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ORIGINAL ARTICLE

Propensity-score-matched comparative analyses of simultaneously administered fixed-ratio insulin glargine 100 U and lixisenatide (iGlarLixi) vs sequential administration of insulin glargine and lixisenatide in uncontrolled type 2 diabetes

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The parent studies for these analyses (GetGoal Duo-1 [NCT00975286], GetGoal Duo-2 [NCT01768559], LixiLan-L [NCT02058160] and LixiLan-O [NCT02058147]) were funded by Sanofi.

Aim: To conduct two exploratory analyses to compare indirectly the efficacy and safety of simultaneous administration of insulin glargine 100 U (iGlar) and the glucagon-like peptide-1 receptor agonist (GLP-1RA) lixisenatide (Lixi) as a single-pen, titratable, fixed-ratio combination (iGlarLixi [LixiLan trials]) vs sequential administration of iGlar + Lixi (GetGoal Duo trials) in people with type 2 diabetes (T2D).

Materials and Methods: Propensity-score matching based on baseline covariates was used to compare simultaneous iGlarLixi vs sequential combination of iGlar + Lixi with the addition of Lixi in patients who did not reach the glycated haemoglobin (HbA1c) goal of <53 mmol/mol (<7%) after short-term use of iGlar alone (LixiLan-O vs GetGoal Duo-1 comparison) and vs sequential addition of Lixi in uncontrolled patients after long-term use of iGlar alone (LixiLan-L vs GetGoal Duo-2 comparison).

Results: In both analyses, compared with sequential iGlar + Lixi, iGlarLixi led to significantly greater HbA1c reductions with associated weight loss and significantly more patients reaching target HbA1c <53 mmol/mol despite lower insulin doses. Symptomatic hypoglycaemia rates were similar, despite greater HbA1c reductions with iGlarLixi. Lower rates of gastrointestinal adverse events were observed with iGlarLixi, probably as a result of the more gradual titration of Lixi with iGlarLixi.

Conclusions: Indirect propensity-score-matched exploratory comparisons suggest that early treatment with a simultaneous, titratable, fixed-ratio combination of basal insulin and a GLP-1RA (iGlarLixi) may be more effective and possess better gastrointestinal tolerability than a sequential approach of adding a GLP-1RA in patients with uncontrolled T2D initiating or intensifying basal insulin therapy.

KEYWORDS

GLP-1, glycaemic control, insulin therapy, type 2 diabetes

1 | INTRODUCTION

Current American Diabetes Association type 2 diabetes (T2D) guidelines recommend that if target glycated haemoglobin (HbA1c) cannot be maintained with oral antidiabetic drugs (OADs) and lifestyle measures, injectable therapy should be initiated with the addition of basal insulin or a glucagon-like peptide-1 receptor agonist (GLP-1RA). Additional recommendations to intensify treatment after basal insulin include either a GLP-1RA or progressive additions of prandial insulin if further glycaemic control is necessary.[1]

The GLP-1RAs have complementary antidiabetic effects to basal insulin, providing a solid clinical rationale for the combination of these

two medication classes.[2,3] Long-acting GLP-1RAs increase glucose-dependent insulin secretion to primarily reduce fasting plasma glucose (FPG), with more limited effects on postprandial plasma glucose (PPG) excursions. By contrast, short-acting GLP-1RAs, such as lixisenatide (Lixi), primarily reduce PPG and prandial glucose excursions, with more limited effects on fasting and interprandial hyperglycaemia.[2] Short-acting GLP-1RAs have demonstrated a greater effect on delaying gastric emptying compared with long-acting GLP-1RAs[4,5]; both GLP-1RA types suppress glucagon release and induce satiety.[2]

Single-pen-administered, titratable fixed-ratio combinations of a GLP-1RA and basal insulin were developed as the next logical step from previous experience using free or sequential combinations to simplify titration and administration. iGlarLixi is a titratable fixed-ratio combination of insulin glargine 100 U (iGlar) and the GLP-1RA Lixi.

The LixiLan-O study demonstrated that the use of this simultaneous iGlarLixi formulation significantly and meaningfully reduced HbA1c without weight gain compared with iGlar or Lixi alone in patients with T2D uncontrolled on OADs.[6] In a similar population of patients, the GetGoal Duo-1 study, using a sequential treatment with Lixi added to short-term iGlar, achieved significant reductions in HbA1c, PPG and body weight compared with iGlar + injectable placebo.[7] In patients with long-standing uncontrolled T2D, the LixiLan-L trial demonstrated that simultaneous iGlarLixi was associated with significantly greater reductions in HbA1c and body weight compared with iGlar alone.[8] In a similar patient population, the GetGoal Duo-2 study showed that sequential treatment intensification with Lixi, added on to long-term iGlar, led to non-inferior reductions in HbA1c vs active control with insulin glulisine once (basal-plus) or thrice (basal-bolus) daily.[9] These two treatment strategies, simultaneous and sequential, have not been tested, however, in head-to-head studies, and it is unclear whether a titratable fixed-ratio combination of a GLP-1RA and basal insulin, such as iGlarLixi, may provide greater efficacy and/or tolerability compared with the sequential combination of both drugs.

In the present paper, we report two exploratory, hypothesis-generating analyses that used propensity-score matching to compare indirectly the outcomes of GetGoal Duo-1 with those of LixiLan-O, and the outcomes of GetGoal Duo-2 with those of LixiLan-L, owing to the similar patient populations of these phase III trials. Propensity-score matching is a well-established statistical approach and has been used to compare therapeutic outcomes indirectly in numerous clinical fields, including T2D, allowing better comparison of different study populations by minimizing confounding factors.[10–14] Aside from the obvious advantage of fixed-ratio combinations in terms of the ease and simplicity of a single injection, the aim of this exploratory indirect analysis was to provide preliminary evidence for any further efficacy or safety benefits in favour of the titratable fixed-ratio combination iGlarLixi vs the separate sequential administration of iGlar and Lixi.

2 | MATERIALS AND METHODS

2.1 | Trial designs

The full methodology of the GetGoal Duo-1 (NCT00975286) and LixiLan-O (NCT02058147) phase III trials in insulin-naïve patients with oral-agent failure, and the GetGoal Duo-2 (NCT01768559) and LixiLan-L (NCT02058160) phase III trials in patients with basal insulin failure, have been described previously in detail. All trials included adult patients with T2D for at least 1 year at screening; patients from GetGoal Duo-1 and LixiLan-O were uncontrolled on OADs for at least 3 months, and patients from GetGoal Duo-2 and LixiLan-L were uncontrolled on basal insulin with or without OADs for at least 6 months.[6–9] Study designs and key outcomes are summarized in Tables S1 and S2.

2.2 | Endpoints

2.2.1 | Efficacy outcomes

Efficacy outcomes analysed were as follows: HbA1c change from baseline, percentage of patients achieving HbA1c <53 mmol/mol (<7.0%), median time to achieve glycaemic control (HbA1c <53 mmol/mol), change from baseline in FPG, change from baseline in 2-hour PPG after a standardized meal, change from baseline in body weight, and insulin dose at treatment end. All efficacy endpoints were evaluated at trial end at week 24 (week 26 for GetGoal Duo-2) other than 2-hour PPG, which was assessed at week 30 (LixiLan-O and -L), week 24 (GetGoal Duo-1) or week 26 (GetGoal Duo-2).

2.2.2 | Safety outcomes

Safety outcomes analysed included adverse events (AEs) by system organ class and AEs of special interest, namely gastrointestinal AEs, serious AEs and symptomatic hypoglycaemia. Symptomatic hypoglycaemia was included in the AE listing for GetGoal Duo-1 and GetGoal Duo-2, but not for LixiLan-O and LixiLan-L. Documented symptomatic hypoglycaemia was defined as typical symptoms of hypoglycaemia accompanied by a self-measured plasma glucose (SMPG) value of ≤3.9 mmol/L (≤70 mg/dL). Severe symptomatic hypoglycaemia was defined as requiring another person's assistance to administer carbohydrate, glucagon or other resuscitative actions.

2.3 | Statistical methods

Propensity-score matching balances the distribution of measured baseline covariates that are similar between matched patients, with patients from different trials being matched based on similar propensity scores. Owing to similarities in trial populations and designs, patients in the iGlarLixi arm (simultaneous administration) of LixiLan-O were propensity-score matched with patients from the iGlar + Lixi arm (sequential administration) of GetGoal Duo-1 (T2D newly initiating basal insulin analysis); similarly, iGlarLixi-treated patients from LixiLan-L (simultaneous administration) were propensity-score matched with iGlar + Lixi-treated patients (sequential administration) from GetGoal Duo-2 (T2D uncontrolled by long-term use of basal insulin ± OADs analysis).

Propensity-score matching was carried out based on baseline covariates to minimize measured confounding factors. Covariates used were as follows: age; race; baseline body mass index; baseline HbA1c; baseline FPG; diabetes duration; and OAD/metformin usage. Patients were matched based on the logit of the propensity score using caliper widths equal to 0.2 of the pooled SD of the logit of the propensity score.[15] The logit of the propensity score was used because this

quantity is more likely to be normally distributed. Using calipers of width equal to 0.2 of the pooled SD of the logit of the propensity score will eliminate ~99% of the bias attributable to the measured confounders.[15,16] Sex was not included as a covariate because the proportions of men and women were comparable between the studies and were therefore not considered in matching. After matching, the proportions of men and women in the studies were confirmed to remain balanced. Additionally, baseline 2-hour PPG was not included as a covariate as only 79 patients from GetGoal Duo-2 had 2-hour PPG measurement at baseline.

Efficacy analyses were evaluated using the modified intention-to-treat population, comprising all randomized patients with a baseline assessment and at least 1 post-baseline assessment of any efficacy variable, irrespective of compliance with the protocol and procedures. The safety population was defined as all randomized patients who received at least 1 dose of study medication.

An analysis of covariance model was used with treatment groups (fixed-ratio combination; free combination), randomization strata of HbA1c (<64 mmol/mol [<8.0%]; ≥64 mmol/mol [≥8.0%]) at screening and country as fixed effects, and baseline value as a covariate. Last observation carried forward data were used to impute missing data values. Time to glycaemic control was estimated using the Kaplan–Meier method and reported as medians, as time-to-event data are mostly highly skewed and involved censored data.[17] Corresponding *P* values were calculated using the log-rank test and hazard ratios (HRs) were calculated using a Cox regression model with treatment as the only factor. Statistical significance was set at $P < 0.05$.

3 | RESULTS

3.1 | Population characteristics after propensity-score matching

3.1.1 | Propensity-score-matched pairs

The LixiLan-O and GetGoal Duo-1 studies included patients with T2D newly initiating basal insulin, and the LixiLan-L and GetGoal Duo-2 studies included patients with T2D who had inadequate control despite long-term basal insulin treatment and multiple OADs. Table 1 shows the baseline demographics and disease characteristics of the study populations after propensity-score matching, which resulted in analysis of 87 matched pairs from LixiLan-O (simultaneous administration; iGlarLixi) and GetGoal Duo-1 (sequential administration; iGlar + Lixi), and 241 matched pairs from LixiLan-L (simultaneous administration; iGlarLixi) and GetGoal Duo-2 (sequential administration; iGlar + Lixi).

3.1.2 | Screening and baseline characteristics

After propensity-score matching, the mean ± SD HbA1c at screening in LixiLan-O (iGlarLixi) and GetGoal Duo-1 (iGlar + Lixi) was 66.3 ± 7.6 mmol/mol (8.2% ± 0.7%) and 70.5 ± 8.4 mmol/mol (8.6% ± 0.8%), and after run-in at baseline was well matched at 60.7 ± 7.9 mmol/mol (7.7% ± 0.7%) and 60.9 ± 5.4 mmol/mol (7.7% ± 0.5%), respectively. Mean ± SD HbA1c at screening in LixiLan-L (iGlarLixi) and GetGoal Duo-2 (iGlar + Lixi) was 68.2 ± 6.8 mmol/mol (8.4% ± 0.6%) and 69.8 ± 7.9 mmol/mol (8.5% ± 0.7%), and at baseline after run-in was 62.3 ± 6.8 mmol/mol (7.9% ± 0.6%) and 62.4 ± 5.9 mmol/mol (7.9% ± 0.5%), respectively (Table 1).

As expected, patients in the basal insulin intensification analysis (LixiLan-L vs GetGoal Duo-2) were slightly older and had a longer duration of disease than patients in the newly initiating basal insulin analysis (LixiLan-O vs GetGoal Duo-1). Patients were more likely to be stratified as having HbA1c <64 mmol/mol (<8.0%) than ≥64 mmol/mol (≥8.0%) at randomization in LixiLan-O and GetGoal Duo-1; this distribution was approximately even in LixiLan-L and GetGoal Duo-2, consistent with longer duration of T2D in these trial populations.

3.2 | LixiLan-O and GetGoal Duo-1: iGlarLixi vs iGlar + Lixi propensity-score-matched outcomes

3.2.1 | LixiLan-O and GetGoal Duo-1: completion of treatment

The treatment period was 24 weeks in LixiLan-O and GetGoal Duo-1. In total, 88.5% and 90.8% of propensity-score-matched patients receiving iGlarLixi (LixiLan-O) and iGlar + Lixi (GetGoal Duo-1) completed study treatment, respectively.

3.2.2 | LixiLan-O and GetGoal Duo-1: efficacy outcomes

Mean ± SD HbA1c at week 24 was 46.1 ± 8.0 mmol/mol (6.4% ± 0.7%) with iGlarLixi compared with 52.7 ± 8.3 mmol/mol (7.0% ± 0.8%) with iGlar + Lixi. The mean change from baseline in HbA1c with simultaneous iGlarLixi was thus significantly greater ($P < 0.0001$) compared with iGlar + Lixi (Figure 1A). The percentages of patients achieving target HbA1c (<53 mmol/mol [<7.0%]) at week 24 with simultaneous and sequential combinations were 79% and 51%, respectively ($P < 0.0001$). The median time to achieve HbA1c <53 mmol/mol (<7.0%) was 57 days vs 58 days for the iGlarLixi and iGlar + Lixi groups, respectively; however, the Kaplan–Meier curve (Figure 2A) shows that after the median time, more patients from the iGlarLixi arm reached HbA1c <53 mmol/mol (<7%) sooner compared with the iGlar + Lixi arm ($P = 0.005$), and the likelihood of achieving glycaemic control was significantly higher with iGlarLixi vs iGlar + Lixi (HR 1.6, 95% confidence interval [CI] 1.1, 2.3). Changes in FPG and PPG from baseline to end of study are shown in Table S3.

Weight reduction at week 24 was significantly greater with iGlarLixi compared with iGlar + Lixi, with a treatment difference of 1.3 kg ($P = 0.01$; Figure 1B). In GetGoal Duo-1, for patients who had newly initiated iGlar, titrated to a fasting SMPG of 4.4 to 5.6 mmol/L (80-100 mg/dL), during run-in, the mean ± SD iGlar dose at baseline was 48 ± 22 U for the iGlar + Lixi arm. Patients in the iGlarLixi arm of LixiLan-O were to start treatment at an iGlar dose of 10 U. At 24 weeks, patients given iGlar + Lixi had a higher mean insulin dose compared with those given iGlarLixi, as shown in Figure 1C.

3.2.3 | LixiLan-O and GetGoal Duo-1: safety outcomes

Serious AEs occurred in 2.3% of patients treated with iGlarLixi and 5.7% of patients treated with iGlar + Lixi (Table 2). Treatment with iGlarLixi vs iGlar + Lixi resulted in numerically lower incidences of

TABLE 1 Screening and baseline demographics and patient characteristics (randomized population)

	Propensity-score-matched pairs			
	LixiLan-O iGlarLixi (*n* = 87)	GetGoal Duo-1 iGlar + Lixi (*n* = 87)	LixiLan-L iGlarLixi (*n* = 241)	GetGoal Duo-2 iGlar + Lixi (*n* = 241)
Mean age, years	57.0 ± 8.9	55.4 ± 9.1	60.5 ± 9.7	59.1 ± 8.6
Male sex	39 (44.8)	38 (43.7)	102 (42.3)	117 (48.5)
Race				
White	72 (82.8)	72 (82.8)	225 (93.4)	222 (92.1)
Black	5 (5.7)	6 (6.9)	11 (4.6)	11 (4.6)
Asian	6 (6.9)	6 (6.9)	5 (2.1)	8 (3.3)
Other	4 (4.6)	3 (3.4)	0	0
Mean HbA1c at screening, %	8.2 ± 0.7	8.6 ± 0.8	8.4 ± 0.6	8.5 ± 0.7
Mean HbA1c at baseline, %[a]	7.7 ± 0.7	7.7 ± 0.5	7.9 ± 0.6[b]	7.9 ± 0.5[c]
HbA1c randomization strata at week −1				
8% (64 mmol/mol)	54 (62.1)	52 (59.8)	116 (48.1)	123 (51.0)
≥8% (64 mmol/mol)	33 (37.9)	35 (40.2)	125 (51.9)	118 (49.0)
Mean FPG, mmol/L[a]	7.7 ± 1.6	7.6 ± 1.8	7.0 ± 1.8	6.8 ± 1.8
Mean 2-h PPG, mmol/L[a]	13.0 ± 3.2	13.3 ± 3.5	14.7 ± 3.8	14.3 ± 3.5
Mean BMI, kg/m^2	32.3 ± 4.2	32.1 ± 5.3	31.8 ± 4.2	31.7 ± 4.4
Mean duration of diabetes, years	7.9 ± 5.7	7.8 ± 4.4	12.1 ± 6.7	11.7 ± 6.5
OAD or metformin use at screening[d]				
Yes	13 (14.9)[e]	14 (16.1)[e]	215 (89.2)[f]	217 (90.0)[f]
No	74 (85.1)[e]	73 (83.9)[e]	26 (10.8)[f]	24 (10.0)[f]
Mean insulin dose at screening, U[a]	N/A	N/A	27.2 ± 8.0	40.5 ± 22.1
Mean insulin dose at baseline, U[a]	N/A	48 ± 22	35 ± 9	66 ± 32

Abbreviations: BMI, body mass index; FPG, fasting plasma glucose; HbA1c, glycated haemoglobin; iGlar, insulin glargine 100 U; Lixi, lixisenatide; N/A, not applicable; mITT, modified intention-to-treat; OAD, oral antidiabetic drug; PPG, postprandial plasma glucose; SD, standard deviation; TZD, thiazolidinedione. Values are mean ± SD or *n* (%). All characteristics/demographics are at baseline unless stated otherwise. No statistically significant differences were found between groups.

[a] LixiLan-O: mITT population, iGlarLixi: *n* = 87, iGlar + Lixi: *n* = 87; LixiLan-L: mITT population *n* = 240, iGlar + Lixi: *n* = 240.

[b] 6-week run-in.

[c] 12-week run-in.

[d] Metformin use for LixiLan-L and GetGoal Duo-2.

[e] OAD use other than metformin for LixiLan-O and GetGoal Duo-1.

[f] In the primary analyses, randomization strata were second OAD use at screening for LixiLan-O, TZD use at screening for GetGoal Duo-1, and metformin use at screening for LixiLan-L and GetGoal Duo-2.

nausea (9.2% vs 20.7%) and vomiting (1.1% vs 10.2%). Incidences of nausea and vomiting leading to discontinuation were 1.1% and 0% with iGlarLixi and 1.1% and 2.3% with iGlar + Lixi, respectively.

The percentage of patients with a symptomatic hypoglycaemia event was lower in the iGlarLixi vs iGlar + Lixi arm (Figure 3). The numbers of patients with symptomatic hypoglycaemia events per patient-year were 0.38 and 0.56 with iGlarLixi and iGlar + Lixi, respectively. No events of severe symptomatic hypoglycaemia occurred.

3.3 | LixiLan-L and GetGoal Duo-2: iGlarLixi vs iGlar + Lixi propensity-score-matched outcomes

3.3.1 | LixiLan-L and GetGoal Duo-2: completion of treatment

The treatment period was 24 weeks in LixiLan-L and 26 weeks in GetGoal Duo-2. Overall, 92.5% and 89.2% of propensity-score-matched patients receiving iGlarLixi (LixiLan-L) and iGlar + Lixi (GetGoal Duo-2) completed the study treatment.

3.3.2 | LixiLan-L and GetGoal Duo-2: efficacy outcomes

Mean ± SD HbA1c was 51.1 ± 8.8 mmol/mol (6.8% ± 0.8%) with iGlarLixi at week 24 vs 55.8 ± 8.4 mmol/mol (7.3% ± 0.8%) with iGlar + Lixi at week 26. Thus, for the same comparison, mean change from baseline in HbA1c was significantly greater with iGlarLixi compared with iGlar + Lixi ($P < 0.0001$; Figure 1A). In this analysis, 62% and 33% of patients who received iGlarLixi and iGlar + Lixi, respectively, achieved the target of HbA1c <53 mmol/mol (<7.0%; $P < 0.0001$). The median time to achieve HbA1c <53 mmol/mol (<7.0%) was significantly shorter with iGlarLixi (85 days) vs iGlar + Lixi (192 days; $P < 0.0001$), and the likelihood of achieving glycaemic control was significantly higher with iGlarLixi vs iGlar + Lixi (HR 2.2, 95% CI 1.8, 2.8; Figure 2B). Changes in FPG and PPG from baseline to end of study are shown in Table S3.

Weight reductions were numerically greater with iGlarLixi at week 24 vs those at week 26 with iGlar + Lixi (−1.0 vs 0.6 kg; $P = 0.38$; Figure 1B). The absolute mean insulin dose was higher at week 26 with iGlar + Lixi compared with iGlarLixi at week

24 (Figure 1C); however, it should be noted that the absolute mean ± SD insulin dose also showed a significant difference at baseline (66 ± 32 vs 35 ± 9 U; $P < 0.0001$). The least squares (LS) mean ± SE change from baseline to end of study was 1 ± 1 U with iGlar + Lixi and 9 ± 1 U with iGlarLixi (LS mean ± SE difference, 8 ± 1 U; $P < 0.0001$).

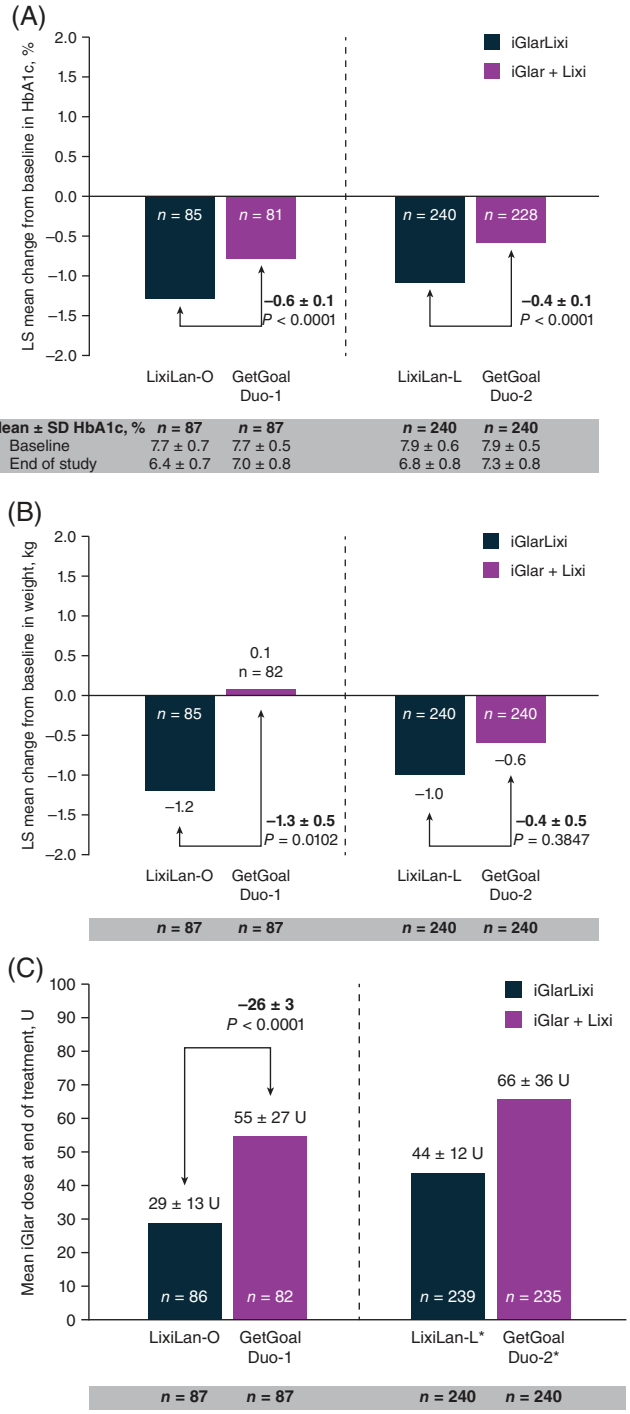

FIGURE 1 End-of-study outcomes including A, change in glycated haemoglobin (HbA1c), B, weight change and C, absolute mean insulin glargine 100 U (iGlar) dose at end of treatment period. *n* indicates number of patients included in analysis (modified intention-to-treat [mITT] population); there were small variations in the number of patients meeting the criteria for inclusion in LixiLan and GetGoal Duo mITT populations based on variable measured. *No least squares (LS) mean difference or *P* value has been included for the comparison of the final mean iGlar dose at end of treatment period in LixiLan-L vs GetGoal Duo-2 as mean insulin doses showed significant difference at baseline (66 ± 32 U vs 35 ± 9 U; $P < 0.0001$). Lixi, lixisenatide

3.3.3 | LixiLan-L and GetGoal Duo-2: safety outcomes

Serious AEs were experienced by 6.3% and 3.3% of patients in the iGlarLixi and iGlar + Lixi arms, respectively (Table 2). Patients treated with iGlarLixi vs those treated with iGlar + Lixi had numerically lower incidences of nausea (10.0% vs 27.0%) and vomiting (3.3% vs 8.7%). Incidences of nausea and vomiting leading to discontinuation were 1.7% and 0% with iGlarLixi and 1.2% and 1.7% with iGlar + Lixi, respectively.

Despite greater HbA1c reductions with iGlarLixi, similar percentages of patients experienced events of symptomatic hypoglycaemia in the iGlarLixi and the iGlar + Lixi arms (Figure 3). The numbers of patients with events of symptomatic hypoglycaemia per patient-year were 0.66 with iGlarLixi vs 0.74 with iGlar + Lixi. Two events (0.8%) of severe hypoglycaemia occurred with iGlarLixi vs no events with iGlar + Lixi.

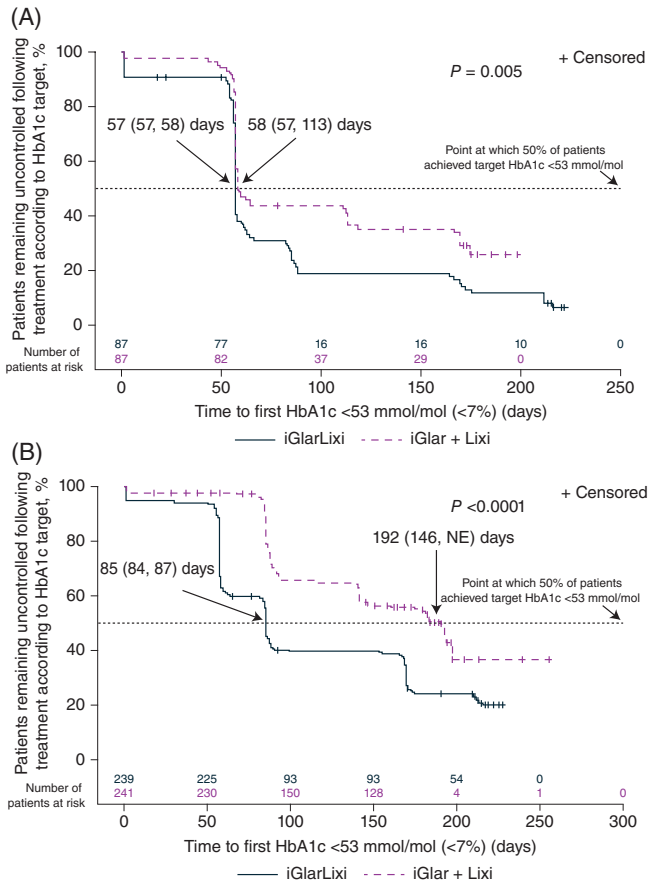

FIGURE 2 A, Time (95% CI) to first glycated haemoglobin (HbA1c) value <53 mmol/mol (<7.0%) with fixed-ratio insulin glargine 100 U and lixisenatide (iGlarLixi) in the LixiLan-O trial and insulin glargine 100 U (iGlar) + lixisenatide (Lixi) in the GetGoal Duo-1 trial (safety population). B, Time (95% CI) to first HbA1c value <53 mmol/mol (<7.0%) with iGlarLixi in LixiLan-L and iGlar + Lixi in GetGoal Duo-2 (safety population). NE, non-evaluable

TABLE 2 Adverse events (safety population)

	Propensity-score-matched pairs			
	LixiLan-O iGlarLixi (*n* = 87)	GetGoal Duo-1 iGlar + Lixi (*n* = 87)	LixiLan-L iGlarLixi (*n* = 239)[a]	GetGoal Duo-2 iGlar + Lixi (*n* = 241)[a]
AE, *n* (%)	52 (59.8)	62 (71.3)[b]	130 (54.4)	179 (74.3)[b]
Serious AE, *n* (%)	2 (2.3)	5 (5.7)	15 (6.3)	8 (3.3)
AE leading to death, *n* (%)	1 (1.1)	0	1 (0.4)	1 (0.4)
AE leading to discontinuation, *n* (%)	6 (6.9)	5 (5.7)	10 (4.2)	12 (5.0)
By preferred term,[c] *n* (%)				
Headache	9 (10.3)	6 (6.9)	13 (5.4)	16 (6.6)
Nasopharyngitis	7 (8.0)	5 (5.7)	22 (9.2)	13 (5.4)
Upper RTI	4 (4.6)	6 (6.9)	6 (2.5)	6 (2.5)
Gastrointestinal AEs				
Diarrhoea	7 (8.0)	4 (4.6)	12 (5.0)	16 (6.6)
Leading to discontinuation	0	0	0	0
Nausea	8 (9.2)	18 (20.7)	24 (10.0)	65 (27.0)
Leading to discontinuation	1 (1.1)	1 (1.1)	4 (1.7)	3 (1.2)
Vomiting	1 (1.1)	9 (10.3)	8 (3.3)	21 (8.7)
Leading to discontinuation	0	2 (2.3)	0	4 (1.7)

Abbreviations: AE, adverse event; iGlar, insulin glargine 100 U; Lixi, lixisenatide; RTI, respiratory tract infection.
[a] *n* = 241 pairs were matched based on randomized patients regardless of their protocol adherence; however, 2 patients in the iGlarLixi cohort did not meet the safety population criteria (did not receive at least 1 dose of study drug).
[b] Symptomatic hypoglycaemia was included in the AE listing for GetGoal Duo-1 and GetGoal Duo-2.
[c] Preferred terms with occurrence ≥5% are shown.

4 | DISCUSSION

These propensity-score-matching analyses permitted exploration of whether simultaneous use of iGlar and Lixi as a titratable fixed-ratio combination resulted in greater efficacy and better safety outcomes, as well as earlier time to reach HbA1c goals, compared with sequential addition of these agents. Differences in the results of the two propensity-score-matched analyses are likely to reflect their different patient populations; LixiLan-O and GetGoal Duo-1 compared patients at an earlier stage of T2D who were newly initiating basal insulin, whereas LixiLan-L and GetGoal Duo-2 compared patients with long-standing T2D who had already failed long-term basal insulin treatment and multiple OADs.

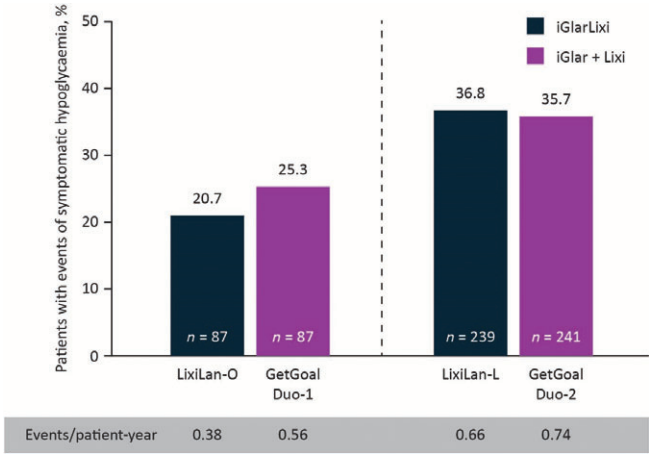

FIGURE 3 Occurrence of symptomatic hypoglycaemia (safety population). Symptomatic hypoglycaemia defined as plasma glucose ≤3.9 mmol/L (≤70 mg/dL). iGlar, insulin glargine 100 U; Lixi, lixisenatide

Both analyses consistently showed that iGlarLixi resulted in lower final HbA1c levels and a higher percentage of patients achieving target HbA1c (<53 mmol/mol [<7.0%]) compared with sequential iGlar + Lixi. Basal insulin and GLP-1RAs are among the most effective classes of drugs available for targeting FPG and PPG, respectively; therefore, it is not surprising that simultaneous use of two such drugs was associated with higher proportions of patients achieving HbA1c <53 mmol/mol (<7%).

Significant body weight reduction occurred with iGlarLixi compared with iGlar + Lixi in the LixiLan-O and GetGoal Duo-1 analysis, but not in the analysis of LixiLan-L and GetGoal Duo-2, suggesting that mitigation of insulin-associated weight gain may be more pronounced in patients newly initiating basal insulin compared with patients who have already experienced insulin-associated weight gain. In both analyses, mean insulin dose at week 24 with iGlarLixi was lower than with iGlar + Lixi at week 24 or week 26; however, it is important to note that the maximum dose of iGlar was 60 U in LixiLan-O and LixiLan-L, whereas there was no dose cap for iGlar in GetGoal Duo-1 and GetGoal Duo-2. Nevertheless, the difference in basal insulin dose may indicate that individualized stepwise titration with the fixed-ratio combination permits tailored dosing to the minimum effective dose of each agent.

The gastrointestinal tolerability profiles of simultaneous iGlarLixi and sequential iGlar + Lixi were clearly different. iGlarLixi resulted in substantially fewer gastrointestinal AEs, which is potentially attributable to gradual titration and lower doses of the GLP-1RA in line with iGlar dose titrations guided by FPG. Notably, iGlarLixi leads to prominent and significant decreases in HbA1c, regardless of gradual

titration and lower drug doses at study end.[18,19] Despite achieving greater HbA1c reductions with iGlarLixi, symptomatic hypoglycaemia was less frequent with iGlarLixi in LixiLan-O than with iGlar + Lixi in GetGoal Duo-1, and comparable with iGlarLixi and iGlar + Lixi in LixiLan-L and GetGoal Duo-2. Severe hypoglycaemia was uncommon.

The pathogenesis of T2D is multifactorial; thus, simultaneously targeting several of these mechanisms should provide greater benefits than addressing one at a time, and most guidelines are advocating for the early use of combination therapy.[20,21] Guidelines suggest treating to target and intensifying therapeutic strategies if glycaemic goals are not achieved within a given timeframe[1,20]; however, longitudinal observational studies of electronic medical records from EU countries and the USA showed that failure to achieve target HbA1c early on (3-6 months) was associated with increased risk of failure to achieve glycaemic control.[22,23] Patients who undergo treatment intensification at lower HbA1c levels are more likely to achieve HbA1c ≤53 mmol/mol (≤7.0%) than patients whose treatment is intensified at higher levels of glycaemia.[24] Furthermore, patients who receive early treatment intensification achieve treatment goals more rapidly than those who do not, regardless of the target HbA1c level.[25] Notably, in both LixiLan-O and -L, iGlarLixi led to glycaemic control (HbA1c <53 mmol/mol [<7.0%]) more quickly after treatment initiation and in more patients compared with iGlar alone.[26] A faster time to glycaemic control with iGlarLixi vs iGlar + Lixi was particularly pronounced in patients with more advanced disease who were intensifying basal insulin; reasons for this observation require further exploration.

Despite clear guidelines and robust data regarding the advantages of early intensification, clinical inertia is common in the treatment of T2D, particularly with injectables, and is often attributable to concerns about weight gain, use of injections and treatment and monitoring complexity when initiating and intensifying insulin.[27] Early intensification with a single-pen, titratable, fixed-ratio combination, such as iGlarLixi, as opposed to sequentially adding medications over time, may allow patients with T2D to achieve and maintain glycaemic control from the initial stages of the disease onwards. Moreover, mitigation of weight gain and no additional risk of symptomatic hypoglycaemia with iGlarLixi, despite significant improvements in HbA1c reduction, may help to alleviate some of the concerns responsible for clinical inertia.

The use of propensity-score matching to indirectly compare patient populations across separate studies is associated with several limitations. Our findings can only be regarded as hypothesis-generating, and this preliminary evidence about simultaneous vs sequential combinations of iGlar and Lixi was not intended to lead to definitive conclusions. Propensity-score matching ensures balance in measured confounders but not in unmeasured confounders; however, the investigated measured confounders were selected to capture the relevant characteristics of patients with T2D. Although propensity-score matching was carried out based on baseline covariates to minimize measured confounding factors, it does not ensure that all measured baseline characteristics will match. Differences in insulin doses at baseline were driven by the study design; the LixiLan-L study inclusion criteria restricted the daily insulin dose to 15 to 40 U at screening, and 20 to 50 U at baseline, whereas the GetGoal Duo-2 was not restricted. This may have led to inclusion of more insulin-resistant individuals selected from GetGoal Duo-2 vs LixiLan-L. Propensity-score matching necessitates that patients who cannot be matched across the studies are lost to the analysis; in particular, the population for the comparison of GetGoal Duo-1 and LixiLan-O was reduced to 87 matched pairs, but a more substantial number of pairs was matched for the GetGoal Duo-2 and LixiLan-L comparison. Still, results for these propensity-score-matched populations mirrored, and even strengthened, the findings for the overall cohorts within each study, indicating that this statistical method did not skew but reinforced the findings of the analyses. Additional potential limitations particular to the present study were the exclusion of baseline 2-hour PPG and sex as covariates. Because of the low number of patients from GetGoal Duo-2 with baseline 2-hour PPG values, its inclusion as a covariate would have significantly reduced the number of patients eligible for matching without addressing other potential confounding factors. Nevertheless, mean 2-hour PPG values were similar in the original studies and after propensity-score matching (LixiLan-O vs GetGoal Duo-1: 13.0 ± 3.2 vs 13.3 ± 3.5 mmol/L; LixiLan-L vs GetGoal Duo-2: 14.7 ± 3.8 vs 14.3 ± 3.5 mmol/L). The proportions of men and women remained balanced after matching (LixiLan-O vs GetGoal Duo-1: 44.8% vs 43.7% men; LixiLan-L vs GetGoal Duo-2: 42.3% vs 48.5% men). Additionally, a previous analysis showed that sex had no significant impact on efficacy in patients treated with iGlarLixi or iGlar in LixiLan-L and LixiLan-O. (Frias J et al. Presented at the American Association of Nurse Practitioners 2017 National Conference; unpublished data).

Furthermore, it is unknown if the timing of the trials would have any impact on the outcomes; the GetGoal Duo-1 and GetGoal Duo-2 trials commenced in 2009 and 2013, and the LixiLan-O and LixiLan-L trials both commenced in 2014. A formal, direct, head-to-head randomized controlled trial is needed to confirm the potential treatment benefits in favour of simultaneous iGlarLixi treatment vs sequential treatment with iGlar + Lixi that were identified during the present indirect comparisons.

In summary, indirect propensity-score-matched comparisons suggest that early simultaneous treatment with a titratable, fixed-ratio combination of basal insulin and a short-acting GLP-1RA may be more effective, with better gastrointestinal tolerability and with the potential for more weight loss, than a sequential approach of adding a GLP-1RA in patients with uncontrolled T2D newly initiating or intensifying basal insulin therapy.

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Conflict of interest

J.R. has served on advisory panels and as a consultant for AstraZeneca, Boehringer Ingelheim, Eli Lilly, Intarcia, Janssen, Novo Nordisk and Sanofi; and has received research support from AstraZeneca,

Boehringer Ingelheim, Bristol-Myers Squibb, Eli Lilly, Genentech, GlaxoSmithKline, Intarcia, Janssen, Lexicon, Merck, Novartis, Novo Nordisk, Pfizer and Sanofi. Y.H. has served on advisory panels and as a consultant for Amgen, AstraZeneca, Boehringer Ingelheim, Eli Lilly, Janssen, Merck, Novo Nordisk, Regeneron and Sanofi, has received research support from Amgen, AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb, Gan & Lee, Grifolis, Hamni, Intarcia, Lexicon, Merck, Novo Nordisk and Sanofi, and has served on a speakers' bureau for Amarin, Amgen, AstraZeneca, Janssen, Merck, Novo Nordisk, Regeneron and Sanofi. J.V. has served on a speakers' bureau for Ethicon, Eli Lilly, Medtronic, MSD, Novo Nordisk and Sanofi, has served on advisory panels for Jansen, Novo Nordisk and Sanofi, and has served as a consultant for Medtronic. F.J.A.B. has served on advisory panels for Abbott, AstraZeneca, Boehringer Ingelheim, Eli Lilly, GlaxoSmithKline, LifeScan, Medtronic, Merck, Novartis, Novo Nordisk, Pfizer, Roche and Sanofi, and has received research support from Abbott, AstraZeneca, Boehringer Ingelheim, Bayer, Eli Lilly, GlaxoSmithKline, LifeScan, Merck, Novo Nordisk, Pfizer, Sanofi and Servier. F.G. has served on advisory panels for AstraZeneca, Novo Nordisk and Sanofi, has served as a consultant for AstraZeneca, Boehringer Ingelheim, Lifescan, Roche Diabetes Care, Sanofi and Takeda, and has received research support from Eli Lilly and Takeda. M. L. has served as a consultant for BDM Consulting, Inc. and Sanofi. R.P. is an employee and stock/shareholder of Sanofi. J.M. has served on a speakers' bureau for AstraZeneca, Berlin-Chemie, Boehringer Ingelheim, Bristol-Myers Squibb, Eli Lilly, Merck Serono, Merck Sharp & Dohme, Novo Nordisk, Novartis, Servier and Sanofi-Aventis, has served on advisory panels for AstraZeneca, Bristol-Myers Squibb, Boehringer Ingelheim, Eli Lilly, Merck Sharp & Dohme, Novo Nordisk and Sanofi-Aventis, and has received research support from Boehringer Ingelheim, Merck Sharp & Dohme, Novo Nordisk and Sanofi-Aventis.

Author contributions

J.R. contributed to the study design; M.L. contributed to the data acquisition and data analysis; J.R., Y.H., J.V., F.J.A.B., F.G., M.L., R.P. and J.J.M. contributed to the data interpretation; J.R., Y.H., J.V., F.J.A.B., F.G., M.L., R.P. and J.J.M. contributed to the critical revision; and J.R., Y.H., J.V., F.J.A.B., F.G., M.L., R.P. and J.J.M. provided their final approval of the manuscript. 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.

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SUPPORTING INFORMATION

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

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