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ORIGINAL ARTICLE

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Efficacy of iGlarLixi in adults with type 2 diabetes inadequately controlled (glycated haemoglobin ≥8%, ≥64 mmol/mol) on two oral antidiabetes drugs: Post hoc analysis of the LixiLan-O randomized trial

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Abstract

Aims: To assess the efficacy and safety of iGlarLixi (the titratable fixed-ratio combination of insulin glargine 100 U/mL [iGlar] plus lixisenatide [Lixi]), in adults with type 2 diabetes (T2D) with glycated haemoglobin (HbA1c) levels ≥8% (≥64 mmol/mol).

Materials and methods: The LixiLan-O study (NCT02058147) compared iGlarLixi with iGlar or Lixi in adults with T2D inadequately controlled on metformin ± a second oral antidiabetes drug (OAD). This exploratory analysis evaluated the LixiLan-O subgroup of participants with baseline HbA1c levels of ≥8% (≥64 mmol/mol) who were receiving metformin plus a second OAD at screening.

Results: The mean diabetes duration was 10.0 years, and the mean duration of second OAD use was 4.5 years. iGlarLixi demonstrated greater mean reductions from baseline in HbA1c and 2-hour postprandial glucose (PPG) compared with iGlar or Lixi (HbA1c −1.9% vs. −1.6% or −1.0% [−20 vs. −17 or −10 mmol/mol; 2-hour PPG −7.2 vs. −4.6 or −5.5 mmol/L). Greater proportions of participants achieved HbA1c <7% (<53 mmol/mol) with iGlarLixi versus iGlar or Lixi (67% vs. 51% or 18%), and the composite endpoints of HbA1c <7% (<53 mmol/mol) with no body weight gain (36% vs. 19% or 16%), and HbA1c <7% (<53 mmol/mol) with no body weight gain and no documented symptomatic hypoglycaemia (plasma glucose ≤3.9 mmol/L; 28% vs. 15% or 15%). The incidence rates of documented symptomatic hypoglycaemia were 29.0%, 27.9% and 12.1% for iGlarLixi, iGlar and Lixi, respectively.

Conclusions: Adults with T2D and HbA1c ≥64 mmol/mol (≥8%) despite two OADs at screening achieved better glycaemic control with iGlarLixi versus iGlar or Lixi, without increased risk of hypoglycaemia versus iGlar.

KEYWORDS
basal insulin, glycaemic control, GLP-1 analogue, insulin therapy, randomized trial, type 2 diabetes

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1 | INTRODUCTION

The American Diabetes Association (ADA) and European Association for the Study of Diabetes (EASD) consensus guidelines recommend a glycated haemoglobin (HbA1c) target of <53 mmol/mol (<7%) for most people with type 2 diabetes (T2D).[1,2] Individuals who do not achieve this target while taking more than one oral antidiabetes drug (OAD) may have more advanced T2D and greater β-cell dysfunction, indicative of disease that has progressed.[2] Additionally, higher baseline HbA1c levels can be considered predictive of a lower likelihood of achieving good glycaemic control in the longer term.[3,4] iGlarLixi, a titratable fixed-ratio combination (FRC) of basal insulin glargine 100 units/mL (iGlar) and lixisenatide (Lixi), a short-acting glucagon-like peptide 1 receptor agonist (GLP-1RA), combines the beneficial effects of a GLP-1RA on glucose homeostasis with the ability of basal insulin to replace normal endogenous basal insulin secretion by pancreatic β cells, while providing the convenience of a single daily injection.[5] These complementary mechanisms of action may benefit people with more advanced T2D and greater β-cell dysfunction.

The LixiLan-O trial (NCT02058147) assessed iGlarLixi, iGlar and Lixi in adults with T2D who did not achieve glycaemic control (with a baseline HbA1c between 53 and 86 mmol/mol [7% and 10%], both inclusive) after treatment with metformin with or without a second OAD.[6] Its primary findings included greater HbA1c reductions at Week 30 with iGlarLixi versus iGlar or Lixi alone, with no increased risk of hypoglycaemia versus iGlar.[6] iGlarLixi also mitigated the body weight gain observed with use of iGlar alone.[6]

The objective of the present exploratory analysis was to evaluate the efficacy of iGlarLixi in a subpopulation of adult participants in the LixiLan-O trial with baseline HbA1c ≥64 mmol/mol (≥8%) who were treated with metformin and a second OAD at screening. These individuals would be expected to be a more difficult-to-treat population, with potentially greater β-cell dysfunction and a lower likelihood of reaching target HbA1c when initiated with basal insulin alone.[7]

2 | MATERIALS AND METHODS

2.1 | Study design and participants

LixiLan-O (NCT02058147) was an open-label, randomized, parallel-group, multinational, multicentre, phase 3 clinical trial, for which the study design and main results have been published previously.[6] Adults with T2D and suboptimal glycaemic control despite treatment with metformin with or without a second OAD were included. During a 4-week run-in, those receiving metformin plus another OAD stopped the second OAD. Metformin was titrated to the maximum tolerated dose (minimum ≥1500 mg/d). At the end of the run-in, participants were randomly assigned in a 2:2:1 ratio to receive iGlarLixi, iGlar or Lixi, respectively, for 30 weeks, stratified by HbA1c (<8%, ≥8% [<64, ≥64 mmol/mol]) and by OAD monotherapy or second OAD at screening. iGlarLixi, iGlar and Lixi were administered once daily as described previously.[6] In this post hoc analysis, the treatment effects of iGlarLixi compared with iGlar and Lixi were assessed in a subpopulation of participants with a baseline HbA1c ≥8% (≥64 mmol/mol) treated with metformin and a second OAD at screening.

The original LixiLan-O study was designed and monitored in accordance with Good Clinical Practice standards.[6] The protocol was approved by local institutional review boards or ethics committees.

2.2 | Endpoints

The primary efficacy endpoint was change in HbA1c from baseline to Week 30. Additional efficacy endpoints included the proportion of participants achieving HbA1c <7% (<53 mmol/mol), the composite of HbA1c <7% (<53 mmol/mol) with no body weight gain, and the composite of HbA1c <7% (<53 mmol/mol), no body weight gain, and no documented symptomatic hypoglycaemia (typical symptoms of hypoglycaemia accompanied by a measured plasma glucose ≤3.9 mmol/L) at Week 30; changes in FPG, 2-hour postprandial glucose (PPG), and body weight from baseline to Week 30; and mean daily iGlar dose (iGlarLixi and iGlar groups only). Rates of documented symptomatic hypoglycaemia (with plasma glucose concentrations of ≤3.9 mmol/L or <3.0 mmol/L)[1,8] per participant-year were evaluated for the on-treatment period, as well as the proportions of participants experiencing a hypoglycaemia event.

2.3 | Statistical methods

The statistical methods have been described previously.[6] The primary efficacy endpoint (change in HbA1c from baseline to Week 30) was analysed using a mixed-effect model with repeated measures (MMRM) with treatment group, visit, treatment-by-visit interaction, and country as fixed effects, and baseline HbA1c value-by-visit interaction as a covariate. An MMRM was also used for comparison of FPG and body weight. The proportions of participants reaching HbA1c levels <7% (<53 mmol/mol) or one of the composite endpoints were compared using the chi-squared test. Change in PPG was compared using an analysis of covariance model with treatment groups and country as fixed effects and baseline 2-hour PPG value as a covariate. iGlar dose differences were compared using an analysis of variance model with treatment group and country as fixed effects. Interaction factors were included in all statistical analyses to reduce bias.

Efficacy analyses were based on the modified intention-to-treat (mITT) population, defined as all randomized participants who had a baseline and one post-baseline assessment of any primary or secondary endpoint. Safety analyses (descriptive statistics) were performed on the subgroup safety population, defined as all randomized participants who received at least one dose of open-label study drug, regardless of the amount of treatment administered. Participants were analysed for safety according to the treatment actually received rather than according to the treatment group to which they were randomized.

3 | RESULTS

3.1 | Participant disposition and baseline characteristics among participants with HbA1c ≥8% (≥64 mmol/mol) who were using two OADs at screening

Baseline characteristics of the subgroup mITT population are shown in Table 1. In total, 137, 135 and 67 participants (29.3%, 29.0% and 28.8%, respectively, of the original LixiLan-O study groups[6]) assigned to iGlarLixi, iGlar and Lixi, respectively, had HbA1c ≥8% (≥64 mmol/mol) and were using two OADs at screening. Other than HbA1c level and OAD use, baseline characteristics in this subgroup were similar to those in the overall population (Table S1).[6]

3.2 | Change from baseline in HbA1c

Participants receiving treatment with iGlarLixi had a significantly greater mean change from baseline in HbA1c versus iGlar alone (−1.9% vs. −1.6% [−20 vs. −17 mmol/mol], respectively; $P = 0.0017$) or versus Lixi alone (−1.9% vs. −1.0% [−20 vs. −10 mmol/mol], respectively; $P < 0.0001$ [Figure 1]). HbA1c values at Week 30 were 50, 53 and 61 mmol/mol (6.7%, 7.0% and 7.7%) for the iGlarLixi, iGlar and Lixi groups, respectively. These results were comparable with results shown in the overall population (efficacy and safety results from the overall population are summarized in Table S2).[6]

3.3 | Proportion of participants achieving HbA1c <7% (<53 mmol/mol) at Week 30

Participants receiving iGlarLixi were more likely to reach target HbA1c (<7% [<53 mmol/mol]) than those receiving iGlar or Lixi (67%, 51% and 18% for iGlarLixi, iGlar and Lixi, respectively; $P = 0.0064$ for iGlarLixi vs. iGlar and $P < 0.0001$ for iGlarLixi vs. Lixi [Figure 2]). Numerically higher proportions of participants taking iGlarLixi reached the composite endpoint of HbA1c <7% (<53 mmol/mol) with no body weight gain compared with either iGlar or Lixi (36%, 19% and 16% for iGlarLixi, iGlar and Lixi, respectively; 95% confidence interval [CI] 7.6% to 28.4% vs. iGlar, 8.2% to 32.1% vs. Lixi) and the triple composite of HbA1c <7% (<53 mmol/mol) with no body weight gain and no documented symptomatic hypoglycaemia (28%, 15% and 15% for iGlarLixi, iGlar and Lixi, respectively; 95% CI 4.1% to 23.3% vs. iGlar, 2.2% to 25.0% vs. Lixi).

3.4 | Mean change in FPG and 2-hour PPG (during a standardized meal test) at Week 30

iGlarLixi reduced FPG more than Lixi did, while reductions were similar between iGlarLixi and iGlar; least squares (LS) mean changes from baseline were −4.5, −4.5 and −2.2 mmol/L for iGlarLixi, iGlar and Lixi, respectively ($P = 0.9464$ for iGlarLixi vs. iGlar and $P < 0.0001$ for iGlarLixi vs. Lixi [Figure 3]). Reductions in 2-hour PPG were highest with iGlarLixi (−7.2 mmol/L vs. −4.6 mmol/L for iGlar and −5.5 mmol/L for

TABLE 1 Baseline characteristics (modified intention-to-treat population)

	iGlarLixi (n = 137)	iGlar (n = 135)	Lixi (n = 67)
Age, years	57.9 ± 10.1	60.3 ± 8.5	59.9 ± 7.7
Female sex, n (%)	74 (54.0)	71 (52.6)	34 (50.7)
Race, n (%)			
White	115 (83.9)	121 (89.6)	59 (88.1)
Black	18 (13.1)	11 (8.1)	4 (6.0)
Asian	2 (1.5)	2 (1.5)	2 (3.0)
Other	2 (1.5)	1 (0.7)	2 (3.0)
BMI, kg/m^2	31.4 ± 4.6	31.4 ± 4.4	32.1 ± 4.5
HbA1c, %	8.55 ± 0.46	8.57 ± 0.51	8.64 ± 0.52
mmol/mol	69.9 ± 5.0	70.1 ± 5.6	70.9 ± 5.7
Duration of diabetes, years	9.4 ± 5.0	10.6 ± 6.4	10.3 ± 6.7
Duration of second OAD treatment, years	4.0 ± 4.4	5.1 ± 5.1	4.1 ± 3.6
Use of second OAD at screening, n (%)	137 (100)	135 (100)	67 (100)
Type of second OAD, n (%)			
Sulphonylureas	132 (96.4)	124 (91.9)	62 (92.5)
Glinides	1 (0.7)	7 (5.2)	3 (4.5)
DPP-4 inhibitors	4 (2.9)	6 (4.4)	2 (3.0)

Note: Data are mean ± SD unless otherwise noted.
Abbreviations: BMI, body mass index; HbA1c, glycated haemoglobin; DPP-4, dipeptidyl peptidase-4; iGlar, insulin glargine 100 units/mL; iGlarLixi, insulin glargine 100 units/mL plus lixisenatide; Lixi, lixisenatide; OAD, oral antidiabetes drug; SD, standard deviation.

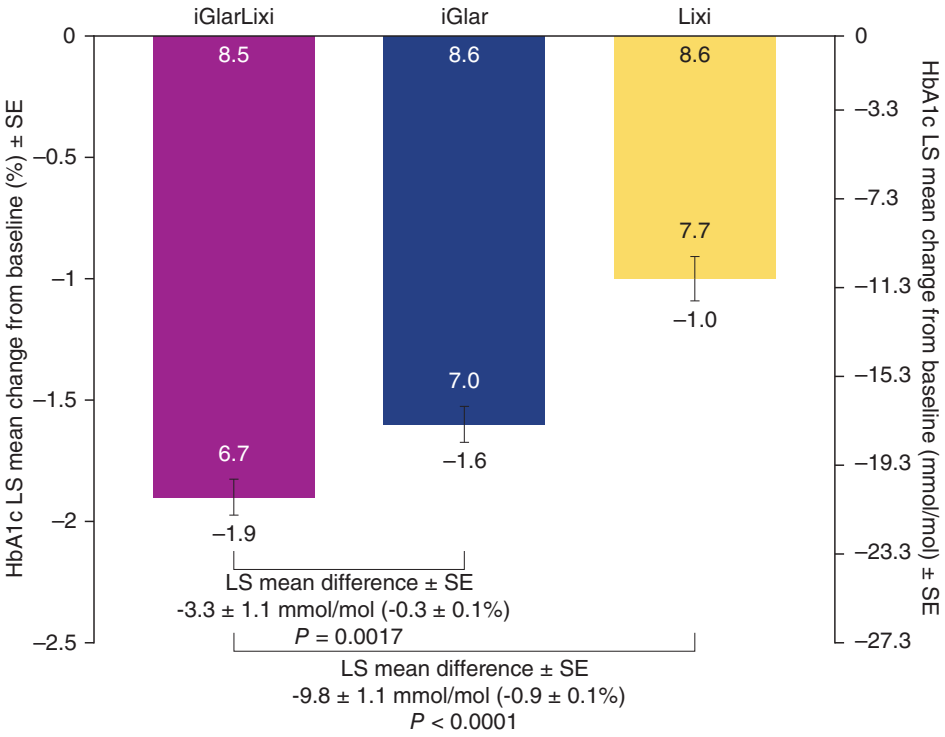

FIGURE 1 Glycated haemoglobin (HbA1c) change from baseline at Week 30 (modified intention-to-treat population). Analysed using a mixed-effect model with repeated measures. Labels at top and bottom of bars indicate mean baseline and Week 30 HbA1c, respectively. iGlar, insulin glargine 100 units/mL; iGlarLixi, insulin glargine 100 units/mL plus lixisenatide; Lixi, lixisenatide; LS, least squares; SE, standard error

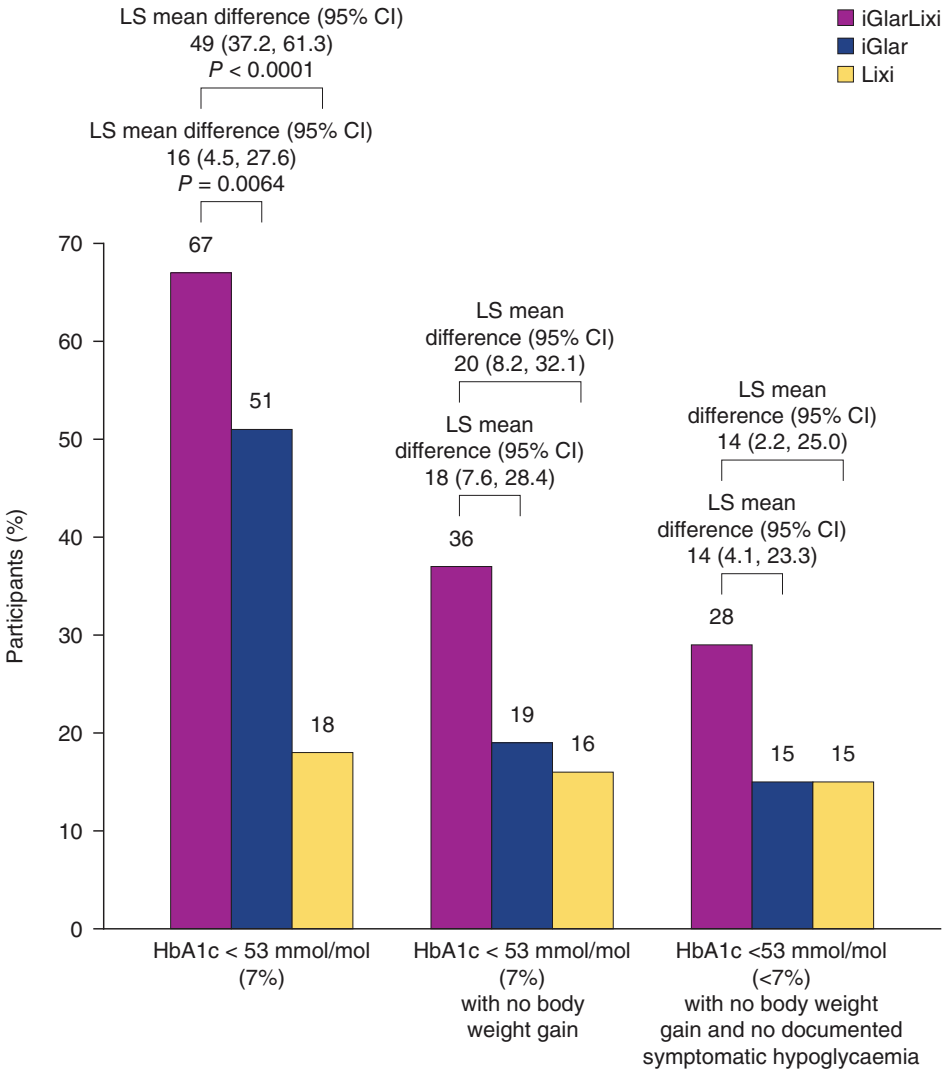

FIGURE 2 Proportion of participants achieving a glycated haemoglobin (HbA1c) level <53 mmol/mol (<7%) at Week 30 (modified intention-to-treat population). Participants were treated as non-responders if they had no HbA1c and/or body weight assessments at Week 30. Documented symptomatic hypoglycaemia included events accompanied by a measured plasma glucose ≤3.9 mmol/L. CI, confidence interval; iGlar, insulin glargine 100 units/mL; iGlarLixi, insulin glargine 100 units/mL plus lixisenatide; Lixi, lixisenatide; LS, least squares

Lixi; 95% CI −3.5 to −1.7 mmol/L vs. iGlar, −2.9 to −0.7 mmol/L vs. Lixi [Figure 3]).

3.5 | Mean change in body weight at Week 30

Body weight at Week 30 in the iGlarLixi group was similar to that at baseline, while body weight increased in the iGlar group (Figure S1). Body weight in participants receiving Lixi decreased over 30 weeks. LS mean changes in body weight from baseline to Week 30 were 0.3, 1.6 and −2.0 kg for iGlarLixi, iGlar and Lixi, respectively (95% CI −2.3 to −0.4 kg for iGlarLixi vs. iGlar, 1.1 to 3.4 kg for iGlarLixi vs. Lixi).

3.6 | Mean daily iGlar dose by visit

Insulin dose at Week 30 was comparable between the iGlarLixi and iGlar groups (40.72 and 40.22 U, respectively; $P = 0.8664$).

3.7 | Adverse events

Serious adverse events (AEs) were uncommon, occurring in 3.6%, 5.1% and 4.5% of participants in the iGlarLixi, iGlar and Lixi treatment groups, respectively (Table S3). All serious AEs were reported in no more than one participant in each treatment group and no patterns in serious AE reporting were observed. The proportion of participants experiencing gastrointestinal AEs in the iGlarLixi group was greater than in the iGlar group, but lower than in the Lixi group (Table S3). This was consistent with results in the overall population, which showed the highest rates of gastrointestinal AEs in those taking Lixi alone (Table S3).[6]

3.7.1 | Documented symptomatic hypoglycaemic events during the on-treatment period

The percentages of participants with at least one symptomatic hypoglycaemia event documented with a plasma glucose value ≤3.9 mmol/L and the corresponding event rates per participant-year were similar between the iGlarLixi group (29.0%; 1.53 events per participant-year) and the iGlar group (27.9%; 1.16 events per participant-year [Figure 4]). In the Lixi group, the percentage of participants and the event rate per participant-year were lower (12.1%; 0.83 events per participant-year).

For symptomatic hypoglycaemia documented with plasma glucose <3.0 mmol/L, the percentages of participants with at least one event were 6.5%, 7.4% and 4.5% for iGlarLixi, iGlar and Lixi,

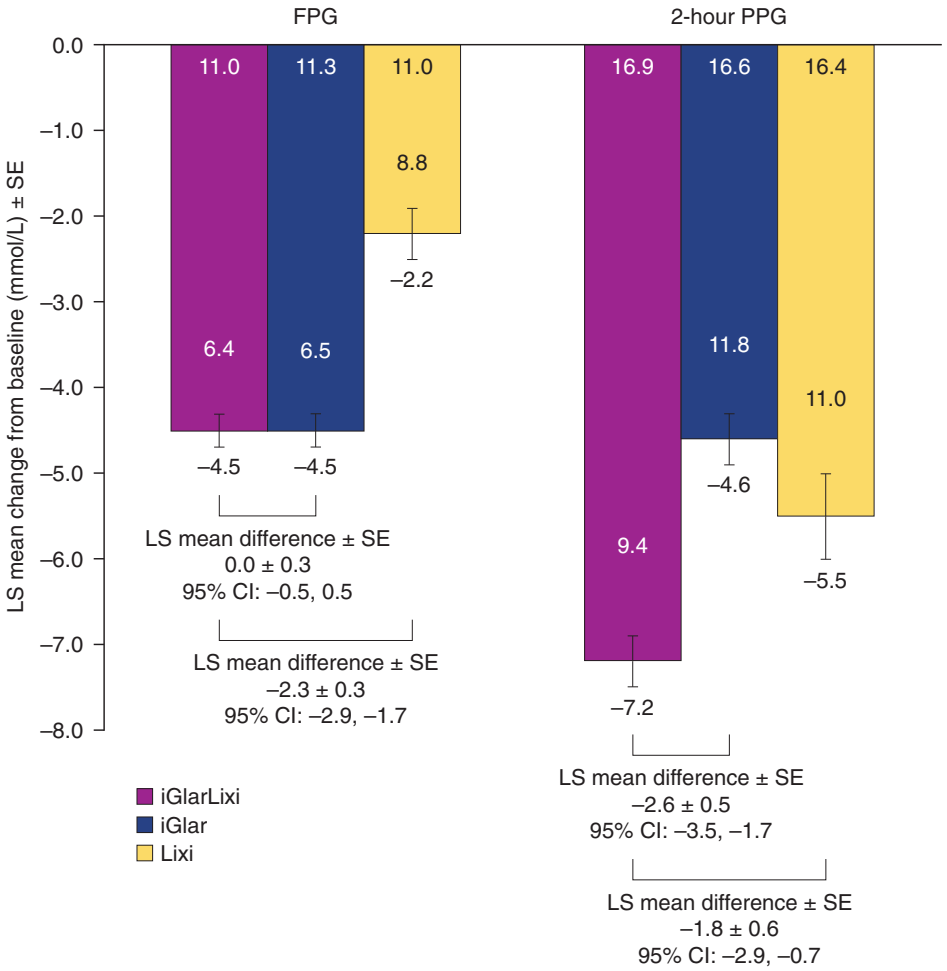

FIGURE 3 Mean change in FPG and 2-hour (PPG; during a standardized meal test) at Week 30 (modified intention-to-treat population). FPG was analysed using a mixed-effect model with repeated measures. Two-hour PPG was analysed using analysis of covariance. Labels at top and bottom of bars indicate baseline and Week 30 mean glucose levels, respectively. CI, confidence interval; iGlar, insulin glargine 100 units/mL; iGlarLixi, insulin glargine 100 units/mL plus lixisenatide; Lixi, lixisenatide; LS, least squares; SE, standard error

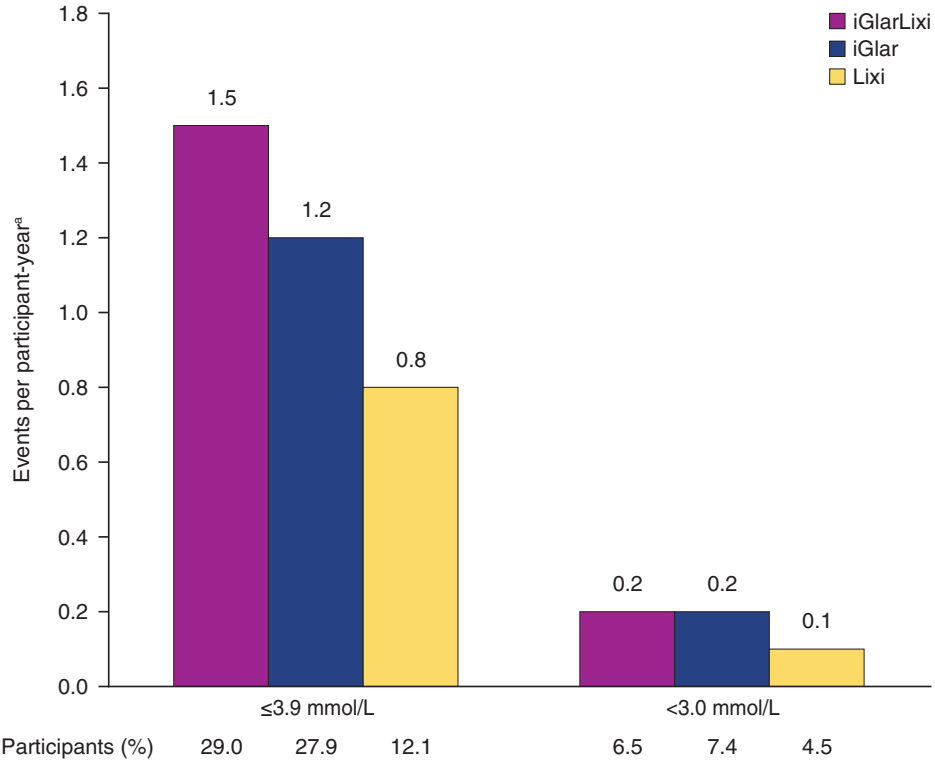

FIGURE 4 Documented symptomatic hypoglycaemia and clinically important hypoglycaemia events during the on-treatment period (modified intention-to-treat population). On-treatment period is the time from first injection up to 1 day after the last injection, regardless of introduction of rescue therapy. [a]Calculated as number of events divided by total participant-years of exposure. iGlar, insulin glargine 100 units/mL; iGlarLixi, insulin glargine 100 units/mL plus lixisenatide; Lixi, lixisenatide

respectively, and the corresponding event rates per participant-year were 0.17, 0.17 and 0.14, respectively (Figure 4).

4 | DISCUSSION

This exploratory analysis examined the efficacy and safety of iGlarLixi in a subgroup of LixiLan-O trial participants insufficiently controlled on metformin and a second OAD with baseline HbA1c ≥8% (≥64 mmol/mol), expected to be a more difficult-to-treat population, with a lower likelihood of reaching target HbA1c when initiated with basal insulin alone or GLP-1RA. iGlarLixi was more effective than iGlar or Lixi (all on a background of metformin) in achieving glycaemic targets, demonstrating an LS mean 20-mmol/mol (1.9%) decrease in HbA1c to 6.7% (50 mmol/mol), with 67% of participants reaching a target of <53 mmol/mol (<7%). iGlarLixi was associated with greater decreases in PPG and FPG compared with either of its components, while mitigating the body weight increase seen with iGlar alone. This subgroup analysis provides an example of a simplified administration of triple therapy that can demonstrate effective glycaemic control in people who had not achieved target HbA1c with two OADs. The results are in accordance with a previous exploratory analysis of the LixiLan-O study examining two other difficult-to-treat subgroups, namely, (a) those with baseline HbA1c ≥9% (≥75 mmol/mol) and (b) those with HbA1c ≥7% and ≤9% (≥53 and ≤75 mmol/mol), despite administration of two OADs at screening.[9]

Numerically higher proportions of participants receiving iGlarLixi achieved composite endpoints including HbA1c <7% (<53 mmol/mol) without body weight gain, or without body weight gain and without documented symptomatic hypoglycaemia. This may be of particular clinical relevance for an FRC containing insulin because of the concerns that individuals and physicians may have regarding body weight gain and hypoglycaemia risks related to the insulin component.[10]

People who do not achieve target HbA1c levels with OADs often intensify treatment with basal insulin alone. In a pooled analysis of individuals with T2D with a mean baseline HbA1c of 8.7% (72 mmol/mol), 54% of the study population did not achieve HbA1c <7% (<53 mmol/mol) following the addition of basal insulin.[3] Baseline HbA1c was the strongest determinant for achieving target HbA1c <7% (<53 mmol/mol). The higher the baseline HbA1c level, the less likely that the glycaemic target will be achieved when basal insulin alone is introduced, even in the controlled conditions of a treat-to-target trial where participants are typically closely supervised. These findings suggest that supplementation of basal insulin therapy may need to be more aggressive in people with a baseline HbA1c >8% (>64 mmol/mol), while also considering hypoglycaemia risk.[3] In individuals who do not achieve an adequate response on basal insulin alone, therapies that address excessive PPG excursions may be an option.[3] For people with persistently poor glycaemic control despite the use of multiple OADs and basal insulin, early introduction of a GLP-1RA may be considered.[11] In routine real-world clinical practice, factors such as poor adherence may exacerbate the difficulty such individuals have in achieving glycaemic control.[12] Real-world evidence suggests that, while initiating basal insulin may allow some people to achieve a recommended HbA1c <7% (<53 mmol/mol), individuals become less and less likely over extended treatment to meet this goal for the first time. Among 6597 individuals in a US retrospective study who had T2D and a mean HbA1c of 9.1%, despite taking at least one OAD, 26.6%

first achieved HbA1c <7% (<53 mmol/mol) over months 3 to 6; while only a further 3.4% achieved the same target over months 21 to 24.[13] In a multinational analysis including over 40 000 people initiating insulin after using OADs, 20.9% achieved the target of HbA1c <7% (<53 mmol/mol) at 3 months; by 24 months this had only increased to 27.8%.[14] Such evidence suggests the need for effective intensification options that alleviate the potential drawbacks of insulin therapy, which may contribute to poor adherence to therapy. An FRC of basal insulin and GLP-1RA treatment, in particular, could be attractive and encourage prompt, proactive intensification in the real-world setting, where therapeutic inertia is a recognized challenge. Current ADA/EASD guidelines identify GLP-1RAs as a preferred first injectable option when OAD therapy is suboptimal for glycaemic control.[2,15] Furthermore, the ADA consider that people with HbA1c of 16 to 22 mmol/mol [1.5%-2.0%] above target may be candidates for first-line combination injectable therapy.[15]

Other recent research has evaluated treatment with an FRC among those who might be candidates for intensification of previous therapy. A recent post hoc analysis compared the FRC of insulin degludec and liraglutide (IDegLira) with basal insulin in participants from the DUAL II and DUAL IX trials, including those whose T2D was inadequately controlled with multiple OADs.[16] Individuals who had been taking a sulphonylurea discontinued it while continuing metformin and beginning randomized treatment with IDegLira or insulin degludec; those who had been taking a dipeptidyl peptidase-4 (DPP-4) inhibitor discontinued it while continuing to take a sodium-glucose cotransporter protein-2 inhibitor (with or without other OADs) and beginning IDegLira or insulin glargine. Those with prior sulphonylurea use had a mean baseline HbA1c of 8.75%-8.85% (72 to 73 mmol/mol), and those with prior DPP-4 inhibitor use had a mean baseline HbA1c of 8.18%-8.20% (66 mmol/mol). In both subgroups, use of IDegLira over 26 weeks was associated with more favourable changes in HbA1c versus basal insulin (−1.13% [−12 mmol/mol] vs. degludec and −0.40% [−4 mmol/mol] vs. glargine), and decreased body weight versus the insulin comparators. Change in 2-hour PPG was not evaluated. As shown in our present subgroup analyses, these post hoc analyses of IDegLira suggest that FRC therapy may be an effective option for people who are unable to reach glycaemic targets despite the use of multiple OADs.

This research is limited by its post hoc nature; the study was not designed or powered to test for differences among treatment arms within the subgroup of participants with HbA1c ≥8% (≥64 mmol/mol) who were taking two OADs at baseline. These findings must therefore be considered exploratory. Additionally, participants who had taken a second OAD were required to stop taking it at the beginning of the run-in phase; the study therefore cannot account for any continued effects of the second OAD that could have occurred with uninterrupted usage.

Intensification with iGlarLixi resulted in people with T2D with baseline HbA1c ≥8% (≥64 mmol/mol) despite using two OADs at screening achieving better glycaemic control and less body weight gain, with similar rates of documented symptomatic hypoglycaemia compared with intensification with iGlar or Lixi alone. People treated with multiple OADs and those with higher HbA1c levels may have difficulty reaching therapeutic targets, and concerns regarding body weight gain can cause individuals to resist the introduction of insulin treatment despite poor glycaemic control.[10,17] iGlarLixi may provide a valuable treatment option for such individuals while being associated with less body weight gain.

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CONFLICTS OF INTEREST

M.J.D. has acted as a consultant, advisory board member and speaker for Novo Nordisk, Sanofi-Aventis, Lilly, Merck Sharp & Dohme, Boehringer Ingelheim, AstraZeneca and Janssen, an advisory board member for Servier and Gilead Sciences Ltd, and as a speaker for NAPP, Mitsubishi Tanabe Pharma Corporation and Takeda Pharmaceuticals International Inc. She has received grant/research support from Novo Nordisk, Sanofi-Aventis, Lilly, Boehringer Ingelheim, AstraZeneca and Janssen. J.R. has acted as a consultant for Boehringer Ingelheim, Eli Lilly, Intarcia, Janssen, Novo Nordisk and Sanofi and has received grant/research support from AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb, Eli Lilly, Genentech, GlaxoSmithKline, Intarcia, Janssen, Lexicon, Merck, Novo Nordisk, Pfizer and Sanofi. A.A. has received research support and honoraria from Amgen, Eli Lilly, Gelesis, NAPP, Novartis, Novo Nordisk and Sanofi. D.R.J. has served on an advisory panel for, served as a board member or consultant for, and received research support from AstraZeneca, Eli Lilly, Novo Nordisk and Sanofi, and has served on a speakers' bureau for AstraZeneca, Boehringer Ingelheim, Eli Lilly, Novo Nordisk, Sanofi and Takeda. E.S., K.P., C.J. and E.N. are employees of Sanofi and may hold shares and/or stock options in the company. N.S. has served on an advisory panel for AstraZeneca, Boehringer Ingelheim, Eli Lilly, GlaxoSmithKline, Intarcia, Janssen, Merck Sharp & Dohme, Mylan, Sanofi and Teva, has received research support from AstraZeneca, Boehringer Ingelheim, GlaxoSmithKline and Sanofi, and has served as a speaker for AstraZeneca, Boehringer Ingelheim and Eli Lilly. These results were previously presented as poster 1134-P at the ADA (San Francisco, California) 2019.

DATA AVAILABILITY STATEMENT

Qualified researchers may request access to patient-level data and related documents. Patient-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.clinicalstudydatarequest.com/.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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