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Benefit of insulin glargine/lixisenatide for reducing residual hyperglycaemia in Japan: Post hoc analysis of the LixiLan JP-O2 trial

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Abstract

Aim: To compare the benefits of iGlarLixi, a fixed-ratio combination of insulin glargine 100 U/mL and lixisenatide (iGlarLixi), with insulin glargine (iGlar) for reducing residual hyperglycaemia (defined as HbA1c ≥ 7% despite fasting plasma glucose [FPG] < 130 mg/dL) in Japanese people with type 2 diabetes (T2D) inadequately controlled on oral antidiabetic drugs.

Materials and Methods: The open-label LixiLan JP-O2 study compared iGlarLixi with iGlar over 26 weeks in 521 people with T2D. This post hoc analysis assessed the proportions of participants with residual hyperglycaemia in the overall population, and in subgroups defined by age and dipeptidyl peptidase-4 inhibitor (DPP4i) use at screening.

Results: At 26 weeks, significantly fewer participants had residual hyperglycaemia in the iGlarLixi versus the iGlar arm (8.1% vs. 19.6%; $P = .0002$). There was also less residual hyperglycaemia with iGlarLixi than iGlar in all subgroup analyses: 9.0% versus 16.8% in participants aged younger than 65 years ($P = .0369$); 6.5% versus 24.2% in participants aged 65 years or older ($P = .0008$); 10.1% versus 20.5% ($P = .0202$) in participants with DPP4i use; and 6.2% versus 18.8% in those without DPP4i use ($P = .0024$). The proportion reaching both HbA1c less than 7% and FPG less than 130 mg/dL was higher with iGlarLixi versus iGlar in the overall population (50.8% vs. 31.5%; $P < .0001$), and in all studied subgroups.

Conclusions: iGlarLixi reduced the prevalence of residual hyperglycaemia in Japanese people with uncontrolled T2D compared with iGlar, both in the overall population and in subgroups defined by age and DPP4i use at screening.

KEYWORDS
GLP-1 analogue, basal insulin, incretin therapy, type 2 diabetes

1 | INTRODUCTION

Achieving an appropriate level of glycaemic control is the therapeutic objective for all people with type 2 diabetes (T2D). The addition of a basal insulin is a recommended next step when oral antidiabetic (OAD) therapy fails to achieve target HbA1c levels.[1,2] However, many people will not achieve glycaemic control despite the addition of basal insulin. In a retrospective analysis of seven clinical trials, 42.7%-54.4% of participants who received basal insulin for 24-36 weeks had residual hyperglycaemia, defined as HbA1c of 7% or more despite fasting plasma glucose (FPG) being below target levels (<130 or <140 mg/dL, depending on national recommendations).[3] Furthermore, 16.9%-38.1% had uncontrolled diabetes, defined as a failure to achieve either HbA1c or FPG targets.[3]

Basal insulin achieves its effects on HbA1c primarily by lowering FPG, and has less impact on postprandial glucose (PPG) levels.[4] As HbA1c approaches 7%, the relative contribution of PPG to HbA1c increases, while that of FPG diminishes[5]; thus, additional treatment to address PPG is often needed to achieve target HbA1c in people with residual hyperglycaemia.[4] Most commonly, attempts to improve PPG control in people receiving basal insulin involve the addition of a bolus dose of a rapid-acting insulin at one or more mealtimes, to create so-called basal-plus or basal-bolus insulin regimens.

In practice, the utility of adding prandial insulin to background OAD therapy may be limited by concerns about treatment complexity and adverse events, such as hypoglycaemia and weight gain.[4] More recently, the addition of a glucagon-like peptide-1 receptor agonist (GLP-1 RA), administered as a separate injection, has been recommended for consideration as an alternative to multidose prandial insulin.[1,2,4] In contrast to insulin, the addition of a GLP-1 RA, such as lixisenatide, to basal insulin has been shown to reduce both PPG and HbA1c, while promoting weight loss and causing minimal hypoglycaemia. However, this approach also carries the burden of an additional injection.[6]

In recent years, co-formulations of basal insulin with GLP-1 RAs have become available, avoiding the need for separate injections. In Japan, these include a 1:1 fixed-ratio combination of lixisenatide with insulin glargine (iGlarLixi). In the randomized LixiLan-L trial, the effects of iGlarLixi on residual hyperglycaemia were compared with those of insulin glargine (iGlar) in people whose T2D was uncontrolled despite treatment with OADs plus basal insulin.[7,8] After 30 weeks of treatment, residual hyperglycaemia was significantly less frequent in participants who received iGlarLixi compared with those receiving iGlar (23.8% vs. 47.1%; $P < .0001$).[9] Similarly, in a comparable trial conducted in Japanese people with T2D (LixiLan JP-L), the proportion with residual hyperglycaemia after 26 weeks was 15.7% with iGlarLixi and 36.9% with iGlar; the difference between the treatment arms was statistically significant (21.1%; 95% confidence interval: 13.7%, 28.5%; $P < .0001$).[10]

However, the effects of iGlarLixi on residual hyperglycaemia in people with T2D not previously treated with basal insulin are unknown. The LixiLan JP-O2 trial (NCT02752828; hereafter referred to as the JP-O2 trial) was a randomized controlled trial that compared the efficacy and safety of iGlarLixi with that of iGlar in Japanese people with uncontrolled T2D on OADs.[11] At 26 weeks, iGlarLixi was significantly more efficacious than iGlar in reducing HbA1c (change from baseline: −1.40% vs. 0.76%; $P < .0001$). Here, we present the results of a post hoc analysis of the JP-O2 trial, undertaken to investigate the effects of iGlarLixi on residual hyperglycaemia in this population.

2 | MATERIALS AND METHODS

2.1 | Trial design

The design of the JP-O2 trial, and the baseline characteristics of the study population, have been described in detail previously.[11] Briefly, JP-O2 was a phase 3 multicentre trial, in which 521 people with uncontrolled T2D were randomized (1:1) to receive either iGlarLixi ($n = 260$) or iGlar ($n = 261$), in addition to existing OAD treatment.[11] The follow-up period was 26 weeks.

People with T2D were included if they had an HbA1c of 7.5% or more (≥58 mmol/mol) to 9.5% or less (≤80 mmol/mol) and an FPG of 10.0 mmol/L or less (≤180 mg/dL), and 1 year or longer had elapsed since their T2D diagnosis. Participants had to be on stable treatment with up to two OADs, or up to three if they were also taking a dipeptidyl peptidase-4 inhibitor (DPP4i).[11] DPP4is were discontinued at randomization.

Insulin was titrated in both groups as described previously.[11] Participants in the iGlarLixi group initially received five dose steps, equivalent to insulin glargine 5 U and lixisenatide 5 μg daily, while those in the iGlar group received an initial daily dose of 5 U. The dose of iGlarLixi or iGlar was subsequently adjusted weekly following the same algorithm (FPG > 140 mg/dL, +2 dose steps; FPG >100 and ≤140 mg/dL, +1 dose step; FPG ≥80 and ≤100 mg/dL, no change; FPG ≥60 and <80 mg/dL, −2 dose steps; and FPG < 60 mg/dL, −3 dose steps or more at the discretion of the study investigator or medically qualified designee). Dose adjustments (once weekly) were based on a median of fasting self-monitored plasma glucose values from the last three measurements, where a daily dose of iGlar of more than 20 U was required to maintain HbA1c below thresholds (HbA1c ≤ 8.5% after week 12); rescue therapy could be introduced without an increase in the dose of iGlarLixi. Rescue therapy was started as a single daily administration (except breakfast in the iGlarLixi group) of short-/rapid-acting insulin.

2.2 | Post hoc analysis

We undertook a post hoc analysis of JP-O2 trial data to assess the impact of randomized treatment on the glycaemic classification of study participants, using categories adapted from those described by Raccah et al.,[3] throughout the 26-week treatment period. Four categories of glycaemic control were defined, according to HbA1c and FPG levels (Figure 1A): 'hyperglycaemia' (neither HbA1c nor FPG at target); 'residual hyperglycaemia' (HbA1c not at target, FPG at target); 'both at target' (both HbA1c and FPG at target); and 'discordant' (HbA1c at target, FPG not at target).

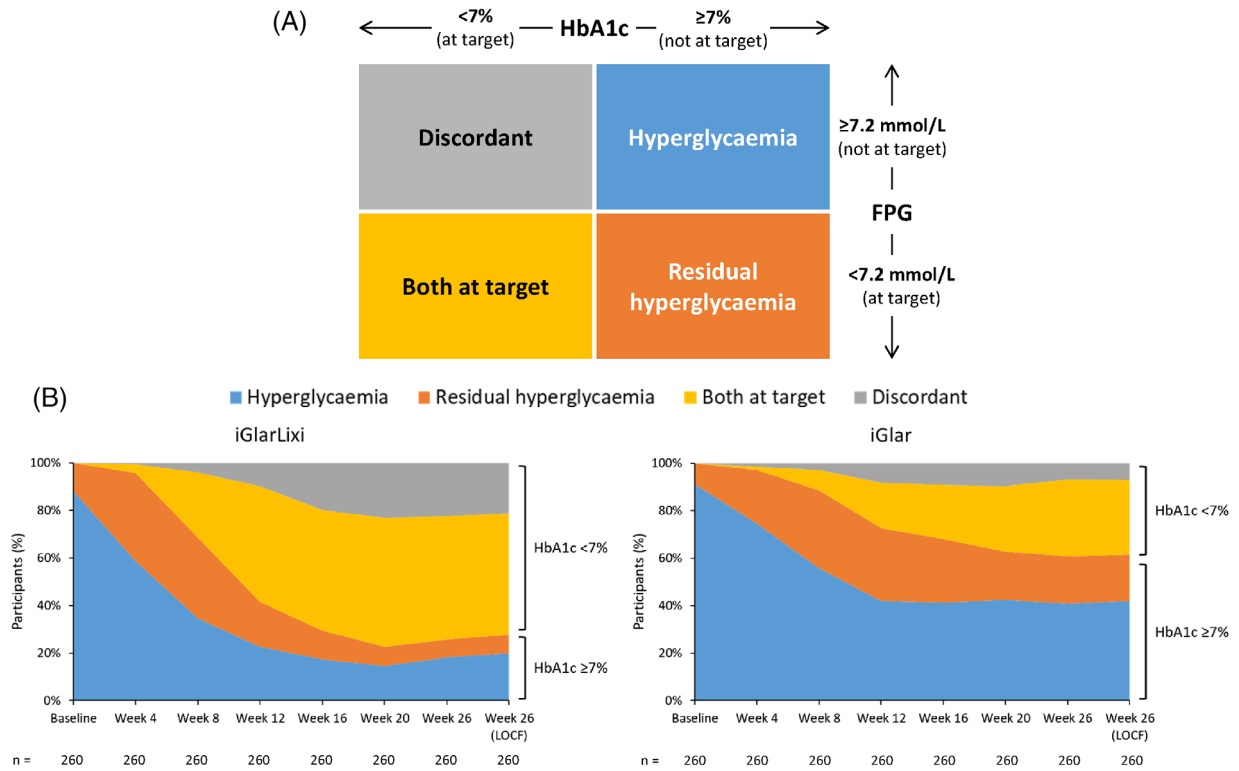

FIGURE 1 A, Glycaemic control categories, and B, The proportion of participants in each glycaemic category over time for iGlarLixi (left) and iGlar (right); n = 260 for both treatments and all time points. FPG, fasting plasma glucose; iGlar, insulin glargine; iGlarLixi, fixed-ratio combination of insulin glargine and lixisenatide; LOCF, last observation carried forward

Although there is general agreement that glycaemic targets need to be individualized based on age, co-morbidities, and risk, general guidance suggests an HbA1c target of less than 7% (<53 mmol/mol), in an attempt to reduce the risk of diabetes-related complications in people aged younger than 65 years.[1] This HbA1c level is assumed to correspond to an FPG of less than 7.2 mmol/L (<130 mg/dL),[1] which was used as the FPG target.

The proportion of participants in each glycaemic control category was assessed at baseline and at 26 weeks, and at other time points during the study, for each treatment arm. The primary outcomes of interest were the proportion of participants with residual hyperglycaemia at 26 weeks, and the change in this variable between baseline and 26 weeks.

Two subgroup analyses were performed to investigate interactions between age and prior DPP4i use at screening on the results. In the first analysis, the data were analysed separately for participants aged younger than 65 and 65 years or older. The mean age of Japanese people with T2D is older than 65 years (66.99 years in 2019), and is increasing annually.[12] Because the risk-benefit ratio of diabetes treatment is often not uniform across the age spectrum, we performed a subgroup analysis to descriptively assess differences between participants aged younger than 65 years and 65 years or older in terms of the effects of iGlarLixi on residual hyperglycaemia. In the second analysis, participants were divided into two subgroups, according to whether they were receiving a DPP4i at screening (referred to hereafter as DPP4i+ and DPP4i−). In Japan, DPP4is are among the most widely prescribed OADs. However, because their mechanism of action is similar to that of GLP-1 RAs, they are often discontinued in people with T2D commencing GLP-1 RA therapy.[13] It is therefore important to assess whether pretreatment with a DPP4i affects response to iGlarLixi treatment.

2.3 | Statistical methods

All post hoc analyses were performed in the modified intent-to-treat (mITT) population (i.e. all randomized participants who received ≥1 dose of study medication, and had both a baseline and ≥1 post-baseline assessment of any efficacy variable). The Cochran-Mantel-Haenszel method was used to test the difference in proportion between the two treatment arms in the overall population and by each subgroup at 26 weeks. Statistical tests were performed at a nominal two-sided significance level of .05; *P* values should therefore be considered nominal. Missing data at 26 weeks were imputed using the last observation carried forward (LOCF) method.

3 | RESULTS

3.1 | Overall population

The mITT population included 520 participants (260 per treatment arm). The proportions of participants in each glycaemic control category at baseline were similar in both arms: most participants were in

the hyperglycaemia category (n = 466; 89.6%), while a minority had residual hyperglycaemia (n = 54; 10.4%). By treatment arm, the percentage of participants with residual hyperglycaemia at baseline was 11.9% (31/260) in the iGlarLixi arm and 8.8% (23/260) in the iGlar arm.

Clinical characteristics of the 54 participants with residual hyperglycaemia at baseline are shown in Table 1. Participants with residual hyperglycaemia at baseline had a similar mean age, duration of diabetes, and body mass index to the overall population at baseline,[11] but had lower mean HbA1c (overall population values: iGlarLixi, 8.08% [64.8 mmol/mol]; iGlar, 8.01% [64.0 mmol/mol]) and FPG (overall population values: iGlarLixi, 8.70 mmol/L; iGlar, 8.79 mmol/L) values. For the participants with residual hyperglycaemia, the mean daily dose of iGlar was 5.00 U in both the iGlarLixi and iGlar arms at baseline, and 13.32 and 16.22 U, respectively, at week 26 (LOCF). In the overall population, daily iGlar doses were 5.00 U in each arm at baseline, and 15.10 and 17.30 U at week 26 (LOCF).[11]

Figure 1B shows how the proportion of participants in each of the glycaemic categories (hyperglycaemia, residual hyperglycaemia, both at target and discordant) changed over time. From baseline to week 26 (LOCF), the percentage of participants with residual hyperglycaemia decreased from 11.9% to 8.1% in the iGlarLixi arm, and increased from 8.8% to 19.6% in the iGlar arm (Table 2). The difference between the treatment arms at week 26 (LOCF) was statistically significant ($P = .0002$).

At the same time point, there was a significantly greater proportion of participants in the both at target category, and a significantly lower proportion of participants in the hyperglycaemia category, in the iGlarLixi versus the iGlar arm (50.8% vs. 31.5% [$P < .0001$], respectively, for the both at target category, and 19.8% vs. 41.9% [$P < .0001$], respectively, for the hyperglycaemia category; Figure 1B).

In participants with residual hyperglycaemia, symptomatic hypoglycaemia with plasma glucose of 70 mg/dL or less was documented in seven participants (22.6%) in the iGlarLixi arm and two participants (8.7%) in the iGlar arm. The corresponding proportions in the overall population were 14.2% and 12.3%, respectively.[11]

3.2 | Subgroup analyses

The results of the subgroup analyses by age and DPP4i use at screening are shown in Table 2, and in Figures 2 and 3, respectively. Overall, temporal patterns of change in glycaemic control categories were similar for the subgroups and for the overall population. In each age and DPP4i subgroup, iGlarLixi was associated with a reduction in residual hyperglycaemia between baseline and week 26 (LOCF), while iGlar was associated with an increase (Table 2); differences between iGlarLixi and iGlar at week 26 (LOCF) were statistically significant for all subgroups.

3.2.1 | By age

Three hundred and twenty-nine participants (63% of the study population; 168 in the iGlarLixi arm and 161 in the iGlar arm) were aged

TABLE 1 Baseline demographics and disease characteristics of the 54 participants in the JP-O2 trial who had residual hyperglycaemia (HbA1c ≥ 7% [≥53 mmol/mol] and fasting plasma glucose < 7.2 mmol/L [<130 mg/dL]) at baseline

Characteristic	iGlarLixi (n = 31)	iGlar (n = 23)
Age, y	61.1 (10.7)	59.4 (7.8)
Duration of diabetes, y	8.23 (5.49)	10.2 (7.9)
Body weight, kg	67.3 (12.1)	69.5 (14.2)
BMI, kg/m^2	25.0 (3.6)	25.4 (3.7)
HbA1c, % [mmol/mol]	7.85 (0.37) [62.0 (4.0)]	7.68 (0.31) [60.0 (3.4)]
FPG, mmol/L [mg/dL]	6.7 (0.4) [120.6 (7.5)]	6.7 (0.4) [120.3 (8.1)]
2-h PPG, mg/dL	234.1 (45.6)	209.4 (40.2)
OAD use, n (%)		
None	1 (3.2)[a]	0
Alpha-glucosidase inhibitor	1 (3.2)	2 (8.7)
Biguanide	12 (38.7)	15 (65.2)
DPP4i	17 (54.8)	11 (47.8)
Glinide	1 (3.2)	0
SGLT-2 inhibitor	9 (29.0)	3 (13.0)
Sulphonylurea	12 (38.7)	9 (39.1)
Thiazolidinedione	2 (6.5)	0

Note: Data are mean (standard deviation) for the modified intent-to-treat population (all randomized participants), unless otherwise stated.
Abbreviations: BMI, body mass index; DPP4i, dipeptidyl peptidase-4 inhibitor; FPG, fasting plasma glucose; iGlar, insulin glargine; iGlarLixi, fixed-ratio combination of insulin glargine and lixisenatide; OAD, oral antidiabetic drug; PPG, postprandial glucose; SGLT-2, sodium-glucose co-transporter-2.
[a]Based on OAD use on the day before randomization.

TABLE 2 Proportion of participants with residual hyperglycaemia (HbA1c ≥ 7% [≥53 mmol/mol] and fasting plasma glucose < 7.2 mmol/L [<130 mg/dL]) at baseline and at week 26 (last observation carried forward [LOCF]) in the JP-O2 trial

Study population	Baseline					Week 26 (LOCF)				
	iGlarLixi (n = 260)	iGlar (n = 260)	Risk difference	95% CI	*P* value[a]	iGlarLixi (n = 258)	iGlar (n = 260)	Risk difference	95% CI	*P* value[a]
Overall population[b]	11.9%	8.8%	3.1%	−2.2%, 8.3%	.2506	8.1%	19.6%	−11.5%	−17.3%, −5.6%	.0002
Subgroup analysis by age[b]										
<65 y	(n = 168)	(n = 161)				(n = 166)	(n = 161)			
	11.3%	11.2%	0.1%	−6.7%, 7.0%	.9704	9.0%	16.8%	−7.7%	−15.0%, −0.5%	.0369
≥65 y	(n = 92)	(n = 99)				(n = 92)	(n = 99)			
	13.0%	5.1%	8.0%	−0.1%, 16.1%	.0532	6.5%	24.2%	−17.7%	−27.6%, −7.9%	.0008
Subgroup analysis by DPP4i use at screening[b]										
Yes (n = 263)	(n = 131)	(n = 132)				(n = 129)	(n = 132)			
	13.7%	9.1%	4.6%	−3.0%, 12.3%	.2365	10.1%	20.5%	−10.4%	−19.0%, −1.8%	.0202
No (n = 257)	(n = 129)	(n = 128)				(n = 129)	(n = 128)			
	10.1%	8.6%	1.5%	−5.6%, 8.6%	.6833	6.2%	18.8%	−12.5%	−20.5%, −4.6%	.0024

Abbreviations: CI, confidence interval; DPP4i, dipeptidyl peptidase-4 inhibitor; FPG, fasting plasma glucose; iGlar, insulin glargine; iGlarLixi, fixed-ratio combination of insulin glargine and lixisenatide.

[a]The Cochran-Mantel-Haenszel method with treatment as the only factor was used to test the risk difference between the two treatment arms.

[b]For each time point, only patients with both HbA1c and FPG data available were included in this analysis.

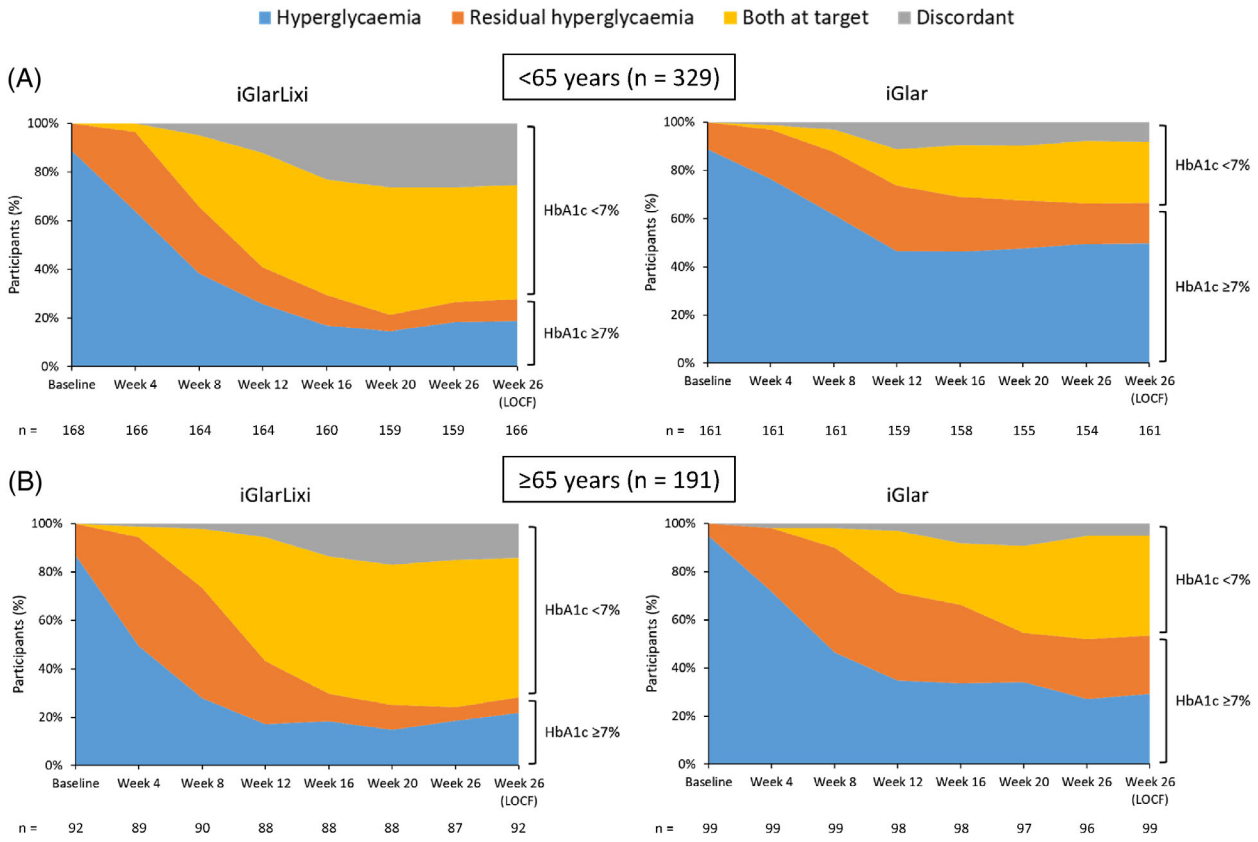

FIGURE 2 Evolution of glycaemic control over time for A, Participants aged <65 years, and B, Participants aged ≥65 years. iGlar, insulin glargine; iGlarLixi, fixed-ratio combination of insulin glargine and lixisenatide; LOCF, last observation carried forward

younger than 65 years. The mean daily iGlar dose was 5.00 U in both the iGlarLixi and iGlar arms for both age subgroups at baseline, but tended to be higher in participants aged younger than 65 years (16.17 and 17.73 U, respectively) than in those aged 65 years or older (13.13 and 16.61 U, respectively) at week 26 (LOCF).

In the iGlarLixi arm, a lower proportion of older versus younger participants had residual hyperglycaemia at 26 weeks (LOCF), with 9.0% of those aged younger than 65 years and 6.5% of those aged 65 years or older having residual hyperglycaemia at 26 weeks (Table 2). By contrast, residual hyperglycaemia at 26 weeks was more common among older participants in the iGlar arm, occurring in 16.8% of participants aged younger than 65 years versus 24.2% of those aged 65 years or older (Table 2). The proportion of participants in the both at target category at 26 weeks was greater in those aged 65 years or older versus those aged younger than 65 years in both the iGlarLixi (57.6% vs. 47.0%) and iGlar (41.4% vs. 25.5%) treatment arms, and was significantly higher for iGlarLixi than iGlar in both the younger ($P < .0001$) and older ($P = .0257$) age categories. Regardless of age group, the proportion of participants in the hyperglycaemia category at 26 weeks (LOCF) was smaller in the iGlarLixi arm than in the iGlar arm; the risk difference between the two treatment arms was greater in those aged younger than 65 years (−31.0%) than in those aged 65 years or older (−7.6%).

The incidence of documented symptomatic hypoglycaemia (plasma glucose ≤ 70 mg/L) was similar across age subgroups, occurring in 22 participants (13.1%) in the iGlarLixi arm and 19 (11.8%) in the iGlar arm among participants aged younger than 65 years, and in 15 (16.3%) and 13 (13.0%) participants, respectively, among those aged 65 years or older.

3.2.2 | By DPP4i use at screening

The number of participants in the DPP4i+ subgroup was 263 (51%; 131 in the iGlarLixi arm and 132 in the iGlar arm). The mean daily iGlar dose was 5.00 U in both the iGlarLixi and iGlar arms for both DPP4i subgroups at baseline, increasing to 14.86 and 17.67 U, respectively, in the DPP4i+ subgroup and 15.33 and 16.91 U, respectively, in the DPP4i− subgroup at week 26 (LOCF). The increase in mean daily iGlar dose was significantly lower in the iGlarLixi arm than the iGlar arm in both the DPP4i+ (least squares mean difference vs. iGlar, −2.81 U; $P < .0001$) and DPP4i− (−1.58 U; $P = .0064$) subgroups.

In the subgroup analysis by DPP4i use at screening, improvements in glycaemic control over 26 weeks favoured iGlarLixi over iGlar, and were better in the DPP4i− versus the DPP4i+ subgroup (Figure 3). Thus, the most favourable changes in glycaemic control profile were observed in participants in the DPP4i− subgroup of the iGlarLixi arm (Figure 3B, left panel), and the least favourable changes were seen for participants in the DPP4i+ subgroup of the iGlar arm (Figure 3A, right panel).

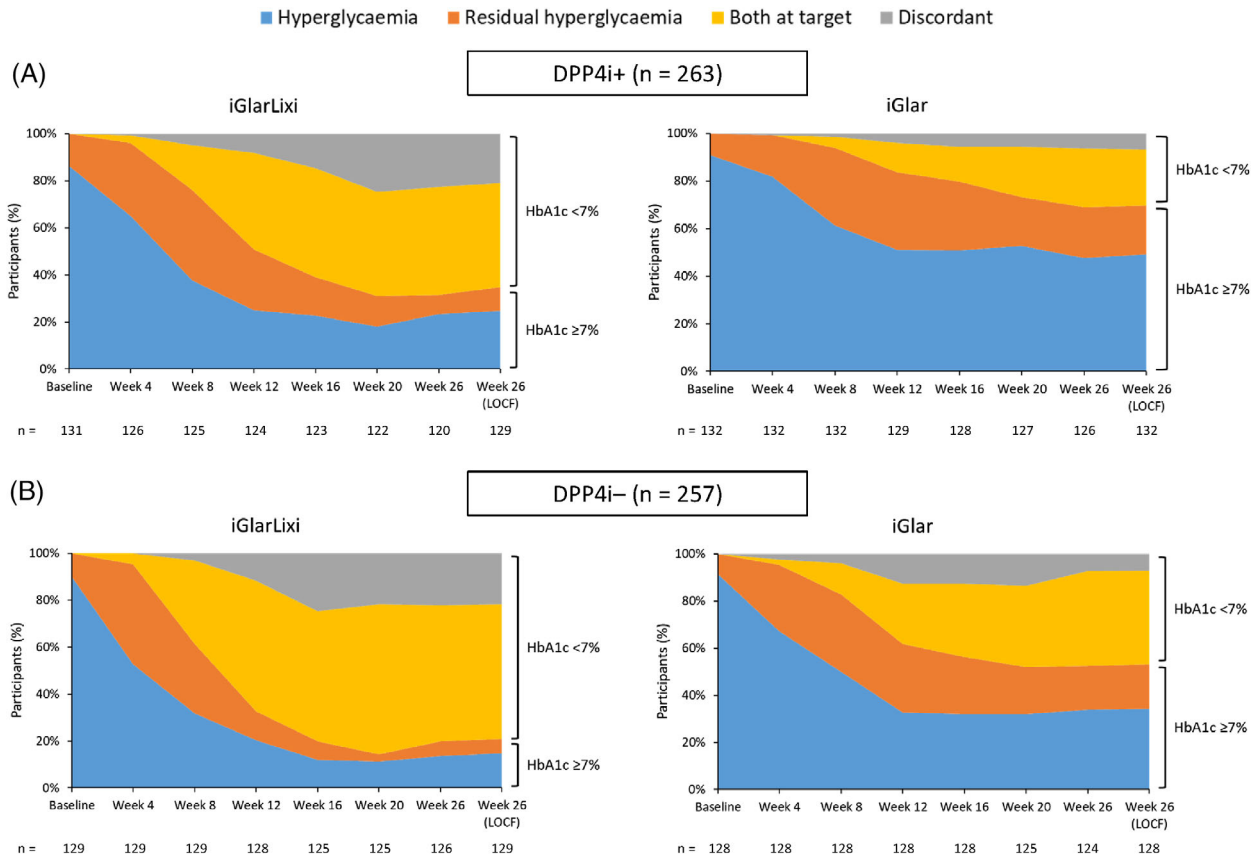

FIGURE 3 Evolution of glycaemic control over time for A, Participants who were taking a DPP4i at screening (DPP4i+), and B, Participants who were not taking a DPP4i at screening (DPP4i−). DPP4i, dipeptidyl peptidase-4 inhibitor; iGlar, insulin glargine; iGlarLixi, fixed-ratio combination of insulin glargine and lixisenatide; LOCF, last observation carried forward

The proportion of participants in the DPP4i+ subgroup who had residual hyperglycaemia at 26 weeks (LOCF) was 10.1% in the iGlarLixi arm versus 20.5% in the iGlar arm (Table 2; $P = .0202$); the corresponding proportions in the DPP4i− subgroup were 6.2% and 18.8%, respectively ($P = .0024$). In the iGlarLixi arm, the absolute reduction between baseline and 26 weeks (LOCF) in the proportion of participants with residual hyperglycaemia was not affected by DPP4i use at screening (difference −3.6% for DPPi+ vs. −3.9% for DPPi−). Similarly, the proportion of participants with residual hyperglycaemia in the iGlar arm did not appear to be affected by DPP4i use at screening, with an absolute increase observed between baseline and 26 weeks (LOCF) in both the DPP4i− and DPP4i+ subgroups (difference +10.2% vs. +11.4%).

Achievement of both HbA1c and FPG targets at 26 weeks (LOCF) was significantly more probable with iGlarLixi than iGlar in both the DPP4i+ (44.2% vs. 23.5%; $P = .0004$) and DPP4i− (57.4% vs. 39.8%; $P = .005$) subgroups. Consistent with this, significantly greater proportions of participants in the iGlar versus the iGlarLixi arm were in the hyperglycaemia category at 26 weeks (LOCF), in both the DPP4i+ (49.2% vs. 24.8%; $P < .0001$) and DPP4i− (34.4% vs. 14.7%; $P = .0003$) subgroups.

A similar incidence of symptomatic hypoglycaemia (plasma glucose ≤ 70 mg/L) was documented in each DPP4i subgroup, occurring in 19 participants (14.5%) in the iGlarLixi arm and 18 participants (13.5%) in the iGlar arm in the DPP4i+ subgroup, and in 18 (14.0%) and 14 participants (10.9%), respectively, in the DPP4i− subgroup.

4 | DISCUSSION

We performed a post hoc analysis of data from the phase 3 JP-O2 trial to compare the effects of iGlarLixi and iGlar on residual hyperglycaemia in 520 Japanese people whose T2D was uncontrolled despite OAD therapy and who had not previously received insulin. In addition to the main analysis, we performed subgroup analyses to investigate whether our findings were different in subgroups defined by age (using a cut-off of 65 years) or DPP4i use at screening.

In the main analysis, the proportion of participants with residual hyperglycaemia decreased from 11.9% at baseline to 8.1% at 26 weeks (LOCF) among those receiving iGlarLixi, and increased from 8.8% to 19.6% in those receiving iGlar over the same period. Residual hyperglycaemia is indicative of suboptimal PPG control, so our results suggest that—consistent with their pharmacology—iGlarLixi attenuates PPG excursions more effectively than iGlar. This is probably the main explanation for the greater achievement of HbA1c less than 7% among participants in the iGlarLixi versus the iGlar arm in the JP-O2 trial (71.5% vs. 38.5%; $P < .0001$).[11]

The same pattern of change in residual hyperglycaemia (i.e. a decrease with iGlarLixi and an increase with iGlar) was observed in all of the subgroups that we studied. Interestingly, the treatment received had less impact on residual hyperglycaemia rates in participants aged 65 years or younger than in those aged 65 years or older, despite the tendency for slightly higher daily iGlar doses in younger versus older participants. This suggests that the relative contribution of PPG to residual hyperglycaemia may be higher in people aged 65 years or older than in younger people, as baseline HbA1c was comparable between age subgroups.[14] This effect may be attributable to the age-related decline in skeletal muscle mass, because muscle tissue is responsible for the majority of glucose disposal following meals, leading to an increase in postprandial residual hyperglycaemia.[15] Moreover, in Japan, HbA1c target values for people with T2D aged 65 years or older are individually determined for each patient based on treatment, severity of their cognitive and functional impairment, and other co-morbidities, and these targets are often higher than 7.0%.[1,16] Thus, it would be interesting to compare different age-specific glycaemic targets to redefine residual hyperglycaemia.

A consistent observation in both the main analysis and the subgroup analyses was that residual hyperglycaemia increased in the first 12 weeks of the trial, regardless of assigned treatment. This is to be expected, because the changes in blood glucose preceded changes in HbA1c by several weeks. At the beginning of the trial, most participants were in the hyperglycaemia category; the subsequent intensification of treatment with either basal insulin or basal insulin plus lixisenatide would quickly lower FPG, but this would not immediately translate into a reduction in HbA1c. Thus, an increase in the proportion of participants with residual hyperglycaemia would be expected. Further, at week 26, an increase in residual hyperglycaemia was seen with iGlar. After the initiation of either iGlar or iGlarLixi, the most immediate effect is the normalization of FBG levels, which in the face of persistent postprandial hyperglycaemia, increases the proportion of participants with residual hyperglycaemia. However, the proportion of participants with residual hyperglycaemia decreases as the postprandial effects of Lixi become apparent with iGlarLixi, whereas with iGlar, the persistent effect of therapy on FBG level without a direct effect on PPG leads to an apparent increase in the proportion of patients with residual hyperglycaemia. In addition, body weight gain in the iGlar group was consistently greater than in the iGlarLixi group (1.33 vs. 0.26 kg).[11] Increased body weight could worsen insulin resistance and therefore increase PPG levels.[16]

The results of the JP-O2 trial are similar to those of the JP-L trial,[7,10] although the magnitude of the iGlarLixi-associated decrease in residual hyperglycaemia was greater in the JP-L than in the JP-O2 trial, perhaps reflecting the higher proportion of participants with residual hyperglycaemia at baseline in the JP-L trial.[7] Taken together, these data suggest that treatment intensification with iGlarLixi is probable to achieve better glycaemic control, with less residual hyperglycaemia, than iGlar alone in Japanese people with treated, but uncontrolled, T2D. This benefit appears to be independent of the previous use of basal insulin.

An important question, however, is how impactful intensification with iGlarLixi is in people with T2D whose existing OAD regimen already targets PPG via the inclusion of a DPP4i. This is particularly important in the Japanese T2D population, because of differences in T2D pathophysiology between East Asian and Caucasian populations. The pathophysiology of T2D in East Asian people is characterized primarily by impaired insulin secretion, because of pancreatic beta-cell secretory dysfunction and decline,[17-19] in contrast to Caucasian populations, where T2D is caused by insulin resistance. Controlling PPG is often a clinical imperative in the management of T2D in East Asian populations, and this is reflected in the greater use of DPP4is in Japan compared with Western countries.[20-22] Approximately half of the participants in JP-O2 were taking a DPP4i at screening; despite this, 13.7% had residual hyperglycaemia, and the reduction in residual hyperglycaemia with iGlarLixi was similar irrespective of prior DPP4i use. In addition, the protocol-mandated discontinuation of DPP4i at randomization did not appear to affect glycaemic control during the early weeks of the trial.

There are several limitations of the current study that should be acknowledged. First, the JP-O2 trial was powered to detect differences between treatments in terms of change in HbA1c, rather than in the proportions of participants with residual hyperglycaemia. For these reasons, *P* values should be considered nominal. Second, because this was an open-label study (as a result of differences in study drug administration devices), the possible influence of investigator bias cannot be discounted. In addition, the JP-O2 trial had a comparatively short treatment duration of 26 weeks and the proportion of participants with residual hyperglycaemia was comparatively low. Therefore, our findings cannot be extended beyond this; longer term studies would be needed to confirm the durability of the treatment effects we observed. Furthermore, our data do not necessarily reflect outcomes in everyday clinical practice, which can only be confirmed through real-world observational research.

In conclusion, we found that iGlarLixi, when added to OAD therapy in Japanese people with uncontrolled T2D, reduced the proportion of participants with residual hyperglycaemia over 26 weeks. This finding was confirmed in subgroups defined by age (using a cut-off of 65 years) or by the use of DPP4i at screening. By contrast, treatment with iGlar was associated with an increase in residual hyperglycaemia over 26 weeks. Residual hyperglycaemia is probable to be increasingly recognized in clinical practice, because of the growing use of continuous glucose monitoring. We conclude that iGlarLixi is an effective strategy for reducing residual hyperglycaemia in Japanese people receiving OAD therapy, including DPP4is.

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CONFLICT OF INTEREST

K.I. has received consulting or speaker fees from Eli Lilly Japan, Merck Sharp & Dohme (MSD), Novo Nordisk Pharma, Nippon Boehringer

Ingelheim, and Taisho Pharmaceutical. M.B. is a previous employee of Sanofi. D.W. is an employee of Sanofi. D.Y. has received consulting or speaker fees from Astellas Pharma Inc., Eli Lilly Japan, MSD, Novo Nordisk Pharma, Nippon Boehringer Ingelheim, Ono Pharmaceutical, Sumitomo Dainippon Pharma, and Takeda Pharmaceutical; and has received clinically commissioned/joint research grants from Ono Pharmaceutical, Novo Nordisk Pharma, Taisho Pharmaceutical, Arklay, and Terumo.

AUTHOR CONTRIBUTIONS

K.I. and D.Y. contributed to study design and analysis, collection, data interpretation and writing of the manuscript, and are the two guarantors of this work. M.B. contributed to the preparation of the initial scoping brief and review of all subsequent drafts of the manuscript, and contributed to construction of the scientific rationale, the design of the paper, and development of the drafts. D.W. contributed to study design, analysis, and writing of the manuscript.

PEER REVIEW

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DATA AVAILABILITY STATEMENT

Qualified researchers can request access to patient-level data and related study documents including the clinical study report, study protocol with any amendments, blank case report forms, statistical analysis plan, and dataset specifications. Patient-level data will be anonymized, and study documents will be redacted to protect the privacy of trial participants. Further details on Sanofis data-sharing criteria, eligible studies, and process for requesting access are at: https://www.clinicalstudydatarequest.com.

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