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Improved glycaemic control and weight benefit with iGlarLixi versus insulin glargine 100 U/mL in Chinese people with type 2 diabetes advancing their therapy from basal insulin plus oral antihyperglycaemic drugs: Results from the LixiLan-L-CN randomized controlled trial

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Abstract

Aims: To evaluate the efficacy and safety of iGlarLixi compared with iGlar in Chinese adults with type 2 diabetes advancing therapy from basal insulin ± oral antihyperglycaemic drugs.

Materials and methods: LixiLan-L-CN (NCT03798080) was a 30-week randomized, active-controlled, open-label, parallel-group, multicentre study. Participants were randomized 1:1 to iGlarLixi or iGlar. The primary objective was to show the superiority of iGlarLixi over iGlar in glycated haemoglobin (HbA1c) change from baseline to Week 30.

Results: In total, 426 participants were randomized to iGlarLixi (n = 212) or iGlar (n = 214). Mean age was 58 years, 67% had a body mass index ≥24 kg/m^2, corresponding to overweight/obesity, and the mean diabetes duration was 12.3 years. From mean baseline HbA1c of 8.1% in both groups, greater decreases were seen with iGlarLixi versus iGlar [least squares mean difference: −0.7 (95% confidence interval: −0.9, −0.6)%; $p < .0001$] to final HbA1c of 6.7% and 7.4%, respectively. HbA1c <7.0% achievement was greater with iGlarLixi (63.3%) versus iGlar (29.9%; $p < .0001$). Mean body weight decreased with iGlarLixi and increased with iGlar [least squares mean difference: −0.9 (95% confidence interval: −1.4, −0.5) kg; $p = .0001$]. Hypoglycaemia incidence was similar between groups. Few gastrointestinal adverse events occurred (rated mild/moderate) with a slightly higher incidence with iGlarLixi than iGlar.

This article has an accompanied Plain Language Summary in the Supporting Information Data S1.

* Some of the data included herein were previously presented as an oral presentation at the Virtual European Association for the Study of Diabetes (EASD) annual meeting, 2021.

Conclusions: iGlarLixi provided better glycaemic control and facilitated more participants to reach glycaemic targets alongside beneficial effects on body weight, no additional risk of hypoglycaemia, and few gastrointestinal AEs, supporting iGlarLixi use as an efficacious and well tolerated therapy option in Chinese people with long-standing T2D advancing therapy from basal insulin.

KEYWORDS
basal insulin, clinical trial, GLP-1 analogue, glycaemic control, iGlarLixi, type 2 diabetes

1 | INTRODUCTION

Diabetes affects 537 million adults worldwide, and China has the largest population of people with diabetes of any country (141 million people aged 20-79 years).[1] The Observational Registry of Basal Insulin Treatment real-world study of basal insulin (BI) use in China showed that 6 months after initiation of BI therapy, approximately 60% of people with type 2 diabetes (T2D) did not reach a glycated haemoglobin (HbA1c) of <7.0% (<53 mmol/mol).[2]

The Chinese Diabetes Society (CDS) guidelines recommend that, for people with T2D and elevated HbA1c on BI, advancement options can include the addition of a glucagon-like peptide-1 receptor agonist (GLP-1 RA).[3] iGlarLixi is a fixed-ratio combination of BI insulin glargine 100 U/mL (iGlar) and the GLP-1 RA lixisenatide (Lixi) that can provide a convenient once-daily titratable therapy option for people advancing their BI therapy. The efficacy and safety of iGlarLixi has been shown in the LixiLan randomized controlled trial programme in both multinational (mainly white populations/people and Japanese people with T2D with elevated HbA1c on oral antihyperglycaemic drugs (OADs),[4-6] BI[7,8] or GLP-1 RAs.[9]

Several different dose ratios of iGlarLixi have been developed to accommodate the clinical needs of different populations. East Asian people with T2D have a distinct pathophysiology to white populations/people, including lower body mass index (BMI), greater postprandial plasma glucose (PPG) excursions and higher insulin sensitivity.[10-12] Based on dose requirements seen in clinical practice[13] and results from the randomized controlled trials,[14,15] a 2:1 ratio, containing 2 U iGlar to 1 μg Lixi, was selected for this study to provide BI doses corresponding to the lower insulin dose requirements of Chinese versus white populations/people,[16] while also providing clinically meaningful doses of Lixi to facilitate PPG and body weight control.

The present study assessed the efficacy and safety of iGlarLixi versus iGlar in Chinese adults with T2D and elevated HbA1c on BI alone or with up to two OADs.

2 | MATERIALS AND METHODS

2.1 | Study design

LixiLan-L-CN was a 30-week randomized, active-controlled, open-label, parallel-group, multicentre study in Chinese adults (≥18 years of age) with T2D and elevated HbA1c [≥7.0 to ≤10.5% (≥53 to ≤91 mmol/mol)] on BI with or without ≤2 OADs. Participants were required to have received BI for 6 months before screening, with a stable dose (±20%) of 10-25 U/day for at least 2 months before screening. Permitted OADs at screening were metformin, sulphonylureas, glinides, alpha-glucosidase inhibitors, sodium glucose co-transporter 2 inhibitors and dipeptidyl-peptidase-4 inhibitors, and participants were required to have been on a stable dose of these for 3 months before screening. In addition, participants were required to have a fasting plasma glucose (FPG) of ≤160 mg/dl (≤8.9 mmol/L) at screening. Key exclusion criteria were the use of any OADs other than those permitted during the 3 months before screening, use of any insulin regimen besides BI during 1 year before screening [except for short-term treatment (≤10 days) because of intercurrent illness], and a mean fasting self-measured plasma glucose (SMPG) of >160 mg/dl (>8.9 mmol/L) during the 7 days before randomization (mean of at least four measurements).

The study was registered on ClinicalTrials.gov (NCT03798080) and conducted in accordance with the Declaration of Helsinki and the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use guidelines for Good Clinical Practice, and all participants provided informed consent. The study duration was 19 February 2019 to 1 December 2020. As the study took place during the COVID-19 pandemic, it was conducted in accordance with health authorities' guidance for conduct of trials during COVID-19.[17-19]

The study included three periods (Figure S1): a screening period of up to 2 weeks; a 30-week, open-label, randomized treatment period; and a 3-day post-treatment safety follow-up period. Participants were randomized 1:1 to receive either iGlarLixi [Suliqua® (Soliqua®), Sanofi, Paris, France] or iGlar (Lantus®, Sanofi, Paris, France), both administered once daily. Randomization was performed centrally by an interactive response technology.

iGlarLixi (2 U iGlar to 1 μg Lixi) was administered once daily, within 1 h before the first meal of the day, using a SoloStar® pen. iGlar was administered once daily, using a SoloStar® pen. The injection time was determined at the time of randomization and was to remain the same throughout the treatment period. Starting doses of iGlarLixi were between 10 and 20 dose steps (from 10 U iGlar/5 μg Lixi to 20 U iGlar/10 μg Lixi; both inclusive), based on the insulin dose on the day before randomization. For participants with a previous BI daily dose of <20 U, the initial iGlarLixi dose was the same as the BI dose on the day before randomization, unless prior BI was administered twice daily, in which case the iGlarLixi initial dose was 80% of the previous dose. All starting doses of iGlar

were also determined in this way. If the previous BI dose was ≥20 U, the start dose of iGlarLixi was 20 dose steps (20 U iGlar/10 μg Lixi).

Both treatments were titrated once a week to a target fasting SMPG ≥80 and ≤100 mg/dl (≥4.4 and ≤5.6 mmol/L) while avoiding hypoglycaemia, with iGlarLixi doses being titrated based on the iGlar component. Titration was conducted using the same algorithm (Table S1) up to a maximum permitted dose of 40 dose steps for iGlarLixi (40 U iGlar/20 μg Lixi) or 40 U for iGlar.

Previous metformin therapy (if applicable) was continued at a stable dose, but all other OADs received at screening were stopped at randomization.

Rescue therapy was administered in the event of a participant having HbA1c >8.0% (>64 mmol/mol) at Week 12 or later and if daily dose >40 dose steps or >40 U was necessary, or if safety concerns (repeated hypoglycaemia, severe gastrointestinal adverse events, or other safety issues) prevented up-titration to 40 dose steps or 40 U. Recommended rescue therapy was the addition of one rapid-acting insulin administered with the main meal. Additional GLP-1 RA, BI, or dipeptidyl-peptidase-4 inhibitors were not permitted as rescue therapy.

2.2 | Study endpoints

The primary objective was to show the superiority of iGlarLixi over iGlar in HbA1c reductions from baseline to Week 30. Secondary efficacy endpoints included the proportion of participants reaching HbA1c <7.0% (<53 mmol/mol) or HbA1c ≤6.5% (<48 mmol/mol) and composite endpoints of HbA1c target achievement <7.0% without weight gain at Week 30, or without weight gain at Week 30 and without hypoglycaemia during the 30-week randomized treatment period, change from baseline to Week 30 in body weight, 2-h PPG, 2-hour PPG excursions, FPG, 7-point SMPG profiles, and the proportion of participants requiring rescue therapy. The change in insulin dose from baseline to Week 30 was also assessed.

Safety endpoints included any adverse events (AEs) incidence and rates of documented hypoglycaemia [thresholds ≤70 mg/dl (≤3.9 mmol/L) or <54 mg/dl (<3.0 mmol/L)], regardless of symptoms, symptomatic, severe hypoglycaemia (defined as requiring another person's assistance to administer actively the carbohydrate, glucagon, or other resuscitative actions) and American Diabetes Association (ADA)-defined hypoglycaemia.[20] Other safety endpoints included laboratory assessments (haematology, clinical chemistry, lipids, amylase, lipase and calcitonin), vital signs (blood pressure, heart rate and electrocardiogram) and the presence of anti-lixisenatide antibodies.

2.3 | Statistical analysis

The study sample size was calculated to provide ≥90% power to detect a mean between-treatment difference in change in HbA1c of 0.4% (4 mmol/mol) from baseline to Week 30 and was calculated to be 213 participants per treatment group. Efficacy endpoints were assessed in the modified intention-to-treat population, comprising all randomized participants who had both a baseline assessment and at least one post-baseline assessment of any primary or secondary efficacy variable, regardless of compliance with the study protocol or receipt of rescue therapy. Safety endpoints were assessed in the safety population, comprising randomized participants who received at least one dose of study drug.

The primary endpoint was analysed using a mixed-effects model with repeated measures under the missing at random framework with treatment group and randomization strata [HbA1c at screening of <8.0/≥8.0% (<64/≥64 mmol/mol), metformin use at screening (yes/no)], in addition to other OADs except metformin at screening (yes/no), visit (Week 8, 12, 24 and 30) and treatment-by-visit as fixed effects, and baseline HbA1c value-by-visit interaction as a covariate. Superiority was assessed using two-sided tests at a 5% significance level.

Key secondary endpoints were assessed in a hierarchical order (Table S2) using two-sided statistical tests for superiority of iGlarLixi over iGlar at the alpha level of 0.05. Testing on secondary efficacy endpoints was only performed if significance on the primary endpoint was reached. Continuous secondary efficacy endpoints were assessed using the same mixed-effects model with repeated measures approach as used for the primary endpoints, except for 2-h PPG and PPG excursions, which were assessed using analysis of covariance, with missing data at Week 30 imputed using last observation carried forward. Categorical secondary efficacy endpoints were analysed using a Cochran-Mantel-Haenszel method stratified by randomization strata (screening HbA1c and screening metformin use) and other OAD use at screening.

3 | RESULTS

Of 641 screened participants, 426 from 44 centres in China were randomized to either iGlarLixi (n = 212) or iGlar (n = 214). A high proportion of participants completed the 30-week randomized treatment period (n = 203, 95.8% with iGlarLixi and n = 201, 93.9% with iGlar) (Figure S2).

There were no major differences in baseline characteristics between groups (Table 1). Mean age was 57.5 years, 58.2% of participants were male, mean BMI was 25.2 kg/m^2, and 66.9% of participants were either overweight or obese (≥24 kg/m^2). Mean diabetes duration was 12.3 years, mean duration of previous BI treatment was 2.7 years, and the most commonly used prior insulin was iGlar (85.0% of participants). At screening, 78.2% of participants used metformin and 58.5% used two OADs; the most frequently used combination of OADs was metformin plus alpha-glucosidase inhibitors (23.9%).

3.1 | Efficacy

Required significance was achieved for all steps of the step-down testing procedure, with the exception of the last endpoint in the testing procedure (change from baseline to Week 30 in FPG; Table S2); thus, all primary and secondary endpoints in the testing order were analysed as planned but are presented here in a clinically relevant order.

TABLE 1 Baseline characteristics (randomized population)

	iGlarLixi (n = 212)	iGlar (n = 214)	Overall (N = 426)
Age, years	58.2 ± 8.7	56.7 ± 9.3	57.5 ± 9.0
Male, n (%)	126 (59.4)	122 (57.0)	248 (58.2)
BMI, kg/m^2	25.2 ± 2.7	25.3 ± 3.0	25.2 ± 2.9
BMI group, kg/m^2; n (%)			
<24	63 (29.7)	78 (36.4)	141 (33.1)
≥24 to <28	115 (54.2)	97 (45.3)	212 (49.8)
≥28	34 (16.0)	39 (18.2)	73 (17.1)
Diabetes duration, years	13.3 ± 6.2	11.4 ± 6.0	12.3 ± 6.2
Mean HbA1c at screening			
%	8.3 ± 0.9	8.3 ± 0.9	8.3 ± 0.9
mmol/mol	67 ± 10	67 ± 10	67 ± 10
HbA1c at screening, n (%)[a]			
≥8.0% (≥64 mmol/mol)	124 (58.5)	125 (58.4)	249 (58.5)
FPG			
mg/dl	135 ± 27	137 ± 25	135 ± 27
mmol/L	7.5 ± 1.5	7.6 ± 1.4	7.5 ± 1.5
Duration of basal insulin therapy, years	2.7 ± 2.4	2.7 ± 2.5	2.7 ± 2.4
Previous basal insulin at screening, n (%)			
iGlar	187 (88.2)	175 (81.8)	362 (85.0)
Insulin detemir	16 (7.5)	33 (15.4)	49 (11.5)
NPH	9 (4.2)	5 (2.3)	14 (3.3)
Insulin degludec	0 (0.0)	1 (0.5)	1 (0.2)
Daily basal insulin dose on day before randomization			
U	18.3 ± 4.4	17.6 ± 4.2	18.0 ± 4.3
U/kg	0.27 ± 0.07	0.26 ± 0.07	0.26 ± 0.07
OAD use at screening, n (%)			
0	15 (7.1)	16 (7.5)	31 (7.3)
1	66 (31.1)	80 (37.4)	146 (34.3)
2	131 (61.8)	118 (55.1)	249 (58.5)
Metformin use at screening, n (%)[a]			
Yes	166 (78.3)	167 (78.0)	333 (78.2)
No	46 (21.7)	47 (22.0)	93 (21.8)
Other OAD use at screening, n (%)			
Yes	147 (69.3)	137 (64.0)	284 (66.7)
No	65 (30.7)	77 (36.0)	142 (33.3)
eGFR at screening, ml/min/1.73 m^2	90.8 ± 22.0	91.8 ± 18.0	91.3 ± 20.1

Note: Data shown are mean ± SD unless otherwise stated.
Abbreviations: BMI, body mass index; FPG, fasting plasma glucose; eGFR, estimated glomerular filtration rate; HbA1c, glycated haemoglobin; iGlar; insulin glargine 100 U/mL; iGlarLixi, a fixed-ratio combination of insulin glargine 100 U/mL and lixisenatide; NPH, neutral protamine Hagedorn; OAD, oral antihyperglycaemic drug; U, units.
[a]Randomization strata.

3.1.1 | Glycaemic efficacy

iGlarLixi was shown to be superior to iGlar in HbA1c reduction from baseline to Week 30 (Figure 1A,B, Table 2); thus, the primary objective was met. The mean HbA1c was reduced from a baseline value of 8.1% (65 mmol/mol) in both groups to 6.7% (50 mmol/mol) with iGlarLixi and 7.4% (57 mmol/mol) with iGlar. Least squares (LS) mean reductions in HbA1c were −1.4% (15 mmol/mol) and −0.7% (8 mmol/mol) for iGlarLixi and iGlar, respectively, with an LS mean difference of −0.7% [95% confidence interval (CI): −0.9, −0.6; −8 mmol/mol (95% CI: −10 to −7); $p < .0001$].

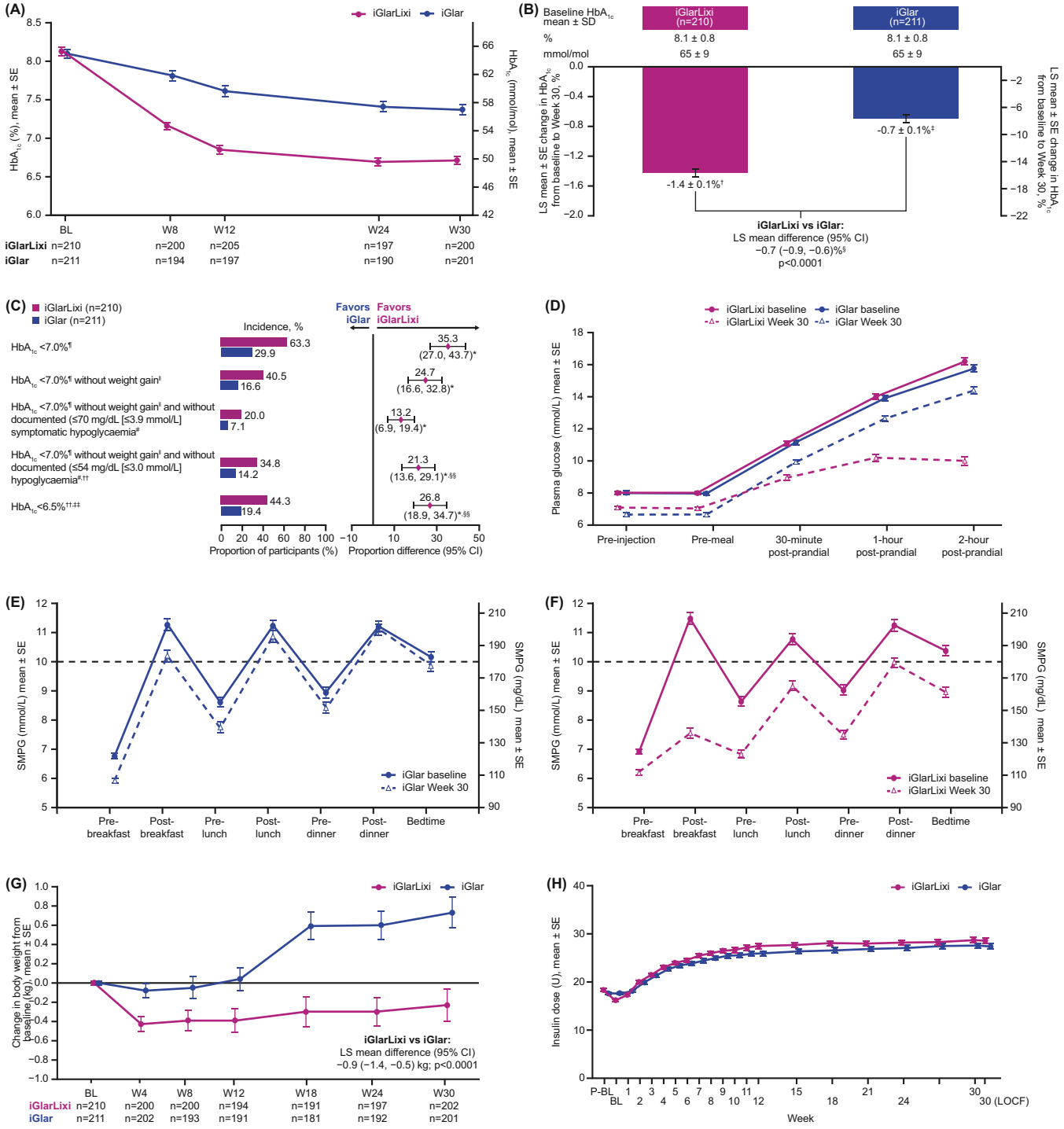

FIGURE 1 Response to therapy (mITT population). A, Mean HbA1c over time; B, change in HbA1c from baseline to Week 30; C, HbA1c target achievement and composite target achievement; D, pre- and postprandial plasma glucose; E, 7-point SMPG profiles at baseline and Week 30 for iGlar; F, 7-point SMPG profiles at baseline and Week 30 for iGlarLixi; G, change in body weight over time; and H, total insulin dose over time (mITT population). *p < .0001; †−15 ± 1 mmol/mol; ‡−8 ± 1 mmol/mol; §−8 (−10, −7) mmol/mol; ¶<53 mmol/mol; ‖at Week 30; #during the 30-week randomized treatment period; ††exploratory endpoint, not included in the hierarchical testing procedure; ‡‡<48 mmol/mol; §§p-value for descriptive purposes only, endpoint not included in the hierarchical testing procedure. BL, baseline; CI, confidence interval; HbA1c, glycated haemoglobin; iGlar, insulin glargine 100 U/mL; iGlarLixi, a fixed-ratio combination of insulin glargine 100 U/mL and lixisenatide; LOCF, last observation carried forward; LS, least squares; P-BL, prior to baseline; SD, standard deviation; SE, standard error; SMPG, self-monitored plasma glucose; U, units; W, week

Significantly greater proportions of participants reached HbA1c <7.0% (<53 mmol/mol) overall, without weight gain and without weight gain or hypoglycaemia with iGlarLixi versus iGlar ($p < .0001$ for all) (Figure 1C, Table 2).

Significantly greater improvements were seen in 2-h PPG from baseline to Week 30 with iGlarLixi versus iGlar (LS mean change: −6.3 mmol/L vs. −1.7 mmol/L, respectively; $p < .0001$; Table 2). Change in 2-h PPG excursions from baseline to Week 30 also

TABLE 2 Efficacy endpoints (mITT population)

Efficacy endpoint	iGlarLixi (n = 210)		iGlar (n = 211)
HbA1c, %[a]			
Baseline	8.1 ± 0.8		8.1 ± 0.8
Week 30	6.7 ± 0.8		7.4 ± 0.9
LS mean ± SE change	−1.4 ± 0.1		−0.7 ± 0.1
LS mean difference (95% CI) iGlarLixi vs. iGlar		−0.7 (−0.9, −0.6) $p < 0.0001$	
HbA1c, mmol/mol[a]			
Baseline	65 ± 9		65 ± 9
Week 30	50 ± 9		57 ± 10
LS mean ± SE change	−15 ± 1		−8 ± 1
LS mean difference (95% CI) iGlarLixi vs. iGlar		−8 (−10, −7) $p < .0001$	
HbA1c < 7.0% (<53 mmol/mol) at Week 30[a]			
n (%)	133 (63.3)		63 (29.9)
Proportion difference iGlarLixi vs. iGlar (95% CI)		35.3% (27.0, 43.7) $p < .0001$	
2-h PPG, mmol/L[a]			
Baseline	16.2 ± 2.9		15.8 ± 3.2
Week 30[b]	10.0 ± 3.6		14.4 ± 3.2
LS mean ± SE change[b]	−6.3 ± 0.3		−1.7 ± 0.2
LS mean difference (95% CI) iGlarLixi vs. iGlar		−4.7 (−5.3, −4.1) $p < .0001$	
2-h PPG excursion, mmol/L[a]			
Baseline	8.2 ± 2.7		7.7 ± 3.0
Week 30[b]	2.9 ± 3.4		7.7 ± 3.0
LS mean ± SE change[b]	−5.4 ± 0.2		−0.2 ± 0.2
LS mean difference (95% CI) iGlarLixi vs. iGlar		−5.1 (−5.7, −4.6) $p < .0001$	
FPG, mmol/L[a]			
Baseline	7.5 ± 1.5		7.6 ± 1.4
Week 30	7.1 ± 1.6		6.7 ± 1.5
LS mean ± SE change	−0.5 ± 0.1		−0.9 ± 0.1
LS mean difference (95% CI) iGlarLixi vs. iGlar		0.4 (0.1, 0.7) $p = .0174$[c]	
Average 7-point SMPG, mmol/L[a]			
Baseline	9.8 ± 1.6		9.8 ± 1.6
Week 30	8.0 ± 1.3		9.2 ± 1.8
LS mean ± SE change	−1.7 ± 0.1		−0.5 ± 0.1
LS mean difference (95% CI) iGlarLixi vs. iGlar		−1.2 (−1.5 to −1.0) $p < .0001$	
Body weight, kg[a]			
Baseline	69.3 ± 10.8		69.8 ± 10.7
Week 30	69.2 ± 10.8		70.7 ± 11.2
LS mean ± SE change	-0.3 ± 0.2		0.7 ± 0.2
LS mean difference (95% CI) iGlarLixi vs. iGlar		−0.9 (−1.4, −0.5) $p = .0001$	
Rescue therapy[a,d]			
n (%)	4 (1.9)		30 (14.2)
Proportion difference (95% CI)		−12.7 (−17.9, −7.6) $p < .0001$	

(Continues)

TABLE 2 (Continued)

Efficacy endpoint	iGlarLixi (n = 210)	iGlar (n = 211)
Insulin dose, U		
Baseline of prior basal insulin,[e] mean ± SD	18.3 ± 4.4	17.6 ± 4.1
Week 30, mean ± SD	28.7 ± 7.9	27.6 ± 8.6
LS mean ± SE change	10.5 ± 0.5	10.0 ± 0.5
LS mean difference (95% CI) iGlarLixi vs. iGlar	0.4 (−1.0, 1.9) $p = .5569$	

Note: Data are mean ± SE unless otherwise stated. *p*-values for superiority of iGlarLixi versus iGlar, unless otherwise stated.
Abbreviations: CI, confidence interval; FPG, fasting plasma glucose; HbA1c, glycated haemoglobin; iGlar, insulin glargine 100 U/mL; iGlarLixi, a fixed-ratio combination of insulin glargine 100 U/mL and lixisenatide; LOCF, last observation carried forward; LS, least squares; mITT, modified intent-to-treat; PPG, post-prandial plasma glucose; SE, standard error; SMPG, self-monitored plasma glucose; U, units.
[a]Endpoints are adjusted for multiplicity (shown according to clinically relevant, not hierarchical, order).
[b]LOCF values used for Week 30.
[c]*p*-value favours iGlar versus iGlarLixi.
[d]During the 30-week treatment period.
[e]Mean of prior basal insulin doses before randomization.

significantly favoured iGlarLixi over iGlar ($p < .0001$; Table 2), with smaller PPG increases seen with iGlarLixi versus iGlar at 30 min, 1- and 2-h time points post-meal (Figure 1D).

Change in FPG from baseline to Week 30 was slightly smaller with iGlarLixi than with iGlar (Table 2), with mean FPG values at Week 30 of 7.1 mmol/L and 6.7 mmol/L, respectively, which are both close to the 4.4-7.0 mmol/L (~80-130 mg/dl) target recommended by the CDS.[21]

Reductions in 7-point SMPG profiles from baseline to Week 30 were greater with iGlarLixi than iGlar for all time points except for the pre-breakfast time point (Figures 1E,F). Reduction in the average daily 7-point SMPG was significantly greater with iGlarLixi versus iGlar [LS mean difference between groups: −1.2 (95% CI: −1.5, −1.0) mmol/L; $p < .0001$] (Table 2).

Fewer participants in the iGlarLixi group required rescue therapy during the 30-week treatment period compared with the iGlar group, with a proportion difference of −12.7% (95% CI: −17.9, −7.6; $p < .0001$) (Table 2).

3.1.2 | Body weight

Mean body weight decreased from baseline to Week 30 in the iGlarLixi group (LS mean change: −0.3 kg) and increased in the iGlar group (LS mean change: 0.7 kg), leading to an LS mean difference of −0.9 (95% CI: −1.4 to −0.5) kg; $p = .0001$ (Figure 1G; Table 2).

3.1.3 | Basal insulin and lixisenatide dose

The daily BI dose measured before randomization was similar in both groups [18.3 ± 4.4 U (0.27 ± 0.07 U/kg) with iGlarLixi and 17.6 ± 4.1 U (0.26 ± 0.07 U/kg) with iGlar]. Mean change in insulin dose from before randomization to Week 30 was similar between groups, with an LS mean difference of 0.4 U (95% CI: −1.0, 1.9) (Figure 1H; Table 2). Doses at Week 30 were also similar between treatments [28.7 ± 7.9 U (0.42 ± 0.11 U/kg) with iGlarLixi

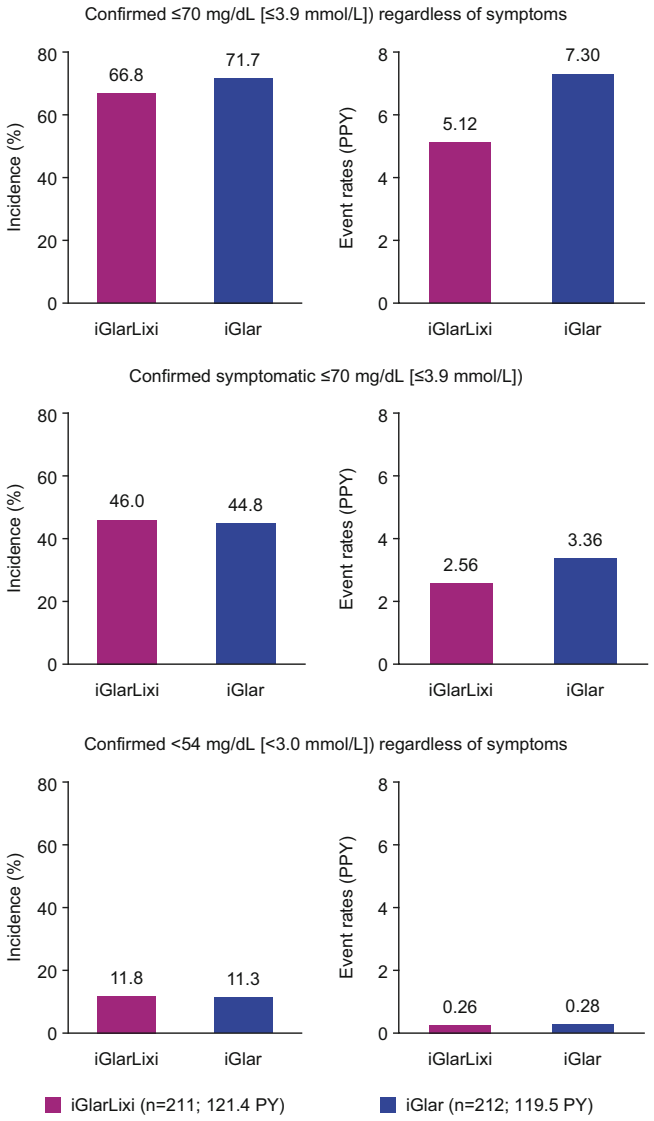

FIGURE 2 Incidence and event rates of hypoglycaemia during the 30-week randomized treatment period (safety population). iGlar, insulin glargine 100 U/mL; iGlarLixi, a fixed-ratio combination of insulin glargine 100 U/mL and lixisenatide; PY, participant-years; PPY, per participant-year

TABLE 3 Treatment-emergent adverse events (safety population)

n (%)	iGlarLixi (n = 211)	iGlar (n = 212)
Any TEAE	144 (68.2)	133 (62.7)
Any serious TEAE	15 (7.1)	15 (7.1)
Any TEAE leading to discontinuation	4 (1.9)	3 (1.4)
Any TEAE leading to death	0 (0.0)	0 (0.0)
GI TEAEs	54 (25.6)	37 (17.5)
Nausea	15 (7.1)	3 (1.4)
Vomiting	1 (0.5)	2 (0.9)
Diarrhoea	9 (4.3)	10 (4.7)
Injection site reactions	3 (1.4)	1 (0.5)
Allergic reactions	4 (1.9)	2 (0.9)

Abbreviations: GI, gastrointestinal; iGlar, insulin glargine 100 U/mL; iGlarLixi, a fixed-ratio combination of insulin glargine 100 U/mL and lixisenatide; TEAE, treatment-emergent adverse event.

vs. 27.6 ± 8.6 U (0.39 ± 0.12 U/kg) with iGlar]. At the end of treatment, 47.9% and 44.8% of participants were on a final dose of ≥30 to ≤40 U for iGlarLixi and iGlar, respectively (Table S3).

The mean daily dose of the lixisenatide component at Week 30 was 14.4 ± 4.0 μg/day. At end of treatment, 47.9% of participants had a final dose of 15-20 μg (Table S3).

3.2 | Safety

3.2.1 | Hypoglycaemia

The incidence of all hypoglycaemia endpoints was similar with iGlarLixi and iGlar (Figure 2; Table S4). Event rates were lower with iGlarLixi than iGlar for documented [≤70 mg/dl (≤3.9 mmol/L)] hypoglycaemia [5.12 vs. 7.30 events per-participant year (PPY); rate ratio (RR): 0.70 (95% CI: 0.54, 0.90)] and for ADA level 1 hypoglycaemia [3.28 vs. 4.83 events PPY; RR: 0.68 (95% CI: 0.51, 0.90)] (Figure 2; Table S4). Event rates were similar between treatment groups for documented [<54 mg/dl (<3.0 mmol/L)] hypoglycaemia (or ADA Level 2 hypoglycaemia) and documented [≤70 mg/dl (≤3.9 mmol/L)] symptomatic hypoglycaemia (Figure 2; Table S4). Incidence and events of documented [≤70 mg/dl (≤3.9 mmol/L)] hypoglycaemia regardless of symptoms by time of day are shown in Figure S3).

Episodes of severe hypoglycaemia were rare, with only two participants in each treatment group reporting severe hypoglycaemic events.

3.2.2 | Adverse events

Treatment-emergent AEs (TEAEs) were reported in 68.2% (n = 144) treated with iGlarLixi and 62.7% (n = 133) treated with iGlar. The difference was largely because of the higher incidence of nausea in the iGlarLixi group (n = 15, 7.1%) than in the iGlar group (n = 3, 1.4%), while incidence of vomiting and diarrhoea was similar between treatment groups (Table 3). However, no gastrointestinal (GI) TEAEs were graded as severe in intensity. Injection site reactions were infrequent and mild. Allergic reactions or hypersensitivity events were infrequent. Few participants discontinued because of TEAEs in either group (iGlarLixi n = 4, 1.9%; iGlar n = 3, 1.4%); of these, two participants in the iGlarLixi group (0.9%) discontinued therapy because of GI TEAEs (nausea), while no participants discontinued because of GI TEAEs in the iGlar group. Serious TEAEs were reported by 15 participants (7.1%) in each treatment group. There were no deaths reported during the study.

3.2.3 | Other safety endpoints

No clinically significant safety concerns were identified from a review of clinical laboratory parameters, vital signs, physical examination, or electrocardiograms. During the on-treatment period, two participants experienced a TEAE of increased lipase (one in each treatment group) and no participants reported a TEAE of increased amylase levels, calcitonin levels, or pancreatitis. Generally, there were no substantial differences in the safety profiles of anti-insulin and anti-Lixi antibody-positive and antibody-negative populations.

4 | DISCUSSION

In summary, iGlarLixi provided better glycaemic control than iGlar, with clinically meaningful greater HbA1c reductions to a final mean HbA1c of 6.7% (50 mmol/mol) and a greater proportion of participants reaching their HbA1c targets in the iGlarLixi group compared with iGlar, all in a population with long-standing T2D (~12 years duration) who had elevated HbA1c despite BI with or without OAD therapy. Moreover, the glycaemic benefits of iGlarLixi over iGlar were observed alongside weight gain prevention and with no additional risk of hypoglycaemia compared with iGlar.

The improved HbA1c reduction and target achievement seen with iGlarLixi versus iGlar is probably related to the complementary action of iGlarLixi on FPG and PPG, reflecting the key mechanism of action of its components,[9] while the effect of iGlar is predominantly on FPG. This dual action of iGlarLixi is of particular clinical benefit in Asian populations with T2D, in whom post-prandial hyperglycaemia is more common than in non-Asian populations.[12] In the present study ~50% in the iGlarLixi group were able to reach a final dose of Lixi of 15-20 μg, probably largely contributing to reductions in PPG and the beneficial body weight profile compared with iGlar. BI doses remained similar between groups and within a range generally corresponding to that of other randomized controlled trials in Asian populations with T2D.[22] Furthermore, the mean FPG at study end was around the target of 4.4-7.0 mmol/L (~80-130 mg/dl) recommended by the CDS,[21] indicating appropriate titration of iGlar in both treatment groups. These results suggest that using a 2:1 ratio of iGlarLixi enabled study participants to utilize appropriate doses of both BI and GLP-1 RA to achieve glycaemic control.

FPG reductions were slightly greater with iGlar than iGlarLixi. It should be noted that 85% of participants in the iGlar group injected in

the evening (data not shown), while all participants in the iGlarLixi group were required by protocol to inject before the first meal of the day. This most probably contributed to the observed between-group differences in FPG change from baseline.

Safety findings were generally similar for both treatments and no unexpected safety signals identified. A higher incidence of nausea was observed with iGlarLixi compared with iGlar, as expected for a therapy containing a GLP-1 RA and observed in other studies comparing iGlarLixi versus iGlar.[4,6-8] However, all events were rated as mild or moderate in intensity. Only two participants (0.9%) discontinued iGlarLixi because of nausea, the only GI TEAE leading to discontinuation. The incidence of vomiting and diarrhoea was similarly low in both treatment groups.

Results of this study confirm findings from the LixiLan-L and LixiLan JP-L trials, which explored the efficacy and safety of iGlarLixi versus iGlar in people with T2D advancing their therapy from BI.[7,8] LixiLan-L was a 30-week study that explored clinical outcomes in predominantly white populations/people and employed either a 3:1 or 2:1 ratio of iGlarLixi,[7] while LixiLan JP-L was a 26-week study that focused on Japanese people and utilized a 1:1 ratio.[8] Both these studies showed that, compared with iGlar, iGlarLixi provided improved glycaemic control alongside weight benefit and no increased risk of hypoglycaemia.[7,8] HbA1c reductions from baseline to end of study observed in both these studies (−1.1% to −1.3%) were similar to those seen in the present study.[7,8] These comparable improvements in glycaemic control were seen alongside differences in final insulin doses [LixiLan-L: 47 U (0.54 U/kg); LixiLan JP-L study: 17 U; LixiLan-L-CN: 29 U (0.42 U/kg)],[7,8,23] but similar Lixi doses (LixiLan-L: 17 μg; LixiLan-L-CN: 14 μg; LixiLan JP-L ~17 μg),[7,8] likely reflecting the different body weights, insulin requirements, and medical practice of these populations and supporting the different pen ratio strategies in providing BI dose ranges previously observed for these respective populations.[13,14,16,24-27]

Similar results were also seen for IDegLira in the DUAL-II CN study.[28] IDegLira provided greater HbA1c reductions than insulin degludec (IDeg), alongside weight benefit in Chinese adults with T2D advancing therapy from BI plus metformin with or without other OADs.[28] However, there are relevant differences in the study designs and populations of these two studies, which should be considered. For instance, DUAL-II-CN included participants with BMI ≥24 kg/m^2 (no BMI inclusion criteria was specified in LixiLan-L-CN) and a higher previous insulin dose than LixiLan-L-CN (20-50 U/day vs. 10-25 U/day); this probably contributed to the higher baseline mean BMI (27.4 kg/m^2 vs. 25.2 kg/m^2) and prior insulin dose (25 U/day vs. 18 U/day) seen in DUAL-II-CN compared with LixiLan-L-CN.[28] Notably, the mean baseline BMI and prior insulin doses seen in LixiLan-L-CN are generally similar to those of the general population of Chinese adults with T2D, while those of DUAL-II-CN are slightly higher.[13,29] Accordingly, the final insulin doses were in DUAL-II-CN [34 U/day (0.45 U/kg)] were also slightly higher than those in LixiLan-L-CN [29 U/day (0.42 U/kg)].[28] Additional differences include the different ratios (16 U IDeg/0.6 mg liraglutide vs. 2 U iGlar/1 μg Lixi), permitted maximum daily dose (50 vs. 40 dose steps) and dose titration algorithms. Accepting the differences in hypoglycaemia definitions between the DUAL-II-CN [confirmed <56 mg/dl (<3.1 mmol/L) or severe hypoglycaemia] and the present study [documented <54 mg/dl (<3.0 mmol/L) hypoglycaemia regardless of symptoms], the incidences of hypoglycaemia were similar for IDegLira (11.3%) and iGlarLixi (11.8%), while the corresponding incidence for the comparator groups were 14.6% with IDeg and 11.3% with iGlar.[28]

The strengths of the present study include its randomized controlled design and the large sample size. Some data were collected during the COVID-19 pandemic; however, the impact on the results was assessed and determined to be minimal. Limitations include the open-label study design. To compensate for the lack of blinding, the investigator and sponsor did not have access to the data of the primary efficacy endpoint (HbA1c measured at a central laboratory) obtained after baseline visit until the end of the study.

In conclusion, for Chinese people with T2D advancing therapy from BI, iGlarLixi provided significantly greater HbA1c reductions and facilitated significantly more participants to reach their HbA1c targets compared with iGlar, while preventing body weight gain and without additional risk of hypoglycaemia. As such, these findings support the use of iGlarLixi as an efficacious and well-tolerated therapy option for advancing therapy from BI with or without OADs in Chinese people with long-standing T2D.

AUTHOR CONTRIBUTIONS

All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, had full access to all the data in this study, and take complete responsibility for the integrity of the data and accuracy of the data analysis. All authors participated in the interpretation of the data, the writing, reviewing, and editing of the manuscript, and had final responsibility for approving the published version.

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CONFLICT OF INTERESTS

XY, XG, JZ, XD, YL and WP declare that they have no competing interests; SG, LP, GN, EN and ES are employees of Sanofi and may hold shares and/or stock options in the company.

DATA AVAILABILITY STATEMENT

Qualified researchers may request access to patient-level data and related documents. Patient-level data will be anonymized, and study documents will be redacted to protect the privacy of trial participants. Further details on Sanofi's data sharing criteria, eligible studies, and process for requesting access can be found at https://www.vivli.org.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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