Lixisenatide treatment improves glycaemic control in Asian patients with type 2 diabetes mellitus inadequately controlled on metformin with or without sulfonylurea: a randomized, double-blind, placebo-controlled, 24-week trial (GetGoal-M-Asia)

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Abstract

Background This study assessed the efficacy and safety of the once-daily glucagon-like peptide-1 receptor agonist, lixisenatide, in Asian patients with type 2 diabetes mellitus inadequately controlled on metformin ± sulfonylurea.

Methods In this 24-week, double-blind, placebo-controlled, multinational study, patients were randomized to lixisenatide 20 μg once daily or placebo. The primary endpoint was absolute change in glycated haemoglobin (HbA1c) from baseline to week 24.

Results A total of 391 patients were randomized. Lixisenatide significantly reduced HbA1c levels compared with placebo (LS mean difference: -0.36%, p = 0.0004). A significantly higher proportion of lixisenatide-treated patients achieved HbA1c targets of <7% (p = 0.003) and ≤6.5% (p = 0.001) versus placebo. Lixisenatide was associated with a statistically significant reduction in 2-h postprandial plasma glucose after a standardized breakfast versus placebo (LS mean difference: -4.28 mmol/L, p < 0.0001) and a significant reduction in fasting plasma glucose (p = 0.0109). There was no difference in weight loss versus placebo, with a modest reduction in body weight reported for both groups (lixisenatide: -1.50 kg, placebo: -1.24 kg; p = 0.296). The incidence of treatment-emergent adverse events (TEAEs) was 64.3% with lixisenatide versus 47.4% with placebo, with serious TEAEs reported in 1.5% versus 2.1% of patients, respectively. The most common TEAE in the lixisenatide group was nausea (16.3% vs 2.6% with placebo). The incidence of symptomatic hypoglycaemia was 5.6% with lixisenatide treatment and 2.6% with placebo (p = 0.1321), with no severe symptomatic hypoglycaemia events reported.

Conclusions In Asian patients with type 2 diabetes mellitus insufficiently controlled on metformin ± sulfonylurea, lixisenatide significantly improved glycaemic control and was well tolerated during the 24-week study. © 2014 The Authors. Diabetes/Metabolism Research and Reviews published by John Wiley & Sons, Ltd.

Keywords lixisenatide; type 2 diabetes mellitus (T2DM); glucagon-like peptide-1 (GLP-1) receptor agonists; Asia
Introduction

Type 2 diabetes mellitus (T2DM) is a major health concern in Asia, with prevalence now reaching epidemic proportions [1]. Asia is believed to account for 60% of the global diabetic population [2], with substantial rises expected over coming decades. According to the International Diabetes Federation, China alone is expected to see an increase of almost 50% in the number of individuals with diabetes between the years 2011 and 2030 (90.0 million to 129.7 million, respectively), compared with a European rise of approximately 20% (52.8 million in 2011 to 64.2 million in 2030) [3].

This increase in diabetes in Asia is primarily attributed to rising obesity levels, with increases in body mass index (BMI) and upper-body adiposity [4]. Among Asian people, lifestyle changes, including diet and urbanization, are all contributing factors [4–6]. In addition, the high consumption of white rice associated with the Asian diet may play a role [7].

In addition to potential environmental causes, there appears to be a strong genetic predisposition to T2DM among Asian people. US Asians have been demonstrated to be more susceptible to diabetes than US Caucasians [8]. Furthermore, a study in healthy young adults of different ethnic origins matched for age, BMI, waist circumference, birth weight and diet demonstrated that Asian individuals had the highest postprandial glycaemia rates and lowest insulin sensitivity [9].

Type 2 diabetes mellitus in Asian patients is characterized by features that are distinct from Western patients, such as a susceptibility to diabetes at a younger age of onset and a lower BMI than Caucasians [6]. The latter is likely owing to higher body fat and abdominal obesity levels among Asian people compared with Caucasians of the same BMI [6]. There may also be a higher risk of hypoglycaemia in Asian patients with T2DM [10].

Glycaemic control is essential for the prevention of diabetes-associated complications, with the International Diabetes Federation and the American Diabetes Association/European Association for the Study of Diabetes proposing respective targets for glycated haemoglobin (HbA1c) of ≤6.5% and <7% in Asian patients with T2DM [3,11]. However, data from Asia and many other regions of the world indicate that these targets are not always achieved. Delayed diagnosis [12] and inadequate therapeutic control are both key contributors, with recent trials revealing poor glycaemic control in Asian patients on oral antidiabetic agents (OADs) alone [13] or on insulin with or without sulfonylureas [14].

Glucagon-like peptide-1 (GLP-1) receptor agonists are glucose-lowering agents that are now an established treatment option for T2DM [15]. GLP-1 receptor agonists can be categorized as being long-acting agents, which mainly affect fasting plasma glucose (FPG), or short-acting (prandial) agents, which predominantly affect postprandial plasma glucose (PPG). Currently available long-acting GLP-1 receptor agonists include exenatide long-acting release [16], given once weekly, and lixisenatide [17], given once daily. Short-acting agents include exenatide immediate release [18], given twice daily, and lixisenatide, once daily.

Results of the phase II dose ranging study [19] were compatible with a once-daily dosing of lixisenatide 20 μg. The efficacy and safety of lixisenatide 20 μg once daily has been demonstrated as monotherapy [20], in combination with OADs [21–23] and as add-on to basal insulin [14,24,25]. Lixisenatide once daily may be effective in treating Asian patients with T2DM, as research suggests that this patient group may have a significant GLP-1 deficit [26]. In a recent study, lixisenatide was demonstrated to significantly improve glycaemic control in Asian patients with T2DM who were inadequately controlled on basal insulin with or without sulfonylurea [14].

This randomized controlled study assessed the effects of once-daily lixisenatide versus placebo on efficacy, safety and tolerability in Asian patients with T2DM who did not achieve adequate control with OADs alone (metformin with or without sulfonylurea).

Materials and methods

Study design

This 24-week, randomized (1 : 1 ratio), double-blind, placebo-controlled, two-arm, parallel-group, multinational study was conducted in 37 centres in China, Malaysia, Thailand and Hong Kong. The study was performed between July 2010 and December 2011.

A dose of 20 μg QD was selected for lixisenatide, as this has previously been demonstrated to have an optimal efficacy-to-tolerability ratio [19]. The first stage of the study was a screening period of up to 3 weeks, which encompassed an initial screening phase of 2 weeks or less and a 1-week blinded placebo run-in phase. After screening, eligible patients entered a 24-week, double-blind, placebo-controlled treatment period and were randomized in a 1 : 1 ratio to receive lixisenatide (10 μg for 2 weeks, then the maintenance dose of 20 μg) or volume-matched placebo, administered, in general, subcutaneously once daily within 1 h before breakfast. Study drug volume was not blinded. To assess the postprandial effects after a standardized breakfast, lixisenatide was administered on that day exactly 30 min before the meal. Randomization was stratified by screening HbA1c (<8.0%, ≥8.0%) and sulfonylurea use (yes, no). Randomization of patients...
and allocation of medication was carried out using an interactive voice response system/interactive Web-based system.

For background therapy, the metformin dose was kept stable at its baseline dose of at least 1.0 g/day throughout the study. In patients with sulphonylurea given in combination with metformin, the dose of sulphonylurea was decreased by 25–50% at randomization in patients with a screening HbA$_{1c}$ <8% in order to decrease the risk of hypoglycaemia; whereas in patients with HbA$_{1c}$ ≥8% at screening, the dose was kept stable at its baseline dose of at least the maximal effective dose (equating to half of the maximum recommended dose according to local labelling). For patients whose sulphonylurea dose was decreased at screening, the sulphonylurea dose was progressively increased, in the absence of hypoglycaemia, to the baseline dose between weeks 4 and 12, according to fasting self-monitored plasma glucose values, unless occurrence of hypoglycaemia prevented this increase. The 24-week treatment period was followed by a 3-day safety follow-up phase for all patients.

The study was approved by the local ethics committee or institutional review board for all 37 study centres and complied with the Declaration of Helsinki and the International Conference on Harmonization—Good Clinical Practice Guidelines and all applicable amendments. The protocol also complied with the laws and regulations, as well as any applicable guidelines, of the countries where the study was conducted. Written informed consent was provided by all patients prior to participation in the study.

**Participants**

The study population comprised male and female Asian participants with T2DM diagnosed for at least 1 year and inadequately controlled on metformin with or without sulphonylurea, with HbA$_{1c}$ ≥7.0% and ≤10.0% and FPG at screening of ≤13.9 mmol/L. The use of OADs other than metformin or sulphonylurea for 3 months prior to screening was not permitted. Metformin dose had to have been at a stable dose of between 1 and 1.5 g/day, and sulphonylurea had to be at a maximum effective dose and stable, for the 3 months prior to screening.

The main exclusion criteria included history of hypoglycaemia unawareness; history of unexplained pancreatitis, chronic pancreatitis, pancreactectomy, stomach/gastric surgery, inflammatory bowel disease or patients considered by the investigator at high risk for acute pancreatitis; personal or family history of medullary thyroid cancer; history of metabolic acidosis, including diabetic ketoacidosis within 1 year prior to screening; renal impairment; and history of gastrointestinal disease associated with prolonged nausea and vomiting within 6 months prior to screening.

**Assessments**

The primary efficacy endpoint was the absolute change in HbA$_{1c}$ from baseline to week 24. Categorical secondary efficacy variables included the percentage of patients with HbA$_{1c}$ <7% or ≤6.5% at week 24. Continuous secondary efficacy variables consisted of change in FPG (mmol/L), 2-h PPG (mmol/L) after a standardized breakfast (Ensure Plus®, Abbott Nutrition), glucose excursion (2-h PPG minus plasma glucose 30 min prior to the meal test before study drug administration) (mmol/L) after a standardized breakfast and body weight (kg) from baseline to week 24. Two-hour PPG and glucose excursion after a standardized breakfast was carried out in sites in China only and was performed in approximately 50% of all randomized patients.

Safety and tolerability were assessed on the basis of the reported treatment-emergent adverse events (TEAEs). These included symptomatic hypoglycaemia and severe symptomatic hypoglycaemia, local tolerability at injection site, allergic events, suspected pancreatitis and increased calcitonin. Symptomatic hypoglycaemia was defined as clinical symptoms that were considered to result from a hypoglycaemic episode with an accompanying plasma glucose of 60 mg/dL (<3.3 mmol/L) or associated with prompt recovery after oral carbohydrate, intravenous glucose or glucagon administration. The dose of sulphonylurea was to be decreased by 25–50% in cases of two or more symptomatic hypoglycaemic episodes or one severe hypoglycaemic episode, as appropriate. Severe symptomatic hypoglycaemia was defined as symptomatic hypoglycaemia in which the patient required the assistance of another person and which was associated with a plasma glucose of 36 mg/dL (<2.0 mmol/L) or with prompt recovery following carbohydrate, intravenous glucose or glucagon administration. Vital signs (heart rate and supine systolic and diastolic blood pressure) were recorded at each onsite visit throughout the study.

**Statistical analyses**

The safety population was defined as all randomized patients who received at least one dose of double-blind treatment. Unless otherwise indicated, all efficacy data were analysed in the modified intent-to-treat population, which consisted of all randomized patients who received at least one dose of double-blind treatment and had both a baseline assessment and at least one post-baseline assessment of efficacy variables. The primary efficacy variable (change in HbA$_{1c}$ from baseline to week 24) was analysed using an analysis of covariance (ANCOVA) model with treatment groups (lixisenatide and placebo), randomization strata of screening HbA$_{1c}$ (<8.0, ≥8.0%)
and sulfonylurea use (yes, no) and country as fixed effects, and baseline HbA1c value as a covariate. Difference between lixisenatide and placebo and two-sided 95% confidence interval (CI), as well as p-value, were estimated within the framework of ANCOVA. The last observation carried forward (LOCF) procedure was used to handle missing data at week 24, by imputing the last available post-baseline, on-treatment HbA1c measurement. HbA1c values over time are given for the observed cases. Continuous secondary efficacy variables were analysed by ANCOVA, whereas categorical secondary efficacy variables were analysed using a Cochran–Mantel–Haenszel method stratified on randomization strata. Summaries of safety data (descriptive statistics or frequency tables) were presented by treatment groups. Data are presented as mean ± standard error (SE) unless indicated otherwise. In a post-hoc analysis, the difference in hypoglycaemia between both treatment groups was calculated using the Cochran–Mantel–Haenszel test stratified by HbA1c at screening (<8% or ≥8%) and sulfonylurea use (yes or no).

## Results

Of the 655 patients screened, a total of 391 patients were randomized (1 : 1) to receive treatment with lixisenatide (n = 196) or placebo (n = 195). The most common reason for screening failure was HbA1c outside of the range (≥7.0% and ≤10.0%). Of the 391 randomized patients, 196 in the lixisenatide group versus 194 in the placebo group were exposed to the study treatment and included in the safety analysis population. A total of 388 patients (195 in the lixisenatide group vs 193 in the placebo group) were included in the modified intent-to-treat population. The majority of patients completed the 24-week treatment period (91.3% in the lixisenatide group and 94.4% in the placebo group). Premature discontinuation from treatment occurred in 8.7% of the lixisenatide group and 5.1% of the placebo group. The main reasons for treatment discontinuation were TEAEs in the lixisenatide group (5.6% and 1.5% in the lixisenatide and placebo groups, respectively) and ‘other reasons’ in the placebo group (2.6% for both groups).

Demographics and efficacy characteristics were well matched between the two treatment groups at baseline (Table 1).

### Efficacy

#### Glycated haemoglobin

Glycated haemoglobin levels declined in both treatment groups during the 24-week, double-blind treatment period (Figure 1A). Lixisenatide treatment significantly reduced HbA1c levels compared with placebo (Figure 1B).

| Table 1. Patient demographics and baseline characteristics (safety population) |
|-----------------------------------------------|
|                          | Lixisenatide (n = 196) | Placebo (n = 194) |
| Mean age, years (SD)     | 54.5 (10.3)            | 55.1 (10.5)       |
| Male, n (%)              | 101 (51.5)             | 91 (46.9)         |
| Race, n (%)              | 196 (100)              | 194 (100)         |
| Sites, n (%)             |                         |                   |
| China                    | 178 (90.8)             | 180 (92.8)        |
| Hong Kong                | 13 (6.6)               | 5 (2.6)           |
| Malaysia                 | 5 (2.6)                | 8 (4.1)           |
| Thailand                 | 0                      | 1 (0.5)           |
| Randomization strata of HbA1c at screening, n (%) | 101 (51.5) | 100 (51.6) |
| HbA1c < 8%               | 95 (48.8)              | 94 (48.5)         |
| HbA1c ≥ 8%               | 89 (45.4)              | 87 (44.9)         |
| Mean BMI, kg/m² ± SD     | 26.8 ± 3.9             | 27.1 ± 3.8        |
| Mean duration of diabetes, years (SD) | 6.5 (4.6) | 6.8 (4.8) |
| Metformin treatment      |                         |                   |
| Duration, years (SD)     | 4.0 (4.0)              | 3.5 (3.1)         |
| Daily dose, mg (SD)      | 1369.9 (219.9)         | 1363.4 (221.9)    |
| SU treatment             |                         |                   |
| Duration, years (SD)     | 3.1 (4.3)              | 2.8 (3.0)         |
| Mean baseline efficacy variables |                     | |
| HbA1c, % (SD)            | 7.95 (0.81)            | 7.85 (0.71)       |
| 2-h PPG, mmol/L (SD)     | 16.07 (3.77)           | 17.19 (4.06)      |
| 2-h glucose excursion%, mmol/L (SD) | 7.12 (3.21) | 8.14 (3.11) |
| FPG, mmol/L (SD)         | 8.84 (2.12)            | 8.74 (1.83)       |
| Body weight, kg (SD)     | 73.18 (13.93)          | 72.74 (13.64)     |

SD, standard deviation; HbA1c, glycosylated haemoglobin; SU, sulfonylurea; BMI, body mass index; PPG, postprandial plasma glucose; FPG, fasting plasma glucose.

*After a standardized breakfast at selected sites only (n = 130 and n = 132 for lixisenatide and placebo, respectively).

The least squares mean change from baseline to week 24 (LOCF) was −0.83% for lixisenatide compared with −0.47% for placebo [least squares mean difference ± SE vs placebo (95% CI): −0.36 ± 0.10 (−0.55 to −0.16); p = 0.0004]. Furthermore, a significantly higher proportion of lixisenatide-treated patients achieved HbA1c targets of <7% (p = 0.003) and ≤6.5% (p = 0.001) at week 24 compared with placebo (LOCF, Figure 1C).

#### Postprandial plasma glucose after a standardized breakfast

The standardized breakfast meal test, performed in the morning 30 min after drug administration, revealed a statistically significant improvement in postprandial glycaemic control with lixisenatide compared with placebo. The least squares mean change in 2-h post-breakfast PPG from baseline to week 24 was −5.61 mmol/L in the lixisenatide treatment group compared with −1.33 mmol/L in the placebo treatment group [least squares mean difference ± SE vs placebo (95% CI): −4.28 ± 0.55 (−5.36 to −3.20); p < 0.0001; Figure 2A]. A similar improvement was noted with lixisenatide versus placebo for post-breakfast glucose...
excursion [least squares mean difference ± SE vs placebo (95% CI): \(-3.99 \pm 0.50 (-4.97 \text{ to } -3.01)\); Figure 2B].

**Fasting plasma glucose**
Lixisenatide significantly reduced FPG levels compared with placebo treatment, resulting in a least squares mean change from baseline to week 24 of \(-0.69 \text{ mmol/L}\) in the lixisenatide group compared with \(-0.21 \text{ mmol/L}\) in the placebo group [least squares mean difference ± SE vs placebo (95% CI): \(-0.48 \pm 0.19 (-0.85 \text{ to } -0.11); p = 0.0109\); Figure 2C].

**Body weight**
There was modest weight loss in both treatment groups, with no significant difference between the groups. Least squares mean change in body weight from baseline to week 24 was \(-1.50 \text{ kg}\) with lixisenatide versus \(-1.24 \text{ kg}\) with placebo [least squares mean difference ± SE vs placebo (95% CI): \(-0.27 \pm 0.26 (-0.78 \text{ to } 0.24); p = 0.296\)].

**Safety and tolerability**
The incidence of TEAEs was higher in the lixisenatide group compared with the placebo group (64.3% vs 47.4%, respectively; Table 2). Serious TEAEs were reported for 1.5% of lixisenatide-treated patients compared with 2.1% of placebo-treated patients. There were no deaths during the study. The most commonly reported TEAE in the lixisenatide group was nausea (16.3% vs 2.6% with placebo). Vomiting was also reported more frequently in the lixisenatide group, as were headaches and dizziness (Table 2).

The incidence of symptomatic hypoglycaemia was 5.6% with lixisenatide and 2.6% with placebo (\(p = 0.1321\)). Rates of symptomatic hypoglycaemia were lower in patients not receiving sulfonylurea treatment in both treatment groups. In the sulfonylurea-negative group, the frequency of symptomatic hypoglycaemia was 3.5% in the lixisenatide group compared with 0.0% in the
placebo group. In the sulfonylurea-positive group, symptomatic hypoglycaemia occurred in 8.5% of lixisenatide-treated patients versus 5.4% of placebo-treated patients. The occurrence of symptomatic hypoglycaemia with a documented blood glucose <3.3 mmol/L was 1.5% in each group (0.1 events per patient year). No events of severe symptomatic hypoglycaemia were reported in either group during the study, and no hypoglycaemia-related TEAEs led to permanent discontinuation of study treatment.

The incidence of injection-site reactions was 2.6% (n = 5) in the lixisenatide group and 1.0% (n = 2) in the placebo group. None of the injection-site reactions were serious or led to permanent treatment discontinuation.

Three patients [1.0% (n = 2) in the lixisenatide group and 0.5% (n = 1) in the placebo group] had a TEAE that was adjudicated as an allergic reaction by the Allergic Reaction Assessment Committee. Two events from two patients (anaphylactic shock and injection-site reaction) in the lixisenatide group were adjudicated as being possibly related to investigational product. The event of anaphylactic shock, which led to permanent treatment discontinuation, occurred after the first injection of lixisenatide. No specific anti-lixisenatide immunoglobulin E (IgE) antibodies were detected, and the patient’s total IgE was within the normal range. Therefore, this event was not consistent with a true allergic reaction linked to an IgE-mediated mechanism and was considered by the Allergic Reaction Assessment Committee to be an anaphylactoid reaction.

A similar percentage of patients in each treatment group had cardiac TEAEs (1.5% in the lixisenatide group vs 2.1% in the placebo group). Overall, three major cardiovascular TEAEs were reported (one cerebral infarction, pericardial effusion, and pericarditis).

Table 2. Treatment-emergent adverse events with lixisenatide and placebo (safety population)

|                      | Lixisenatide (n = 196) | Placebo (n = 194) |
|----------------------|------------------------|-------------------|
| Patients with any TEAE, n (%) | 126 (64.3) | 92 (47.4) |
| Patients with any serious TEAE, n (%) | 3 (1.5) | 4 (2.1) |
| Patients with any TEAE leading to death, n (%) | 0 | 0 |
| Patients with any TEAE leading to permanent treatment discontinuation, n (%) | 11 (5.6) | 3 (1.6) |
| Gastrointestinal disorders, n (%) | 57 (29.1) | 18 (9.3) |
| Diarrhoea | 7 (3.6) | 2 (1.0) |
| Nausea | 32 (16.3) | 5 (2.6) |
| Vomiting | 15 (7.7) | 2 (1.0) |
| Headache, n (%) | 5 (2.6) | 2 (1.0) |
| Dizziness, n (%) | 17 (8.7) | 8 (4.1) |
| Any injection-site reactions, n (%) | 5 (2.6) | 2 (1.0) |
| Cardiac disorders, n (%) | 3 (1.5) | 4 (2.1) |
| Calcitonin ≤ ULN, n (%) | 183/184 (99.5) | 185/185 (100.0) |
| Symptomatic hypoglycaemiaa, n (%) | 11 (5.6) | 5 (2.6) |
| Number of events per patient year | 0.2 | 0.1 |
| Symptomatic hypoglycaemia, blood glucose <3.3 mmol/L, n (%) | 3 (1.5) | 3 (1.6) |
| Number of events per patient year | 0.1 | 0.1 |
| Severe symptomatic hypoglycaemia, n (%) | 0 | 0 |

TEAE, treatment-emergent adverse event; ULN, upper limit of normal. *p = 0.1321 based on a post-hoc analysis.
one acute myocardial infarction in the lixisenatide group, and one lacunar infarction for placebo). No patient in either treatment group had any events of increased pancreatic enzymes, lipase or amylase reported during the treatment period. No patient in either treatment group had increased blood calcitonin levels during the study or calcitonin levels ≥50 ng/L. No pancreatitis or cancer-related TEAEs were reported. Heart rate was stable from baseline to endpoint in both treatment groups (mean change from baseline: 0.7 and 0.0 bpm for lixisenatide and placebo, respectively). Small and similar reductions were observed in systolic and diastolic blood pressure in both treatment groups (lixisenatide: systolic/diastolic = 1.3/−1.7 mmHg, placebo: −2.7/−1.6 mmHg).

**Discussion**

In the present study in Asian patients with T2DM inadequately controlled on OADs (metformin with or without sulfonylureas), lixisenatide once-daily treatment over 24 weeks significantly reduced HbA1c from baseline compared with placebo. Lixisenatide also enabled a significantly higher proportion of patients to reach their HbA1c targets of <7% or ≤6.5%. The magnitude of HbA1c reduction (least squares mean difference: −0.36%) was less substantial than that observed in the GetGoal-S study (least squares mean difference: −0.74% [27] vs −0.36% in the present study), in which lixisenatide treatment as add-on to sulfonylurea with or without metformin was assessed over 24 weeks in a mixed Caucasian (52.33%) and Asian (44.67%) patient population. The lower HbA1c reduction compared with placebo in the present study may be explained by the low baseline HbA1c levels (<8%), allowing limited scope for further decreases. Furthermore, there was a substantial placebo effect in the study that could be related to the short placebo run-in period. That said, the proportion of patients achieving a target HbA1c of <7% was similar to that in other GLP-1 receptor agonist studies conducted in Asia [28,29].

It is now well recognized that PPG excursions are an important component of overall glycaemic control, with reductions in PPG levels associated with a lower risk of T2DM complications, including cardiovascular disease [30]. PPG has also been shown to be superior to FPG at predicting cardiovascular disease and all-cause mortality [31]. Administration of lixisenatide within 1 h before breakfast had a marked effect, resulting in a highly statistically significant reduction in 2-h PPG following breakfast (least squares mean difference: −4.28 mmol/L) along with a marked reduction in glucose excursion (least squares mean difference: −3.99 mmol/L) compared with placebo. The post-breakfast glycaemic results from the current study are consistent with evidence from the GetGoal programme and demonstrate the distinct effects of lixisenatide, believed to be related to the slowing of gastric emptying [32]. The magnitude of the post-breakfast PPG and glucose excursion reduction in the current study was similar to that observed in the GetGoal-M study [LS mean difference: −4.5 mmol/L (PPG) and −3.9 mmol/L (glucose excursion)] [21]. In our study, glucose profiles throughout the day were not monitored, and the distinct effect of lixisenatide on PPG after a standardized breakfast is reported. Although, on the basis of these data, no assumptions can be made on the overall effect of lixisenatide on PPG, other studies suggest that, despite the greatest PPG effects being seen post-breakfast, lixisenatide may provide coverage up to the evening meal [33–35].

Glucagon-like peptide-1 receptor agonists in general are known to be associated with beneficial effects on body weight [37,38]. Lixisenatide has also previously been reported to have a beneficial effect on body weight [24,25,27,39]. In the present study, there was a trend towards greater weight loss in the lixisenatide group compared with the placebo group, with no significant difference between the groups. Considering that nearly half of all patients in the trial were being treated with sulfonylureas, which are normally associated with weight gain, this outcome is still important. This study was also consistent with the results of the GetGoal-L-Asia trial, in which all patients were on basal insulin ± sulfonylureas [14]. The lower baseline body weight in both studies, typically observed in Asian patients, may have also contributed to the limited weight reduction. In the present study, the average baseline BMI was 26.91 kg/m², compared with 32.9 kg/m² in the GetGoal-M trial [21]. Finally, there may be some differences in terms of weight loss with GLP-1 receptor agonists in different Asian populations. In a study in Japanese patients in which liraglutide 0.6 mg (maximum dosage in accordance with approved labelling in Japan) was added to sulfonylurea monotherapy, there was no change in mean body weight at the end of treatment with liraglutide [40]. In another study in mixed Asian patients, in which approximately 50% were of Chinese origin, with 80% on sulfonylurea, exenatide twice daily did reduce body weight versus placebo with a 1.1-kg significant treatment difference [29].

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Lixisenatide was well tolerated during the 24-week treatment period, with comparable incidences of serious TEAEs in the lixisenatide and placebo groups. As expected, there was a higher frequency of gastrointestinal disorders associated with lixisenatide treatment. These incidents were mostly mild and transient and resolved spontaneously without sequelae. Most cases occurred during the first 3 weeks of treatment and progressively decreased during the following weeks. The incidence of nausea in the current study was 16.3% with lixisenatide versus 2.6% with placebo, which was lower than that previously reported in GetGoal-M (22.0% vs 7.6% with placebo) [21] or GetGoal-S (25.3% vs 7.0% with placebo) [27].

The incidence of symptomatic hypoglycaemia reported in the current study (5.6% with lixisenatide vs 2.6% with placebo, \( p = 0.1321 \)) was lower than that reported in the GetGoal-S study, which was conducted in patients treated with lixisenatide as add-on to sulfonylurea with or without metformin (15.3% with lixisenatide vs 12.3% with placebo) [27]. The occurrence of symptomatic hypoglycaemia in this study was lower than that reported for exenatide treatment in an Asian patient population (35.5% vs 9.1% with placebo [29]).

In conclusion, this study supports the use of once-daily lixisenatide treatment in Asian patients with T2DM who were not achieving adequate glycaemic control with OADs alone (metformin with or without sulfonylurea). Lixisenatide provided significant improvements in HbA1c levels and had a marked effect on post-breakfast PPG control. Lixisenatide was shown to be an effective and well-tolerated treatment option in Asian patients with T2DM.

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Author contributions

Chang Yu Pan, Ping Han, Xiaoming Liu, Shengli Yan, Ping Feng, Zhiguang Zhou, Xiaofeng Lv, Hui Tian, Jin Kui Yang and Benli Su all contributed to the study conduct, data collection and reviewing of the manuscript. Shuhua Shang contributed to the reviewing of the results and preparation of the manuscript. Elisabeth Niemoeller contributed to the medical supervision of the study, reporting of the results and preparation of the manuscript.

Conflicts of interest

Chang Yu Pan has received lecture fees and research funding from Sanofi-aventis, Novo Nordisk, Eli Lilly, Novartis, Roche, AstraZeneca and Bayer. Ping Han has no conflicts to disclose. Xiaoming Liu has no conflicts to disclose. Shengli Yan received research funding from Boehringer Ingelheim, Sanofi and Novo Nordisk. Ping Feng received research funding from Sanofi-aventis, Novo Nordisk and Eli Lilly. Zhiguang Zhou received research funding from Sanofi-aventis, Novo Nordisk, Eli Lilly, Bristol-Myers Squibb and Bayer. Xiaofeng Lv received research funding from Sanofi-aventis, Novo Nordisk and Eli Lilly. Hui Tian received research funding from Sanofi-aventis, Bristol-Myers Squibb and Novo Nordisk. Jin Kui Yang has no conflicts to disclose. Benli Su received research funding from Sanofi-aventis, Novo Nordisk, Bristol-Myers Squibb and Bayer. Shuhua Shang and Elisabeth Niemoeller both work for Sanofi.
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