

ORIGINAL ARTICLE

Efficacy and safety of lixisenatide in a predominantly Asian population with type 2 diabetes insufficiently controlled with basal insulin: The GetGoal-L-C randomized trial

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Aims: To assess the effects on glycaemic control of lixisenatide vs placebo as add-on treatment to basal insulin (BI) ± metformin and effects on glycated haemoglobin (HbA1c) reduction in patients with insufficiently controlled type 2 diabetes (T2D).

Methods: Patients (n = 448) with inadequately controlled T2D were randomized (1:1) to lixisenatide or placebo as add-on to BI ± metformin for 24 weeks after an 8-week run-in phase, during which BI was titrated to a target self-monitored plasma glucose (SMPG; 4.4–5.6 mmol/L). The primary endpoint was absolute change in HbA1c from baseline to week 24. Secondary efficacy endpoints included: percentage of responders; changes in 2-hour postprandial plasma glucose (PPG); 7-point SMPG (daily average); body weight (BW); total daily BI dose; fasting plasma glucose; and safety assessments.

Results: Baseline demographics were similar in the two treatment groups. After insulin optimization during run-in, lixisenatide was superior to placebo in mean change from baseline (7.9% [standard deviation {s.d.}, 0.66] and 7.9% [0.70], respectively) to week 24 in HbA1c (least squares mean [standard error {s.e.}] change −0.62% [0.09] vs −0.11% [0.09]; $P < .0001$, respectively) and higher proportions of patients achieved HbA1c targets. Two-hour PPG, daily mean SMPG and mean BW were reduced further and daily BI dose was lower with lixisenatide than placebo (−1.12 kg vs 0.04 kg [$P < .0001$]; −3.0 U vs −1.9 U [$P = .0033$], respectively). Treatment-emergent adverse events were greater with lixisenatide than placebo (63.8% vs 40.8%, respectively). The incidence of symptomatic hypoglycaemia was similar (lixisenatide 15.6% vs placebo 13.5%).

Conclusions: In Asian patients insufficiently controlled on BI ± metformin, lixisenatide was superior to placebo in glycaemic control, with a tolerability profile in line with other glucagon-like peptide-1 receptor agonists.

Clinical trial number: NCT01632163 (clinicaltrials.gov).

KEYWORDS

GLP-1, incretin therapy, incretins, randomized trial

1 | INTRODUCTION

Type 2 diabetes (T2D) is a significant health concern in Asia, with an estimated prevalence of 11.6% in the Chinese adult population, with

50.1% having prediabetes.^{1,2} Overall, diabetes is increasing in the Chinese population, which is ageing and gaining weight, probably as a result of lifestyle changes such as diet (eg, poor nutrition in utero and intake of high-energy foods in later life), occupation (a decrease in

manual labour and physical activity) and urbanization (an increase in the urban population driven by rural to urban migration).^{1–5} In addition to these environmental influences, there may also be a genetic predisposition to T2D in the Asian population.⁶

In China, T2D is undertreated; a cross-sectional survey in 2010 revealed that only 26% of patients received treatment for diabetes and only 40% of those treated had adequate glycaemic control within guideline ranges.^{1,7,8} Despite guidance provided by diabetes treatment algorithms, glycaemic control targets are not always achieved for those patients who receive treatment; therefore, further treatment options are required in this population with T2D.⁹

Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) are incretin-based therapies that lower plasma glucose and are an established treatment option for T2D.¹⁰ GLP-1 RAs were demonstrated to improve glycaemic control with some weight loss and have a low risk of hypoglycaemia. Generally, treatment guidelines recommend lifestyle management plus metformin before combining metformin with other treatments such as basal insulin (BI) or GLP-1 RAs. With T2D being a progressive disease, a substantial proportion of patients with T2D will require treatment with BI and/or GLP-1 RAs to reach their glycaemic targets. The GLP-1 RAs currently available have been investigated and shown to improve glycaemic control in Asian populations.^{11,12}

Lixisenatide (Sanofi, Paris, France/Bridgewater, New Jersey) is a once-daily, short-acting, selective GLP-1 RA, approved for use in >60 countries, including countries in Europe, the USA, South Korea and Japan (not yet approved in China), with oral glucose-lowering agents and/or BI in the treatment of adults with T2D when the use of these agents with diet and exercise has provided inadequate glycaemic control.¹³ Lixisenatide has been evaluated in a series of trials (the GetGoal clinical trial programme) as monotherapy, in combination with oral antidiabetic drugs (OADs) and as add-on therapy to BI.^{14–22} GetGoal-L, which enrolled a global population with T2D, and GetGoal-L-Asia, were double-blind, parallel-group, placebo-controlled trials investigating the effects of lixisenatide added to BI.^{18,22} The present trial, GetGoal-L-C, follows a similar design but investigates a more targeted population with the objective of assessing the efficacy and safety of lixisenatide compared with placebo as an add-on treatment to BI with or without metformin after an 8-week treat-to-target optimization of established therapy with BI. The study was performed in Asian patients (predominantly from China) with inadequately controlled T2D over a period of 24 weeks.

2 | METHODS

2.1 | Trial design

This was a phase III, double-blind, 1:1 randomized, placebo-controlled, two-arm parallel-group, multicentre, multinational study over a 24-week period (NCT01632163), conducted in 51 centres in 4 countries (China, India, Korea and Russia) from October 2012 to May 2015. The protocol, protocol amendment, consent form and written patient information were reviewed and approved by the local independent ethics committees and/or institutional review boards before study initiation. The study was conducted in accordance with the recommendations of the Declaration of Helsinki and Good

Clinical Practice guidelines. All participants gave written informed consent. An independent Data Monitoring Committee provided an ongoing review of unmasked efficacy and safety data, and an Allergic Reaction Assessment Committee, a Cardiovascular Event Adjudication Committee and a Pancreatic Safety Assessment Committee reviewed masked events (Appendix S2).

2.2 | Trial population

Adults with T2D diagnosed ≥ 1 year before the screening visit were eligible for inclusion if they had glycated haemoglobin (HbA1c) $\geq 7\%$ and $\leq 10.5\%$ at screening despite BI treatment, with or without metformin. Exclusion criteria included: patients receiving BI treatment not on a stable regimen for ≥ 3 months and/or not at a stable dose ($\pm 20\%$) of ≥ 15 U/d for ≥ 2 months prior to screening visit; those not at a stable dose of ≥ 1.0 g/d for ≥ 3 months prior to screening visit if taking metformin; HbA1c $< 7\%$ or $> 9.5\%$ at visit 9 (week -1) or mean fasting self-monitored plasma glucose (SMPG) calculated for the week prior to randomization visit > 7.8 mmol/L.

2.3 | Randomization and interventions

Patients were randomized (1:1 through an interactive voice response system/interactive web response system which allocated the patient treatments) to either lixisenatide or placebo once daily during the randomized, double-blind treatment period and were stratified at randomization by HbA1c ($< 8\%$, $\geq 8\%$) at visit 9 (week -1) and metformin use (yes/no) at screening.

During the 8-week run-in phase, existing BI was optimally titrated to a target SMPG of 4.4 to 5.6 mmol/L (Table S1, Appendix S1). At the end of run-in, eligible patients (HbA1c $\geq 7\%$ and $\leq 9.5\%$, fasting SMPG ≤ 7.8 mmol/L) entered the 24-week randomized, double-blind treatment phase, during which the optimized BI was to be kept stable. A 3-day safety follow-up period followed permanent study treatment discontinuation (Figure 1). Lixisenatide or volume-matched placebo were self-injected subcutaneously within 1 hour before breakfast using a pen-type injector. Lixisenatide treatment was initiated at a starting dose of 10 μg once daily for 2 weeks and then increased to a maintenance dose of 20 μg once daily. Lixisenatide and placebo treatments were indistinguishable, but the titration step was unblinded as the injected volume differed according to the initiation or maintenance period. If the target maintenance dose was not tolerated, the lixisenatide dose (or volume-matched placebo) could be reduced back to 10 μg once daily and another increase to 20 μg once daily attempted within 4 weeks. If this was again not tolerated, the patient remained on 10 μg once daily throughout the remainder of the treatment period. Background treatments (BI and metformin, if applicable) at stable doses were continued during the treatment period. If HbA1c at week -1 was $\geq 7\%$ but $\leq 7.5\%$, the daily dose of BI was reduced by 20% at randomization in order to avoid hypoglycaemia when starting the combination with lixisenatide. After randomization, the regimen of BI (timing/frequency of injection, type of BI) was stably maintained during the treatment period. The adjustment of BI dose was kept within $\pm 20\%$. If metformin was given, it was continued at a stable dose of ≥ 1.0 g/d throughout the study. No

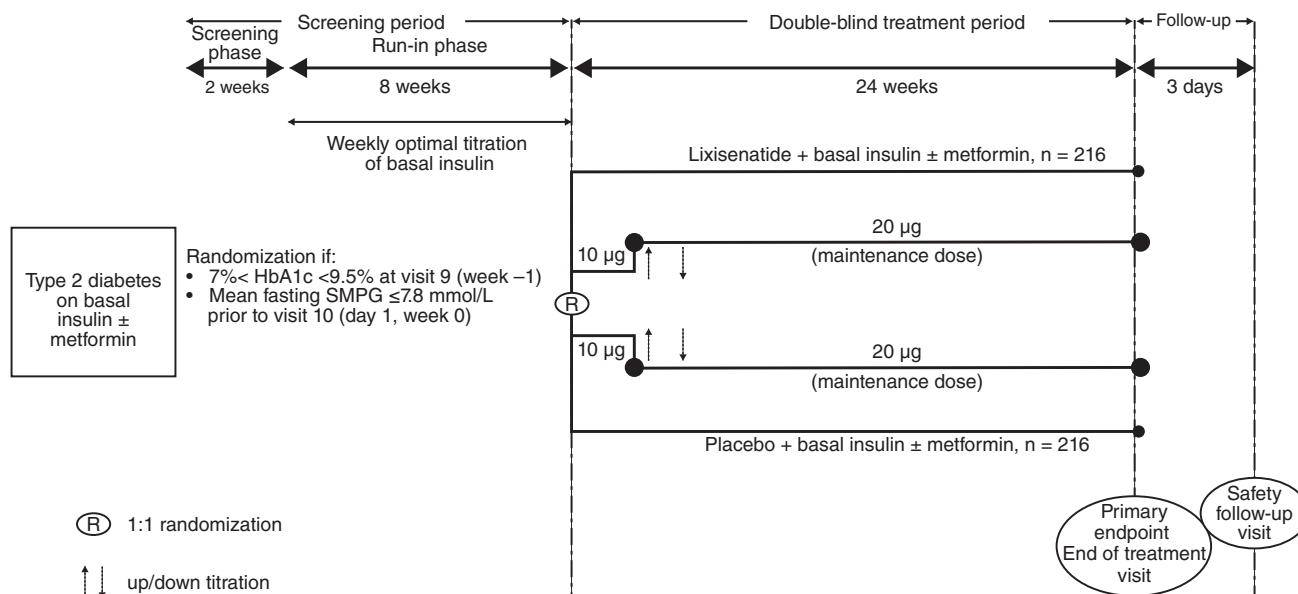


FIGURE 1 Study design

rescue therapy was used. If no reason could be found for insufficient glucose control, or if appropriate actions failed to decrease fasting plasma glucose (FPG) or HbA1c under the threshold values (Table S2, Appendix S1), patients were withdrawn from the study.

2.4 | Study endpoints

The primary efficacy endpoint was the absolute change in HbA1c from baseline to week 24. Secondary efficacy endpoints included: percentage of patients reaching the HbA1c target of <7% or \leq 6.5% at week 24; change in 2-hour postprandial plasma glucose (PPG) and PPG excursions (2-hour PPG minus FPG 30 minutes prior to the meal test before study medication administration) during standardized meal test from baseline to week 24; changes in FPG, the daily average of the 7-point SMPG profile (including each timepoint), body weight (BW) and total daily BI dose from baseline to week 24.

The HbA1c and FPG samples were measured by a certified level I “National Glycohemoglobin Standardization Program” central laboratory (Covance Central Laboratory Services). Patients underwent a standardized meal challenge test (Ensure Plus® [Abbott] or Nutrison [Nutricia]; consumed between 15 and 30 minutes after study drug administration) to assess 2-hour PPG and plasma glucose excursions once during the run-in phase and at week 24. Patients performed fasting SMPG once daily until week 4 and then \geq 3 times a week until the end of the study and, in addition, 7 times over a 24-hour period (preprandial, 2 hours after each meal and at bedtime) during the week before each visit. Insulin dose, SMPG and symptoms of hypoglycaemia were recorded in the patient diary and then transferred into the electronic case report forms. BW was recorded at screening, run-in, randomization and at weeks 4, 8, 16 and 24 of the treatment period.

Safety endpoints included: occurrence of adverse events (AEs), treatment-emergent AEs (TEAEs) and serious TEAEs; symptomatic hypoglycaemia (defined as an event with clinical symptoms that were considered to result from a hypoglycaemic episode with an accompanying plasma glucose <3.3 mmol/L or associated with prompt

recovery after oral carbohydrate, intravenous glucose or glucagon administration) recorded on a specific AE form; severe symptomatic hypoglycaemia (defined as an event with clinical symptoms that were considered to result from hypoglycaemia in which the patient required the assistance of another person because the patient could not treat themselves due to acute neurological impairment directly resulting from the hypoglycaemic event with an accompanying plasma glucose <2.0 mmol/L or, if no plasma glucose measurement was available, associated with prompt recovery after oral carbohydrate, intravenous glucose or glucagon administration); vital signs, electrocardiogram and safety laboratory values.

2.5 | Statistical analyses

The efficacy analysis population was the modified intention-to-treat (mITT) population (defined as all randomized patients who received \geq 1 dose of study medication and had both a baseline assessment and at least 1 post-baseline assessment of any primary or secondary endpoint). The safety analysis population was the randomized and treated population, defined as all randomized patients exposed to \geq 1 dose of double-blind investigational drug.

Absolute change in HbA1c from baseline to week 24 was analysed using analysis of covariance (ANCOVA), with treatment (lixisenatide or placebo), HbA1c (<8.0%, \geq 8.0%), randomization strata of metformin use (yes/no) and country as fixed effects and baseline HbA1c as a covariate. Superiority of lixisenatide compared with placebo was assessed based on the predefined primary analysis of least squares (LS) mean changes from baseline to week 24 in HbA1c. The sample size calculation based on this endpoint estimated that enrolment of 432 and 216 participants in the lixisenatide and placebo arms, respectively, would provide a 97% power of detecting a 0.5% difference between treatments, with a 2-sided test at the 5% significance level and a common standard deviation (s.d.) of 1.3%. Once the primary efficacy variable was statistically significant at the 5% level (2-sided), a step-down testing procedure was performed to test the secondary efficacy

variables change from baseline to week 24: 2-hour PPG, FPG, daily average of 7-point SMPG, BW and total daily insulin dose. For the primary efficacy variable, differences between lixisenatide and placebo and associated 2-sided 95% confidence intervals (CIs) were estimated using ANCOVA. An ANCOVA model was also applied on continuous secondary efficacy endpoints and all categorical efficacy endpoints were analysed using a Cochran–Mantel–Haenszel method stratified by randomization strata. In cases of premature discontinuation of the double-blind treatments, efficacy variables were assessed at the time of treatment discontinuation. For week 24 analyses, the last observation carried forward procedure was used by identifying the last available post-baseline measurement in the on-treatment period as the week 24 value. AEs were summarized using descriptive statistics.

3 | RESULTS

3.1 | Population characteristics

Overall, 789 patients were screened; 597 entered the run-in phase (149 patients failed the run-in phase, most commonly [12.7%] because of HbA1c levels outside of the predefined range) and 448 patients

TABLE 1 Baseline or screening demographics and disease characteristics of the randomized population

Characteristic	Lixisenatide (n = 224)	Placebo (n = 224)	All (n = 448)
Age, years	53.9 (9.9)	56.2 (9.1)	55.0 (9.6)
Male, n (%)	105 (46.9)	98 (43.8)	203 (45.3)
Race, n (%)			
Asian	195 (87.1)	190 (84.8)	385 (85.9)
White	29 (12.9)	34 (15.2)	63 (14.1)
Country, n (%)			
China	122 (54.5)	129 (57.6)	251 (56.0)
Korea	42 (18.8)	37 (16.5)	79 (17.6)
India	31 (13.8)	24 (10.7)	55 (12.3)
Russia	29 (12.9)	34 (15.2)	63 (14.1)
BMI at screening, kg/m ²	27.5 (4.46)	27.9 (4.52)	27.7 (4.49)
BMI at baseline, ^a kg/m ²	27.5 (4.39)	27.9 (4.48)	27.7 (4.44)
HbA1c at screening, %	8.6 (0.84)	8.6 (0.86)	8.6 (0.85)
HbA1c at baseline, %	7.9 (0.66)	7.9 (0.70)	7.9 (0.68)
Duration of T2D, years	10.3 (6.1)	10.2 (6.2)	10.3 (6.1)
Duration of BI treatment, years	2.3 (2.4)	2.1 (2.1)	2.2 (2.2)
Daily BI dose at screening, U	27.4 (14.0)	25.2 (11.1)	26.3 (12.7)
Insulin glargine, n (%)	182 (81.3)	189 (84.4)	371 (82.8)
NPH, n (%)	27 (12.1)	23 (10.3)	50 (11.2)
Detemir, n (%)	15 (6.7)	12 (5.4)	27 (6.0)
Daily BI dose at baseline, ^a U	39.8 (19.0)	37.3 (15.9)	38.5 (17.5)
Metformin use at screening, n (%)	198 (88.4)	199 (88.8)	397 (88.6)

Data are mean (s.d.) unless stated otherwise. Percentages may not total 100% because of rounding. BMI, body mass index; BI, basal insulin; NPH, neutral protamine Hagedorn.

^a Lixisenatide n = 224; placebo n = 223.

from four countries were randomized (Table 1 and Figure S1, Appendix S1), with 224 patients in each group. One patient was randomized to the placebo group but did not receive treatment; 447 were included in the safety population and 446 in the mITT population. From the lixisenatide and placebo groups 8.0% and 14.3% of patients, respectively, discontinued the study prematurely; this was mainly because of AEs, which were primarily in the gastrointestinal (GI) system organ class (lixisenatide, n = 8 [3.6%]; placebo, n = 6 [2.7%]), and lack of efficacy (lixisenatide, n = 4 [1.8%]; placebo, n = 16 [7.1%]). No rescue therapy was permitted, instead a stopping rule was implemented (Table S2, Appendix S1).

Baseline demographics and characteristics were similar across treatment groups (Table 1); >50% of patients were from China.

3.2 | Primary efficacy endpoint

After optimization of established treatment with BI during run-in, mean (s.d.) HbA1c decreased from 8.63 (0.85)% at screening to

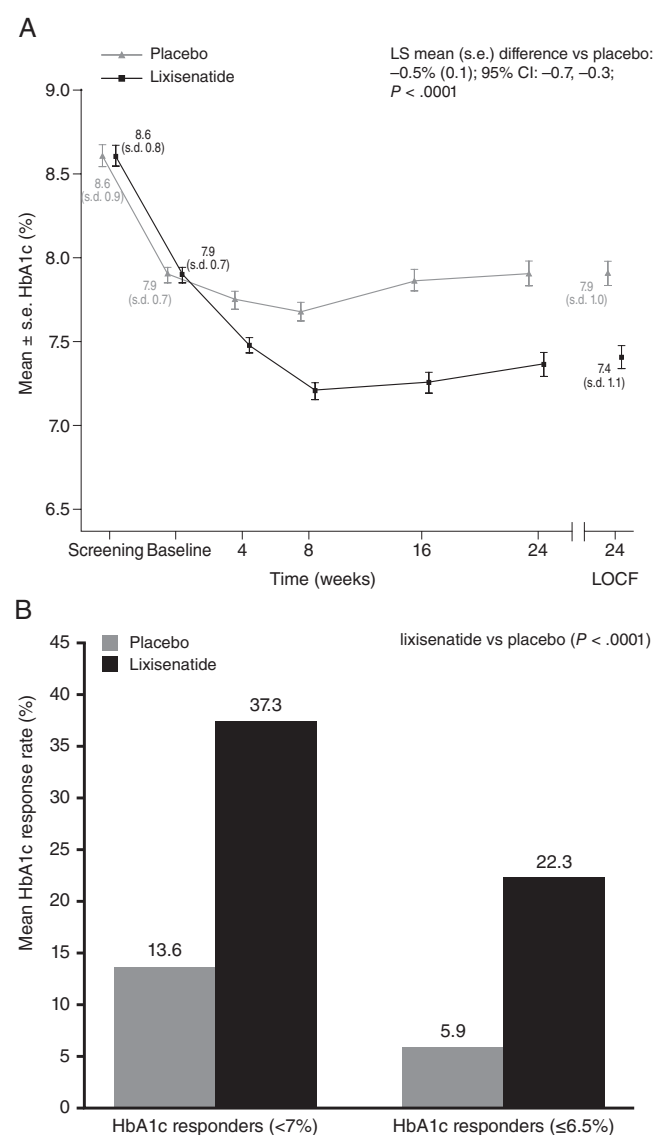


FIGURE 2 A, Mean ± s.e. HbA1c (%) and B, mean HbA1c response rate by visit to week 24 LOCF (mITT population). Measurements obtained up to 14 days after the last injection of lixisenatide/placebo are included

TABLE 2 Response to treatment at week 24

Efficacy endpoint	Lixisenatide (n = 223)	Placebo (n = 223)
2-h PPG, mmol/L		
Baseline	13.71 (4.26)	14.07 (3.62)
Week 24 LOCF	10.67 (4.95)	14.29 (4.10)
LS mean (s.e.) change from baseline to week 24 LOCF	-4.06 (0.41)	-0.61 (0.42)
LS mean (s.e.) difference vs placebo	-3.45 (0.40)	-
95% CI	-4.231, -2.673	-
P	<.0001	-
2-h plasma glucose excursion, mmol/L		
Baseline	6.44 (3.47)	6.83 (3.22)
Week 24 LOCF	3.46 (4.33)	6.79 (3.59)
LS mean (s.e.) change from baseline to week 24 LOCF	-3.87 (0.37)	-0.74 (0.38)
LS mean (s.e.) difference vs placebo	-3.13 (0.36)	-
95% CI	-3.832, -2.433	-
P	<.0001	-
FPG, mmol/L		
Screening ^a	9.0 (2.1)	8.8 (2.2)
Baseline	7.1 (2.1)	6.9 (1.8)
Week 24 LOCF	7.3 (2.2)	7.6 (2.4)
LS mean (s.e.) change from baseline to week 24 LOCF	0.2 (0.2)	0.6 (0.2)
LS mean (s.e.) difference vs placebo	-0.4 (0.2)	-
95% CI	-0.8, 0.0	-
P	.0650	-
Daily average 7-point SMPG, mmol/L		
Baseline	9.2 (1.9)	9.3 (1.9)
Week 24 LOCF	8.9 (1.8)	9.5 (1.9)
LS mean (s.e.) change from baseline to week 24 LOCF	-0.5 (0.2)	0.1 (0.2)
LS mean (s.e.) difference vs placebo	-0.5 (0.27)	-
95% CI	-0.9, -0.2	-
P	.0014	-
BW, kg		
Screening ^a	73.9 (14.3)	74.6 (13.4)
Baseline	74.2 (14.1)	74.6 (13.3)
Week 24 LOCF	73.1 (13.8)	74.6 (13.3)
LS mean (s.e.) change from baseline to week 24 LOCF	-1.2 (0.2)	-0.1 (0.2)
LS mean (s.e.) difference vs placebo	-1.2 (0.2)	-
95% CI	-1.6, -0.7	-
P	<.0001	-
Basal insulin total daily dose, U		
Screening ^a	27.4 (14.0)	25.2 (11.1)
Baseline	39.9 (19.2)	37.5 (16.1)
Week 24 LOCF	37.8 (18.7)	36.8 (16.0)
LS mean (s.e.) change from baseline to week 24 LOCF	-3.0 (0.4)	-1.9 (0.4)
LS mean (s.e.) difference vs placebo	-1.1 (0.4)	-
95% CI	-1.9, -0.4	-
P	.0033	-

Data are mean (s.d.) unless stated otherwise. Efficacy results were analysed for the modified intent-to-treat population, n = 446. Background therapy was basal insulin ± metformin. PPG, postprandial plasma glucose; LOCF, last observation carried forward; LS, least squares; CI, confidence interval; FPG, fasting plasma glucose.

^a Lixisenatide n = 224; placebo n = 224.

7.92 (0.68)% at baseline. Addition of lixisenatide was shown to be superior to placebo in mean change from baseline to week 24 in HbA1c. The mean (s.d.) HbA1c levels achieved after 24 weeks of

treatment were 7.41 (1.08)% for lixisenatide and 7.94 (1.01)% for placebo. LS mean (standard error [s.e.]) changes were -0.62 (0.09)% and -0.11 (0.09)% in the lixisenatide and placebo groups, respectively,

and the LS mean (s.e.) difference for lixisenatide vs placebo was -0.51 (0.09)% (95% CI -0.685 , -0.341 ; $P < .0001$; Figure 2A). This improvement in HbA1c was also reflected in the greater proportion of patients achieving HbA1c targets $<7\%$ or $\leq 6.5\%$ at week 24 with lixisenatide vs placebo ($P < .0001$; Figure 2B).

3.3 | Secondary efficacy endpoints

During the run-in period, after titration of BI, the daily dose increased in both lixisenatide and placebo treatment groups from (mean [s.d.]) 27.4 (14.0) U and 25.2 (11.1) U, respectively, at screening to 39.9 (19.2) and 37.5 (16.1), respectively, before randomization. Furthermore, FPG levels decreased while BW remained relatively stable in both treatment groups.

While mean change in FPG levels from baseline to week 24 was similar in each group, lixisenatide significantly improved postprandial glycaemic control after a standardized liquid breakfast meal, as demonstrated by the difference between groups in mean change from baseline to week 24 in 2-hour plasma glucose excursion (-3.13 mmol/L; $P < .0001$; Table 2) and 2-hour PPG (-3.45 mmol/L; $P < .0001$; Table 2) compared with placebo.

After 24 weeks, values on the 7-point SMPG profiles were lower at all timepoints in the lixisenatide group compared with placebo, with the exception of pre-breakfast values, which were similar for both groups. The LS mean difference in mean 7-point SMPG values was statistically greater for the lixisenatide group compared with the placebo group ($P = .0014$; Table 2).

The superior improvement in glycaemic control was not associated with a negative impact on BW: lixisenatide led to a significant mean reduction in BW (-1.12 kg) from baseline to week 24, which was superior compared with placebo (0.04 kg; $P < .0001$; Figure S2, Appendix S1). The mean difference in BI total daily dose from baseline to week 24 was significantly greater for lixisenatide vs placebo (LS mean difference -1.1 U; Table 2).

3.4 | Adverse events

Safety and tolerability data (Table 3) were consistent with the established safety profile of lixisenatide. Nausea, vomiting and decreased appetite were more frequent with lixisenatide than with placebo. There were no deaths during the study. No cases of pancreatitis (adjudicated by the Pancreatic Safety Assessment Committee) or confirmed increase in lipase/amylase or blood calcitonin increase were reported.

In the lixisenatide group TEAEs were more frequent than in the placebo group (Table 3); the difference was predominantly attributable to metabolic and GI TEAEs, which were primarily nausea and vomiting (mostly mild to moderate in severity and transient in nature), with few events leading to treatment discontinuation (Table 3). Similarly, the percentage of patients with TEAEs related to the investigational drug was higher with lixisenatide compared with placebo (41.5% [93/224] and 13.0% [29/223], respectively); again, this was mainly attributable to a higher proportion of patients with disorders in the GI system organ class (30.8% [69/224] and 6.3% [14/223], respectively).

TABLE 3 Number of patients in the safety population reporting TEAEs

Patients, n (%)	Lixisenatide (n = 224)	Placebo (n = 223)
At least one TEAE		
Any TEAE	143 (63.8)	91 (40.8)
Serious TEAE	11 (4.9)	2 (0.9)
TEAE leading to death	0	0
TEAE leading to discontinuation	8 (3.6)	4 (1.8)
AE by organ class		
Metabolism and nutrition disorders	75 (33.5)	48 (21.5)
Decreased appetite	16 (7.1)	2 (0.9)
Discontinuation because of decreased appetite	1 (0.4)	0
Gastrointestinal disorders (overall)	75 (33.5)	23 (10.3)
Nausea	51 (22.8)	12 (5.4)
Discontinuation because of nausea	3 (1.3)	0
Vomiting	25 (11.2)	2 (0.9)
Discontinuation because of vomiting	1 (0.4)	0
ARAC positively adjudicated allergic events ^a	1 (0.4)	0
Symptomatic hypoglycaemia ^b		
Confirmed with plasma glucose value <3.3 mmol/L		
Number of patients with events, n (%) ^c	20 (8.9)	20 (9.0)
Number of events per patient-year ^d	0.5	0.3
Severe symptomatic hypoglycaemia ^e	0	0

Abbreviations: TEAE, treatment-emergent adverse event; ARAC, Allergic Reaction Assessment Committee.

^a 1 (0.4) patient in the lixisenatide group experienced a serious allergic event (urticaria) that was considered to be related to treatment and discontinued. An additional patient experienced a mild dermatitis, not related to lixisenatide, and was able to complete the study on lixisenatide.

^b Symptomatic hypoglycaemia was defined as an event with clinical symptoms that were considered to result from a hypoglycaemic episode with an accompanying plasma glucose of <3.3 mmol/L; or associated with prompt recovery after oral carbohydrate, intravenous glucose, or glucagon administration.

^c Percent is calculated using the number of safety patients as the denominator.

^d Calculated as (number of events, divided by total exposure +3 days in patient-years).

^e Severe symptomatic hypoglycaemia was defined as an event with clinical symptoms that were considered to result from hypoglycaemia in which the patient required the assistance of another person, because the patient could not treat themselves due to acute neurological impairment directly resulting from the hypoglycaemic event with an accompanying plasma glucose of <2.0 mmol/L, or if no plasma glucose measurement was available, associated with prompt recovery after oral carbohydrate, intravenous glucose, or glucagon administration.

Serious TEAEs were reported in 11 (4.9%) and 2 (0.9%) patients in the lixisenatide and placebo groups, respectively. The percentage of patients with TEAEs leading to treatment discontinuation was higher in the lixisenatide group than the placebo group; this difference was attributable mainly to a higher proportion of patients in the lixisenatide group with GI TEAEs leading to discontinuation.

Out of the 5 events sent to the Allergic Reaction Assessment Committee for adjudication, 1 was positively adjudicated to be an allergic event related to treatment with lixisenatide (Table 3).

3.5 | Symptomatic hypoglycaemic events

The incidence of protocol-defined symptomatic hypoglycaemia was similar in the two arms (Table 3; any incidence, lixisenatide 15.6% [35/224] vs placebo 13.5% [30/223]). Hypoglycaemia (with loss of consciousness) was reported as a serious TEAE in 1 patient (0.4%) in the lixisenatide group, but this event did not meet the criteria for severe symptomatic hypoglycaemia, as the first glycaemic value measured at the time of the event was above the defined threshold for severe hypoglycaemia.

4 | DISCUSSION

In a T2D population insufficiently controlled despite optimized treatment with BI (with or without metformin) during an 8-week run-in period, lixisenatide showed superior efficacy to placebo in Asian patients over a 24-week period. Higher proportions of patients achieved the HbA1c target of <7% or $\leq 6.5\%$ after lixisenatide treatment. Furthermore, a prominent reduction in PPG was shown with lixisenatide treatment vs placebo after a standardized meal test, which was also reflected in a corresponding improvement in 7-point SMPG values at all timepoints except pre-breakfast. The improvement in glycaemic control was not achieved at the expense of increased BW. At the end of the study, BW was significantly reduced and daily BI dose was lower with lixisenatide treatment relative to placebo. Lixisenatide was well tolerated and the safety profile was consistent with the known effects of the GLP-1 RA class.

The clinical efficacy of lixisenatide has been demonstrated previously and it has been shown to be well tolerated while providing overall glycaemic control as a monotherapy or in combination with OADs and/or BI in the phase III GetGoal trials.^{18,22,23} In a study enrolling Asian populations with T2D insufficiently controlled with BI and/or sulphonylurea, lixisenatide also significantly improved glycaemic control over 24 weeks.²² The mean difference for lixisenatide vs placebo in the present study (HbA1c -0.51%) was clinically relevant and extended that seen in the global population of the GetGoal-L trial (HbA1c -0.4%).¹⁸ In contrast to the GetGoal-L trial, in the present study, the established treatment regimen was further improved by a treat-to-target titration on FPG before randomization to identify those patients requiring treatment intensification. Lixisenatide is known to reduce HbA1c in patients with T2D, with a pronounced effect on PPG, and these data confirm these findings through significantly improved 2-hour PPG levels over the 24-week study. As FPG was primarily tackled before randomization via BI titration, and BI was to be kept stable after randomization, it did not notably further improve after randomization.

Previous literature has indicated that PPG is a more important predictor of cardiovascular disease and all-cause mortality than FPG.^{24,25} The significant reductions in 2-hour PPG and plasma glucose excursion shown here were also demonstrated in the GetGoal-L-Asia trial.²² These post-breakfast glycaemic results are consistent with evidence from other GetGoal trials and are believed to be related to the slowing of gastric emptying by lixisenatide.²⁶ The weight benefits of GLP-1 RAs make them suitable for diabetes

treatment, especially in an overweight patient population or in those taking BI, which can lead to weight gain.^{8,18} In the present study, weight with placebo remained steady, but fell significantly with lixisenatide treatment. The small, although statistically significant, decrease in the daily BI dose at week 24 with lixisenatide may be considered clinically unimpressive and less relevant for helping to reduce further the likelihood of weight gain and hypoglycaemia associated with insulin treatment.

Lixisenatide was associated with a small but significantly greater decrease in mean overall 7-point SMPG at all 7 timepoints apart from pre-breakfast values. Taken together with the reduction in 2-hour PPG after the standardized meal challenge, this indicates a significant reduction in plasma glucose from baseline when compared with those patients in the placebo group.

Consistent with the known safety profile of lixisenatide and the GLP-1 RA class of molecules, mild-to-moderate nausea and vomiting were reported more frequently with lixisenatide than with placebo.^{18,27} The incidence of symptomatic hypoglycaemia was similar in the lixisenatide and placebo groups, showing that the glucose-lowering benefit of adding lixisenatide to BI was not gained at the expense of an elevated risk of hypoglycaemia; the incidence of symptomatic hypoglycaemia reported was in the range reported for a patient population treated with background BI.²⁸

Furthermore, other GLP-1 RA treatments have also been investigated in Asian populations and have shown favourable treatment responses. Liraglutide (0.9 mg/d) showed a significant reduction in HbA1c and FPG in combination with an OAD in Japanese patients whose T2D was inadequately controlled with a single OAD over 52 weeks, compared with those given an additional OAD.¹² Exenatide exhibited improved glycaemic control and greater weight reduction compared with placebo ($P < .001$) and had a similar safety profile to non-Asian populations.¹¹

The GetGoal programme has addressed different populations treated with lixisenatide in combination with OADs and/or BI (GetGoal-L trial: global population; GetGoal-L-Asia: Asian population; GetGoal-L-C: predominantly Chinese population).^{18,22,23} GetGoal-L-C was a phase III trial enrolling a predominantly Chinese population, in which generally T2D remains insufficiently controlled to a large extent. Results from this study and another study also enrolling a large proportion of Chinese patients²⁹ have indicated that lixisenatide with OADs and/or BI is a valid treatment option in patients with inadequately controlled diabetes, making the results highly relevant to Asian, and more specifically Chinese, clinical practice. Indeed, addition of lixisenatide in patients with optimized BI treatment may go some way to addressing the unmet treatment needs in this patient population with T2D.

As GetGoal-L-C was designed to identify the population that really requires further treatment intensification despite optimized BI, the run-in period aimed to optimize the existing BI regimen. After randomization, no further titration of BI was permitted, to allow for the evaluation of lixisenatide under stable background treatment. Although greater than that achieved with placebo, further titration of BI dose in combination with lixisenatide may have increased the proportion of patients with HbA1c <7%; this would need to be investigated in a different study. Even though patients' glycaemic control

with BI was improved during the run-in period, the addition of lixisenatide further reduced HbA1c from baseline in these difficult-to-treat patients (HbA1c $\geq 7\%$ and $\leq 9.5\%$), along with slightly lower BI doses. The present study, therefore, evaluated a population for whom improving glycaemic control may be expected to be challenging.

In conclusion, adding lixisenatide achieved higher levels of glycaemic control in advanced T2D inadequately controlled with BI with/without metformin, with a beneficial effect on weight, no additional risk of hypoglycaemia, and a tolerability profile consistent with previous data. Lixisenatide may therefore be considered a treatment option for Asian, including Chinese, patients when added to BI in this population, and could possibly help a higher proportion of these patients to meet glycaemic control targets.

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Conflict of interest

W. Y. attended the advisory board of Novo Nordisk, received investigator-initiated trial research funds from AstraZeneca, has been a speaker for AstraZeneca, Bayer, Boehringer Ingelheim, Eli Lilly, Merck Sharp & Dohme China, Novo Nordisk, Sanofi Aventis and Servier, and has received honoraria and travel support as the advisory board member from Merck & Co., Inc, outside the submitted work.

K. M., Z. Z., L. L., X. X., D. Z., A. V. R. have no conflict of interest to declare. L. S. M. was an investigator for AstraZeneca, Boehringer Ingelheim, Novartis, Novo Nordisk and Sanofi. N. X. Z., I. L., E. N., S. S. are employees of Sanofi.

Author contributions

Author contributions were as follows: W. Y.: design, conduct/data collection, analysis and writing of the manuscript; K. M.: clinical study protocol set-up, study conduct supervision and reporting, data

collection, review and comment on manuscript; Z. Z., L. L., X. X. and D. Z.: data analysis/interpretation; A. V. R.: conduct/data collection; L. S. M.: conduct of the study; N. X. Z.: study conduct/data collection and analyses; I. L.: statistical analysis; E. N.: clinical study protocol set-up, study conduct supervision and reporting; and S. S.: study conduct supervision and reporting.

All authors confirm that they meet the International Committee of Medical Journal Editors uniform requirements for authorship and that all authors have read, reviewed and agreed to the final version of the manuscript.

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SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

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