group vs the placebo (17.1 vs 9.8%, respectively), and no severe symptomatic hypoglycemia was reported in either group. This is similar to symptomatic hypoglycemia incidence levels in the overall GetGoal-S population, in which only one patient (in the lixisenatide group) experienced a severe hypoglycemic event. As in the present study, the incidence of symptomatic hypoglycemia in the GetGoal-L-Asia study was also higher with lixisenatide than with the placebo; however, in patients not receiving SU, the incidence was similar to the placebo, suggesting possible involvement of SUs in symptomatic hypoglycemia[14]. In comparison, with exenatide 10 μg twice daily in a similar population of Japanese patients, the rate of any treatment-emergent AE was 94%, the rate of nausea was 36% and the proportion of patients who experienced an AE leading to study withdrawal was 25%[21]. The rate of symptomatic hypoglycemia regardless of blood glucose levels was also notably higher with exenatide than with the placebo[21].

Different to exenatide, lixisenatide is administered once daily. Pharmacological studies have shown that once-daily lixisenatide administration before breakfast is as effective as twice-daily dosing before breakfast and the evening meal in both Japanese and Caucasian patients with type 2 diabetes mellitus[35,36]. A lixisenatide dose of 20 μg once daily, as used in the current study, showed the best efficacy-to-tolerability ratio reduces the burden of injection for patients compared with twice-daily dosing[36]. Administering lixisenatide before breakfast controls morning postprandial hyperglycemia, which is typically the largest postmeal excursion of the day because of hepatic glucose production in response to the overnight fast (the dawn phenomenon)[37]. However, the timing of peaks in postprandial glucose can vary between patients depending on the distribution of carbohydrate between the meals of the day[38], which is often highest at the evening meal for Japanese patients. The GetGoal-M study of lixisenatide added to metformin in a global population of patients with type 2 diabetes mellitus has shown comparable improvements in glycemic control with morning or evening administration of lixisenatide[9]. Finally, a recently published 24-week study showed that once-daily lixisenatide is as effective when administered at patients' self-reported main meal of the day compared with pre-breakfast administration[39].

The Japanese population in the current study had been diagnosed with type 2 diabetes mellitus for approximately 12 years, and 60–70% of individuals had received a combination of SU and metformin; as such, this population might be considered as being at a relatively advanced stage of diabetes, with reduced β-cell function[40,41]. Other studies have shown that liraglutide significantly reduces HbA$_{1c}$ in Japanese patients treated with SU[21,42]. Recently, however, it has been shown that the glucose-lowering efficacy of some GLP-1 receptor agonists might depend on the remaining β-cell function[43,44], and in such a population, lixisenatide could offer a well-tolerated alternative to treatment intensification with basal insulin, and might compensate for reduced β-cell function.

Limitations of the present study include that the analysis was not prespecified, and that there were some differences in baseline characteristics.

This analysis of lixisenatide carried out in a Japanese subpopulation of the GetGoal-S study showed that lixisenatide was well tolerated and provided significant improvement in glycemic control, as assessed by change in HbA$_{1c}$, with a pronounced improvement in PPG control. The current results showed the efficacy–tolerability profile of lixisenatide once daily in the context of SU-based oral agent failure, and emphasize its potential as an important and beneficial option for the treatment of type 2 diabetes mellitus in the Japanese population.

ACKNOWLEDGMENTS

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SUPPORTING INFORMATION

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

Table S1 | Criteria for initiation of rescue therapy.
Figure S1 | Patient disposition flow.