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iGlarLixi provides improved early glycaemic control after 12 weeks of treatment compared with basal insulin in Asian people with type 2 diabetes: A post hoc analysis of the LixiLan-O-AP and LixiLan-L-CN studies

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Abstract

Aims: To evaluate early glycaemic control (glycated haemoglobin [HbA1c] < 7.0% [<53.0 mmol/mol], fasting plasma glucose [FPG] ≤ 7.0 mmol/L or postprandial glucose [PPG] ≤ 10.0 mmol/L) with iGlarLixi versus insulin glargine 100 U/mL (Gla-100) in Asian people with suboptimally controlled type 2 diabetes (T2D) on oral antidiabetic drugs (OADs) in LixiLan-O-AP or basal insulin (BI) ± OADs in LixiLan-L-CN.

Materials and Methods: This post hoc analysis evaluated changes from baseline to Week 12 in HbA1c, FPG and PPG, hypoglycaemia incidence and the rates of target HbA1c achievement at Weeks 8 and 12. Median time to glycaemic control (i.e., time to 50% achieving target HbA1c, FPG or PPG) was also assessed.

Results: At Week 12, mean HbA1c reductions were greater with iGlarLixi versus Gla-100 in LixiLan-O-AP (−1.6% vs. −1.1% [−17.0 vs. −12.0 mmol/mol]) and LixiLan-L-CN (−1.3% vs. −0.5% [−13.9 vs. −5.4 mmol/mol]). PPG reductions were greater with iGlarLixi, while FPG reductions and hypoglycaemia incidence were similar. At Weeks 8 and 12, more participants had achieved target HbA1c or PPG with iGlarLixi versus Gla-100 in both studies. Median time to achieve HbA1c and PPG targets was shorter with iGlarLixi versus Gla-100 in LixiLan-O-AP (85 vs. 126 days and 84 vs. 167 days) and LixiLan-L-CN (85 vs. 239 days and 85 days vs. not estimable); median time to achieve FPG target was similar in LixiLan-O-AP (57 vs. 57 days) and LixiLan-L-CN (29 vs. 30 days).

Conclusions: In Asian people with T2D suboptimally controlled on OADs or BI, iGlarLixi provided comprehensive earlier glycaemic control than Gla-100.

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

Lulu Song and Xiaoyong Yuan are co-first authors.

1 | INTRODUCTION

Once-daily iGlarLixi is a fixed-ratio combination (FRC) of the basal insulin (BI) insulin glargine 100 U/mL (Gla-100) and lixisenatide, a short-acting glucagon-like peptide-1 receptor agonist (GLP-1 RA), that is, a treatment option for people with type 2 diabetes (T2D) who require treatment intensification. The combination of a BI and GLP-1 RA provides complementary glycaemic benefits, with Gla-100 reducing fasting plasma glucose (FPG) levels and lixisenatide reducing postprandial glucose (PPG) by enhancing glucose-mediate insulin release, suppressing glucagon secretion and delaying gastric emptying.[1,2] iGlarLixi is approved in more than 70 countries globally, including China,[3] Japan,[4] the United States[5] and Europe.[6]

Compared with Western populations, East Asian people with T2D have reduced insulin secretion due to decreased β-cell function.[7] In addition, Asian people with T2D are known to have higher PPG excursions than non-Asian populations.[8] Incretin-based therapies, such as GLP-1 RAs and dipeptidyl peptidase-4 inhibitors, which are known to restore β-cell function via stimulation of incretin activity,[9,10] are therefore considered to be effective treatment options in East Asian people with T2D. Indeed, addition of GLP-1 RA therapy is recommended by the Chinese Diabetes Society (CDS) in people with T2D and elevated glycated haemoglobin (HbA1c) on BI therapy.[11]

Two phase 3 randomised studies have evaluated the efficacy and safety of iGlarLixi in Asian populations with suboptimally controlled T2D: LixiLan-O-AP was conducted in Asia Pacific people previously on oral antidiabetic drugs (OADs) alone,[12] and LixiLan-L-CN was conducted in Chinese people previously on BI therapy (with or without OADs).[13] In both of these studies, iGlarLixi provided significantly improved glycaemic control and allowed more participants to achieve glycaemic targets compared with Gla-100, with no additional risk of hypoglycaemia.[12,13] iGlarLixi was also associated with significantly greater HbA1c reductions from baseline to Week 24 in LixiLan-O-AP (least squares [LS] mean difference −1.0% [−10.5 mmol/mol]; $p < 0.0001$),[13] and from baseline to Week 30 in LixiLan-L-CN (LS mean difference −0.7% [8.0 mmol/mol]; $p < 0.0001$) versus Gla-100.[12] The proportion of participants who achieved the HbA1c target <7.0% (<53.0 mmol/mol) at study end was also significantly higher with iGlarLixi than with Gla-100 in LixiLan-O-AP (79.0% vs. 60.5%; $p < 0.0001$)[13] and LixiLan-L-CN (63.3% vs. 29.9%; $p < 0.0001$).[12]

In a previous post hoc analysis of LixiLan-O-AP and LixiLan-L-CN, iGlarLixi provided better derived time-in-range (i.e., the percentage of time with plasm glucose [PG] in the range of 3.9 to 10.0 mmol/L) versus Gla-100 at Week 12 (LixiLan-O-AP: 85.3% vs. 69.0%; LixiLan-L-CN: 79.3% vs. 59.4%).[14] This indicates that iGlarLixi treatment provides better control than Gla-100 over glycaemic fluctuations from as early as 12 weeks after treatment initiation. A previous post hoc analysis of the global LixiLan-O[2] and LixiLan-L[15] studies also demonstrated that iGlarLixi provided more effective glycaemic control than Gla-100 at early time points.[16]

The current post hoc analysis of LixiLan-O-AP and LixiLan-L-CN evaluated the time to glycaemic control (i.e., achievement of target HbA1c or FPG) with iGlarLixi versus Gla-100 in Asian people with suboptimally controlled T2D, with a focus on the efficacy and hypoglycaemia outcomes at early study visits (i.e., Weeks 8 and 12) and the time taken to achieve HbA1c and FPG targets.

2 | MATERIALS AND METHODS

2.1 | Study designs

LixiLan-O-AP (NCT03798054) and LixiLan-L-CN (NCT03798080) were phase 3, open-label, randomised multicentre trials. The designs of these studies have been previously described in full (see Table S1 for details).[12,13] Briefly, LixiLan-O-AP was a 24-week study in Asia Pacific people with T2D and suboptimal glycaemic control on metformin (with or without a second OAD),[13] and LixiLan-L-CN was a 30-week study in Chinese people with T2D and suboptimal glycaemic control on BI therapy (with or without up to two OADs).[12] In both studies, iGlarLixi was self-administered once daily within 1 h before the first meal of the day, while Glar-100 was self-administered once daily at any time (at approximately the same time) each day throughout the randomised treatment period.

The studies were both conducted in accordance with the ethical principles of the Declaration of Helsinki and the International Conference on Harmonisation guidelines for good clinical practice. Approval of the study protocols was provided by the relevant independent ethics committees and/or institutional review boards, and all participants provided informed consent.

2.2 | Post hoc analysis

The primary efficacy end-point of LixiLan-O-AP and LixiLan-L-CN was the change in HbA1c from baseline to study end. This post hoc analysis assessed efficacy and hypoglycaemia outcomes for the iGlarLixi and Gla-100 treatment arms at earlier study visits. The lixisenatide treatment arm of the LixiLan-O-AP study was excluded from this analysis.

At Week 12, changes from baseline in HbA1c, FPG, 7-point self-measured plasma glucose (SMPG), 2-h PPG and body weight were assessed, as well as insulin daily dose and the incidence of documented symptomatic hypoglycaemia (with plasma glucose [PG] ≤ 3.9 mmol/L) and severe hypoglycaemia (defined as requiring assistance for administration of carbohydrate, glucagon or other resuscitative measures).

In the responder analysis, the proportion of participants who achieved American Diabetes Association (ADA)-recommended target HbA1c (<7.0% [<53.0 mmol/mol])[17] or CDS-recommended target FPG (≤7.0 mmol/L) or 2-h PPG (<10.0 mmol/L)[11] at Weeks 8 and 12 was assessed. The proportion of participants who achieved target HbA1c without body weight gain or documented hypoglycaemia (PG <3.0 mmol/L, regardless of symptoms) at Week 12 was also assessed. HbA1c, FPG and 2-h PPG measurements at scheduled in-person study visits (Weeks 2, 3, 4, 8, 12, 18 and 24 in LixiLan-A-OP

and Weeks 2, 4, 6, 8, 12, 18, 24 and 30 in LixiLan-L-CN) were used to calculate the median time to glycaemic control achievement, defined as the time taken for 50% of participants to reach target HbA1c, FPG or 2-h PPG.

2.3 | Statistical analysis

Descriptive statistics, including means and standard deviations (SD), were used to summarise the data, with 95% confidence intervals (CIs) presented when applicable. The efficacy outcome summary, including the responder and time-to-control analyses, was based on the modified intent-to-treat (mITT) population, defined as all randomised participants with a baseline assessment plus at least one post-baseline assessment of any efficacy variable, regardless of protocol deviations or use of rescue therapy. Hypoglycaemia outcomes were assessed in the safety population, defined as all randomised participants who received at least one dose of study drug.

The difference in the proportion of participants who achieved target HbA1c or FPG levels was determined by the weighted average proportion difference between treatment groups within each randomisation stratum (HbA1c [<8% or ≥8%] at Week−1 in both studies; other OAD use in addition to metformin before run-in phase [yes/no] in both studies; metformin use at screening [yes/no] in LixiLan-L-CN; and geographic region in LixiLan-O-AP) using the Cochran–Mantel–Haenszel method. Participants with no available assessments at Week 8 or Week 12 were treated as non-responders. The time to glycaemic control (defined as the time taken to reach first HbA1c or FPG target) was estimated using the Kaplan–Meier method. Hazard ratios (HR) were estimated using a stratified Cox regression model, with the treatment arm as the model factor and stratified by the randomisation strata. P-values were calculated using the stratified log-rank test and considered nominal, with no formal hypothesis testing.

All statistical analyses were undertaken using SAS version 9.4 software (SAS Institute; Cary, NC, USA).

3 | RESULTS

3.1 | Study participants

The LixiLan-O-AP and LixiLan-L-CN studies enrolled 878 Asia Pacific and 426 Chinese people with T2D, respectively.[12,13] In LixiLan-O-AP, participants were randomised to treatment with iGlarLixi ($n = 351$), Gla-100 ($n = 350$) or lixisenatide ($n = 177$), and in LixiLan-L-CN, 212 and 214 participants were randomised to the iGlarLixi and Gla-100 arms, respectively. The participants' baseline characteristics were similar across the treatment arms in both studies, and have been described previously (Table S2). Briefly, LixiLan-O-AP participants had a mean age of 56.0 years, a mean duration of T2D of 8.6 years and a mean body mass index (BMI) of 26.0 kg/m^2, and in LixiLan-L-CN, the mean age was 57.5 years, the mean T2D duration was 12.3 years and the mean BMI was 25.3 kg/m^2. In both studies, the mean baseline HbA1c was 8.3% (67.0 mmol/mol).

3.2 | Efficacy and hypoglycaemia outcomes at Week 12

3.2.1 | HbA1c change from baseline

At Week 12, participants in the iGlarLixi arm of both LixiLan-O-AP and LixiLan-L-CN had numerically greater reductions in HbA1c from baseline and lower mean HbA1c levels than those in the Gla-100 arm (Table 1). The mean ± SD change from baseline to Week 12 was −1.6 ± 0.7% (−17.0 ± 7.9 mmol/mol) with iGlarLixi versus −1.1 ± 0.7% (−12.0 ± 7.8 mmol/mol) with Gla-100 in LixiLan-O-AP, and − 1.3 ± 0.8% (−13.9 ± 8.9 mmol/mol) versus −0.5 ± 0.9% (−5.4 ± 9.6 mmol/mol) in the respective arms in LixiLan-L-CN. In both studies, the mean ± SD HbA1c at Week 12 was already within the HbA1c target of <7.0% (<53.0 mmol/mol) in the iGlarLixi arm (LixiLan-O-AP: 6.7 ± 0.8% [49.8 ± 8.2 mmol/mol]; LixiLan-L-CN: 6.9 ± 0.7% [51.3 ± 8.1 mmol/mol]).

3.2.2 | Fasting plasma glucose, self-measured plasma glucose and postprandial glucose outcomes

Mean FPG levels at Week 12 were similar in the iGlarLixi and Gla-100 arms of both studies, and met the CDS-recommended FPG target of ≤7.0 mmol/L (Table 1). The mean ± SD reductions from baseline in FPG were similar with iGlarLixi versus Gla-100 in both LixiLan-O-AP (−3.3 ± 2.3 vs. −3.2 ± 2.3 mmol/L) and LixiLan-L-CN (−0.6 ± 1.2 vs. −1.0 ± 1.8 mmol/L).

Participants in the iGlarLixi arm had numerically greater mean ± SD reductions from baseline in average 7-point SMPG at Week 12 than those in the Gla-100 arm in both LixiLan-O-AP (−3.6 ± 2.1 vs. −2.6 ± 2.0 mmol/L) and LixiLan-L-CN (−1.7 ± 1.9 vs. −0.1 ± 1.7 mmol/L; Table 1). The differences in SMPG between the iGlarLixi and Gla-100 arms at Week 12 were evident at all time points except for the pre-breakfast (i.e., fasting) time point in both LixiLan-O-AP (Figure S1a) and LixiLan-L-CN (Figure S1b).

At Week 12, participants in the iGlarLixi arm also had numerically lower mean 2-h PPG than those in the Gla-100 arm in both LixiLan-O-AP (8.5 ± 1.9 vs. 10.4 ± 1.9 mmol/L) and LixiLan-L-CN (8.9 ± 1.9 vs. 11.4 ± 2.6 mmol/L; Table 1).

3.2.3 | Basal insulin dose

BI daily doses at Week 12 were similar in the iGlarLixi and Gla-100 arms of both the LixiLan-O-AP (mean ± SD 22.4 ± 9.4 vs. 22.9

TABLE 1 Efficacy and hypoglycaemia outcomes at Week 12 with iGlarLixi and Gla-100 in the LixiLan-O-AP and LixiLan-L-CN studies.

	LixiLan-O-AP		LixiLan-L-CN	
	iGlarLixi	Gla-100	iGlarLixi	Gla-100
Efficacy outcomes[a]				
HbA1c, % (mmol/mol)	$n = 321$	$n = 328$	$n = 205$	$n = 197$
At Week 12	6.7 ± 0.8 (49.8 ± 8.2)	7.2 ± 0.8 (54.9 ± 8.8)	6.9 ± 0.7 (51.3 ± 8.1)	7.6 ± 1.0 (59.6 ± 10.7)
Change from baseline to Week 12	−1.6 ± 0.7 (−17.0 ± 7.9)	−1.1 ± 0.7 (−12.0 ± 7.8)	−1.3 ± 0.8 (−13.9 ± 8.9)	−0.5 ± 0.9 (−5.4 ± 9.6)
FPG, mmol/L	$n = 317$	$n = 325$	$n = 197$	$n = 190$
At Week 12	6.6 ± 1.3	6.6 ± 1.5	6.9 ± 1.2	6.6 ± 1.5
Change from baseline to Week 12	−3.3 ± 2.3	−3.2 ± 2.3	−0.6 ± 1.7	−1.0 ± 1.8
7-point SMPG, mmol/L	$n = 280$	$n = 285$	$n = 188$	$n = 188$
At Week 12	7.7 ± 1.4	8.9 ± 1.6	8.1 ± 1.6	9.7 ± 2.1
Change from baseline to Week 12	−3.6 ± 2.1	−2.6 ± 2.0	−1.7 ± 1.9	−0.1 ± 1.7
2-h PPG, mmol/L	$n = 270$	$n = 269$	$n = 182$	$n = 184$
At Week 12	8.5 ± 1.9	10.4 ± 1.9	8.9 ± 1.9	11.4 ± 2.6
Change from baseline to Week 12	−4.2 ± 2.6	−2.5 ± 2.2	−2.2 ± 2.4	+0.1 ± 2.2
BIasal insulin daily dose, U	$n = 334$	$n = 341$	$n = 209$	$n = 203$
At Week 12	22.4 ± 9.4	22.9 ± 9.8	27.5 ± 7.5	25.9 ± 7.6
Body weight, kg	$n = 318$	$n = 324$	$n = 194$	$n = 191$
At Week 12	70.4 ± 12.8	70.3 ± 3.1	68.7 ± 10.3	70.2 ± 10.9
Change from baseline to Week 12	−0.1 ± 2.1	+0.6 ± 2.2	−0.4 ± 1.7	+0.04 ± 1.7
BMI, kg/m^2	$n = 318$	$n = 324$	$n = 194$	$n = 191$
At Week 12	26.0 ± 3.6	26.0 ± 3.8	24.9 ± 2.6	25.3 ± 3.0
Change from baseline to Week 12	−0.03 ± 0.8	+0.2 ± 0.8	−0.1 ± 0.6	+0.01 ± 0.6
Hypoglycaemia events at study end[b]	$n = 348$	$n = 349$	$n = 211$	$n = 212$
Documented symptomatic hypoglycaemia (PG ≤ 3.9 mmol/L)				
Number of patients, *n* (%)	43 (12.4)	39 (11.2)	50 (23.7)	47 (22.2)
Number of events	72	68	88	129
Severe hypoglycaemia[c]				
Number of patients, *n* (%)	1 (0.3)	0	1 (0.5)	1 (0.5)
Number of events	2	0	1	1

Abbreviations: BI, basal insulin; BMI, body mass index; FPG, fasting plasma glucose; Gla-100, insulin glargine 100 U/mL; HbA1c, glycated haemoglobin; iGlarLixi, insulin glargine 100 U/mL and lixisenatide; mITT, modified intent-to-treat; PG, plasma glucose; PPG, postprandial glucose; SD, standard deviation; SMPG, self-measured plasma glucose.

[a]Data are presented as mean ± SD, based on the mITT population.

[b]Hypoglycaemia events recorded on or before Day 84, based on the safety population.

[c]Defined as hypoglycaemia requiring assistance to administer carbohydrates, glucagon or other resuscitative actions.

± 9.8 U) and LixiLan-L-CN (27.5 ± 7.5 vs. 25.9 ± 7.6 U) studies (Table 1).

3.2.4 | Body weight

In both studies, participants in the iGlarLixi arm had a slight decrease in mean ± SD body weight at Week 12 (−0.1 ± 2.1 kg in LixiLan-O-AP and − 0.4 ± 1.7 kg in LixiLan-L-CN), whereas those in the Gla-100 arm had a slight increase in mean ± SD body weight (+0.6 ± 2.2 kg and + 0.04 ± 1.7 kg in the respective studies; Table 1).

3.2.5 | Hypoglycaemia outcomes

By the end of each study, similar proportions of participants reported documented symptomatic hypoglycaemia (PG ≤ 3.9 mmol/L) in the iGlarLixi and Gla-100 arms among LixiLan-O-AP participants who had previously received OADs (12.4% and 11.2%, respectively) and LixiLan-L-CN participants who had previously received BI ± OADs (23.7% and 22.2%, respectively; Table 1). Severe hypoglycaemia occurred in 0.3% and 0% of participants in the iGlarLixi and Gla-100 arms, respectively, in LixiLan-O-AP and in 0.5% of participants in both the iGlarLixi and Gla-100 arms in LixiLan-L-CN.

TABLE 2 Achievement of glycaemic targets in the LixiLan-O-AP and LixiLan-L-CN studies (mITT population).

	LixiLan-O-AP		LixiLan-L-CN	
	iGlarLixi	Gla-100	iGlarLixi	Gla-100
	n = 348	n = 349	*n* = 210	*n* = 211
Target HbA1c < 7.0% (<53.0 mmol/mol)				
Participants achieving target, n (%)				
At Week 8	147 (42.2)	78 (22.3)	79 (37.6)	38 (18.0)
Proportion difference versus Gla-100 (95% CI)[a]	+20.0 (+14.0, +26.0)		+21.2 (+13.6, +28.7)	
p-value	<0.0001		<0.0001	
At Week 12	223 (64.1)	150 (43.0)	122 (58.1)	51 (24.2)
Proportion difference versus Gla-100 (95% CI)[a]	+21.2 (+14.5, +27.9)		+35.7 (+27.6, +43.7)	
p-value[a]	<0.0001		<0.0001	
Time to first HbA1c target,[b] days, median (95% CI)	85 (83, 85)	126 (92, 127)	85 (84, 89)	239 (214, NE)
HR versus Gla-100 (95% CI)[c]	1.807 (1.519, 2.149)		2.797 (2.117, 3.695)	
p-value	<0.0001		<0.0001	
Target HbA1c < 7.0% (<53.0 mmol/mol) without body weight gain or documented hypoglycaemia (PG < 3.0 mmol/L, regardless of symptoms)				
Participants achieving target at study end, *n* (%)	153 (44.0)	76 (21.8)	73 (34.8)	30 (14.2)
Proportion difference versus Gla-100 (95% CI)[a]	+22.2 (15.5, 28.9)		+21.3 (+13.6, +29.1)	
p-value	<0.0001		<0.0001	
Target FPG ≤ 7.0 mmol/L				
Participants achieving target, *n* (%)				
At Week 8	193 (55.5)	181 (51.9)	106 (50.5)	109 (51.7)
Proportion difference versus Gla-100 (95% CI)[a]	+3.7 (−3.6, +10.9)		−1.0 (−10.5, +8.5)	
p-value	0.3337		0.8399	
At Week 12	217 (62.4)	227 (65.0)	120 (57.1)	129 (61.1)
Proportion difference versus Gla-100 (95% CI)[a]	−2.6 (−9.7, +4.5)		−3.9 (−13.2, +5.4)	
p-value	0.4756		0.4231	
Time to first FPG target,[b] days, median (95% CI)	57 (55, 57)	57 (56, 57)	29 (29, 54)	30 (29, 56)
HR versus Gla-100 (95% CI)[c]	0.953 (0.812, 1.119)		0.935 (0.760, 1.149)	
p-value	0.5552		0.5224	
Target 2-h PPG < 10.0 mmol/L				
Participants achieving target, *n* (%)				
At Week 12	276 (79.3)	196 (56.2)	168 (80.0)	92 (43.6)
Proportion difference versus Gla-100 (95% CI)[a]	+24.4 (+17.2, +31.3)		+36.5 (+27.9, +45.1)	
p-value	<0.0001		<0.0001	
Time to first PPG target,[b] days, median (95% CI)	84 (84, 85)	167 (166, 171)	85 (84, 86)	NE
HR versus Gla-100 (95% CI)[c]	1.95 (1.62, 2.35)		2.87 (2.19, 3.76)	
p-value	<0.0001		<0.0001	

Abbreviations: CI, confidence interval; FPG, fasting plasma glucose; Gla-100, insulin glargine 100 U/mL; HbA1c, glycated haemoglobin; HR, hazard ratio; iGlarLixi, insulin glargine 100 U/mL and lixisenatide; mITT, modified intent-to-treat; NE, not estimable; PG, plasma glucose; PPG, postprandial glucose.
[a]Weighted average proportion difference between treatment groups for each stratum calculated using the Cochran–Mantel–Haenszel method.
[b]Defined as the time taken for 50% of participants to reach the target, as estimated using the Kaplan–Meier method.
[c]Estimated using a stratified Cox regression model, with treatment as the model factor and stratified by randomisation strata.

3.3 | Time to achieve glycaemic control

3.3.1 | Responder analysis

In LixiLan-O-AP, target HbA1c (<7.0% [<53.0 mmol/mol]) was achieved at Weeks 8 and 12 by 42.2% and 64.1% of participants, respectively, in the iGlarLixi arm versus 22.3% and 43.0%, respectively, in the Gla-100 arm (Table 2). In this study, the average proportion difference for HbA1c target achievement with iGlarLixi versus Gla-100 was 20.0% higher at Week 8 and 21.2% higher at Week 12 ($p < 0.0001$ for both time points). In LixiLan-L-CN, the proportion of participants achieving target HbA1c in the iGlarLixi and Gla-100

arms was 37.6% versus 18.0%, respectively, at Week 8 and 58.1% versus 24.2%, respectively, at Week 12. The average proportion difference for HbA1c target achievement with iGlarLixi versus Gla-100 was 21.2% higher at Week 8 and 35.7% higher at Week 12 ($p < 0.0001$ for both time points).

By the end of each study, the proportion of participants who achieved target HbA1c without body weight gain or documented hypoglycaemia (PG <3.0 mmol/L, regardless of symptoms) was higher with iGlarLixi versus Gla-100 in LixiLan-O-AP (44.0% vs. 21.8%; proportion difference + 22.2%; $p < 0.0001$) and LixiLan-L-CN (34.8% vs. 14.2%; proportion difference + 21.3%; $p < 0.0001$; Table 2).

In LixiLan-O-AP, target FPG (≤7.0 mmol/L) was achieved by similar proportions of participants in the iGlarLixi and Gla-100 arms at Week 8 (55.5% vs. 51.9%) and Week 12 (62.4% vs. 65.0%; Table 2). Similarly, in LixiLan-L-CN, the proportion of participants who achieved target FPG in the iGlarLixi and Gla-100 arms was 50.5% and 51.7%, respectively, at Week 8 and 57.1% and 61.1%, respectively, at Week 12.

The proportion of participants who achieved target 2-h PPG (<10.0 mmol/L) at Week 12 was higher with iGlarLixi versus Gla-100 in both LixiLan-O-AP (79.3% vs. 56.2%; $p < 0.0001$) and LixiLan-L-CN (80.0% vs. 43.6%; $p < 0.0001$; Table 2).

3.3.2 | Time-to-control analysis

In LixiLan-O-AP, the time taken for 50% of participants to achieve the HbA1c target was significantly shorter in the iGlarLixi arm than in the Gla-100 arm (median time 85 vs. 126 days; HR 1.807; $p < 0.001$; Table 2 and Figure S2a). In LixiLan-L-CN, the median time to achieve first HbA1c target was also significantly shorter with iGlarLixi versus Gla-100 (median time 85 vs. 239 days; HR 2.797; $p < 0.0001$; Figure S2b). The median time to achieve first 2-h PPG target was also significantly shorter with iGlarLixi versus Gla-100 in LixiLan-O-AP (median time 84 vs. 167 days; HR 1.95; $p < 0.0001$; Figure S3a) and in LixiLan-L-CN (85 days vs. not estimable; HR 2.87; $p < 0.0001$; Figure S3b and Table 2). The median time to achieve first target FPG was similar with iGlarLixi versus Gla-100 in both LixiLan-O-AP (median time 57 vs. 57 days; HR 0.953; Figure S4a) and LixiLan-L-CN (29 vs. 30 days; HR 0.935; Figure S4b and Table 2).

4 | DISCUSSION

In this post hoc analysis of the LixiLan-O-AP and LixiLan-L-CN studies in Asian people with suboptimally controlled T2D on OADs or BI therapy, iGlarLixi was associated with higher rates of glycaemic control achievement in the early stages of treatment compared with Gla-100. Specifically, iGlarLixi demonstrated greater improvements in glycaemic control (as defined by the proportion of participants who achieved target HbA1c < 7.0% [53.0 mmol/mol] at Weeks 8 and 12), as well as higher rates of target HbA1c achievement without body weight gain or documented hypoglycaemia (PG < 3.0 mmol/L, regardless of symptoms) and higher rates of 2-h PPG target achievement at Week 12. In addition, iGlarLixi was associated with a significantly shorter time to HbA1c target achievement compared with Gla-100, as well as a significantly shorter time to 2-h PPG target achievement, greater reductions in 7-point average SMPG than Gla-100 across all non-fasting time points and decreases in body weight. These findings emphasise the clinical benefits of early comprehensive glycaemic control with this FRC over Gla-100.

The increased proportion of participants achieving HbA1c targets overall and without body weight gain or documented hypoglycaemia with iGlarLixi versus Gla-100, as well as the shorter time to glycaemic control, was most likely attributable to the PPG reductions provided by the GLP-1 RA component (lixisenatide).[1,2] Similar changes in FPG from baseline to Week 12 were observed between treatment arms in both studies and BI daily doses at Week 12 were also similar, confirming that Gla-100 provides FPG control and is often insufficient for achieving target HbA1c in individuals with residual postprandial hyperglycaemia. In contrast, iGlarLixi was associated with numerically greater reductions in mean 2-h PPG from baseline to Week 12 than Gla-100, emphasising the PPG-reducing benefits provided by the GLP-1 RA component of the FRC.

The results of the current post hoc analysis are consistent with those of the previous time-to-control analysis of the global LixiLan-O and LixiLan-L studies, in which the median time to 50% of participants achieving the HbA1c target (<7.0% [<53.0 mmol/mol]) with iGlarLixi was almost half that with Gla-100 in LixiLan-O (85.0 vs. 166.0 days; $p < 0.0001$), and was 153.0 days with iGlarLixi and not reached with Gla-100 in LixiLan-L.[16] Therefore, BI plus GLP-1 RA FRCs may allow for more people with T2D to achieve glycaemic control earlier than BI therapy.

Early intensive glycaemic control appears to provide lifelong benefits in people with T2D. Post-trial monitoring of participants from the UK Prospective Diabetes Study, which enrolled people with newly diagnosed T2D, revealed that early intensive glycaemic control reduced the risk of all-cause mortality and myocardial infarction compared with conventional glycaemic control over 24 years of follow-up.[18] Therefore, early glycaemic control with iGlarLixi may reduce the lifetime risk of diabetes-related complications in people with T2D.

In addition to early glycaemic control, once-daily treatment with iGlarLixi may offer a simplified regimen for treatment intensification that could overcome therapeutic inertia, which is common among people with suboptimally controlled T2D on OADs or BI therapy.[19] Indeed, a retrospective cohort study of Chinese people with non-newly diagnosed T2D in primary care found that therapeutic inertia was associated with poorer glycaemic control, with lack of treatment intensification being physician-related therapeutic inertia and poor adherence to diet, exercise, medications and SMPG measurement being patient-related therapeutic inertia.[20] This study also reported that people with HbA1c reductions of ≥0.5% (≥5.5 mmol/mol) by the first follow-up visit were more likely to achieve long-term good glycaemic control than those with HbA1c reductions of <0.5% (<5.5 mmol/mol).[20] Taken together with the low rates of hypoglycaemia and minimal body weight change observed with iGlarLixi in the

current analysis, treatment with iGlarLixi FRC may help to mitigate therapeutic inertia and optimise long-term glycaemic control among people with T2D who require treatment intensification.

The limitations of this analysis include its post hoc nature, meaning that the sample size and power calculations conducted for the primary efficacy end-points of the studies may not be applicable. Therefore, prospective studies that focus on early glycaemic efficacy and treatment durability are needed to confirm the findings of this analysis. Furthermore, the participants in this analysis were enrolled in phase 3 randomised studies, which may not be representative of people with T2D treated in routine clinical practice. As such, real-world studies to confirm early glycaemic control with iGlarLixi are warranted.

In conclusion, iGlarLixi enabled more Asian people with suboptimally controlled T2D on OADs or BI therapy to achieve early glycaemic control (i.e., after 8 or 12 weeks of treatment) compared with Gla-100. These findings, when added to the previous results of the LixiLan clinical study programme, provide further evidence of the benefits of iGlarLixi once-daily injection for providing comprehensive glycaemic control and body weight benefits without increasing the risk of hypoglycaemia in people with T2D who require treatment intensification.

AUTHOR CONTRIBUTIONS

All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article and had full access to all the data in this study, and take full responsibility for the integrity of the data and accuracy of the data analysis. *Concept and design*: Qin Du, Lei Kang, Wenying Yang and Xiaohui Guo. *Conduct and data collection*: Lulu Song, Shan Huang, Yawei Zhang and Xiaohui Guo. *Analysis*: Zhini Wang. *Writing the manuscript*: Jie Zhang. All authors had final responsibility for approving the published version.

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CONFLICT OF INTEREST STATEMENT

Wenying Yang has received honoraria for speakers' bureau and advisory board participation from AstraZeneca, Bayer, Boehringer Ingelheim, Eli Lilly, Merck Sharp & Dohme, Novo Nordisk, Sanofi Aventis and Servier; and has received investigator-initiated trial research grants from AstraZeneca, outside of the submitted work. Felipe Lauand, Zhini Wang, Jie Zhang, Qin Du and Lei Kang are employees of Sanofi and may hold shares and/or stock options in the company. Lulu Song, Shan Huang, Yawei Zhang, Xiaoyong Yuan and Xiaohui Guo have no conflicts of interest to declare.

PEER REVIEW

The peer review history for this article is available at https://www.webofscience.com/api/gateway/wos/peer-review/10.1111/dom.16260.

DATA AVAILABILITY STATEMENT

Qualified researchers may request access to participant-level data and related documents. Participant-level data will be anonymised, 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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