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ORIGINAL ARTICLE

iGlarLixi reduces residual hyperglycemia in Japanese patients with type 2 diabetes uncontrolled on basal insulin: A *post-hoc* analysis of the LixiLan JP-L trial

Daisuke Yabe[1,2,3]*, Katsumi Iizuka[1,4], Mike Baxter[5,6], Daisuke Watanabe[7], Hideaki Kaneto[8]

[1]Department of Diabetes, Endocrinology and Metabolism, Gifu University Graduate School of Medicine, Gifu, Japan, [2]Yutaka Seino Distinguished Center for Diabetes Research, Kansai Electric Power Medical Research Institute, Kobe, Japan, [3]Division of Molecular and Metabolic Medicine, Kobe University Graduate School of Medicine, Kobe, Japan, [4]Center for Nutritional Support and Infection Control, Gifu University Hospital, Gifu, Japan, [5]Medical Affairs, Sanofi, Reading, UK, [6]Department of Diabetes and Endocrinology, University of Swansea, Swansea, UK, [7]Research & Development, Sanofi K.K., Tokyo, Japan, and [8]Division of Diabetes, Metabolism and Endocrinology, Kawasaki Medical School, Kurashiki, Japan

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***Correspondence**
Daisuke Yabe
Tel.: +81-58-230-6371
Fax: +81-58-230-6376
E-mail address:
ydaisuke-kyoto@umin.ac.jp

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ABSTRACT

Introduction: Treatments for type 2 diabetes targeting baseline glucose levels but not postprandial glucose can result in normalized fasting blood glucose but suboptimal overall glycemic control (high glycated hemoglobin): residual hyperglycemia. In Japanese patients with type 2 diabetes the predominant pathophysiology is a lower insulin secretory capacity, and residual hyperglycemia is common with basal insulin treatment. Single-injection, fixed-ratio combinations of glucagon-like peptide-1 receptor agonists and basal insulin have been developed. iGlarLixi (insulin glargine 100 units/mL [iGlar]: lixisenatide ratio of 1 unit:1 μg) is for specific use in Japan. *Post-hoc* analysis of the LixiLan JP-L trial (NCT02752412) compared the effect of iGlarLixi with iGlar on this specific subpopulation with residual hyperglycemia.

Materials and Methods: Outcomes at week 26 (based on the last observation carried forward) were assessed in patients in the modified intent-to-treat population with baseline residual hyperglycemia.

Results: Overall, 83 (32.5%) patients in the iGlarLixi group and 79 (30.7%) patients in the iGlar group had baseline residual hyperglycemia. The proportion of patients with residual hyperglycemia at week 26 decreased to 15.7% in the iGlarLixi group, and increased to 36.9% in the iGlar group. Patients in the iGlarLixi group had significantly greater reductions in glycated hemoglobin compared with the iGlar group (–0.72% difference between groups; $P < 0.0001$).

Conclusions: New data from this *post-hoc* analysis of the JP-L trial show that treatment with the fixed-ratio combination iGlarLixi reduced the proportion of Japanese patients with residual hyperglycemia from baseline to week 26 and significantly reduced glycated hemoglobin vs similar doses of iGlar alone.

INTRODUCTION

Overall glycemic control in patients with type 2 diabetes is currently evaluated based on a glycated hemoglobin (HbA1c) target[1]. HbA1c reflects the dynamics of both fasting plasma glucose (FPG) and postprandial plasma glucose (PPG) and, as such, acts as an index of overall glycemic load. The widely adopted use of basal insulin in the treatment of type 2 diabetes is based on the titration of the basal insulin dose to achieve a target FPG[1,2]. The control of FPG may be sufficient to achieve a level of overall glycemic control that delivers an optimal HbA1c in a significant number of patients[3]. However, PPG continues to contribute to the overall glycemic load in many patients, and this can manifest as a failure to achieve target HbA1c despite having achieved FPG control. In many patients

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with type 2 diabetes, adequate control of PPG is essential for achieving the recommended HbA1c goals[4].

It is well recognized that as HbA1c levels approach 7% there is an increase in the relative contribution of PPG to HbA1c[4–6]. This dynamic means that many patients on basal insulin fail to achieve HbA1c <7% as a consequence of persistent postprandial hyperglycemia, despite achieving FPG control. This has been described as residual hyperglycemia, and is defined as HbA1c ≥7% with FPG <130 mg/dL for Asian and Latin American countries (according to regional specifications) or <140 mg/dL for the rest of the world[7–9].

An analysis combining data from randomized controlled clinical trials, clinical trial registries, and medical records across the world found that substantial proportions of patients with type 2 diabetes treated with basal insulin had residual hyperglycemia (28–36%)[9]. The relative importance of PPG appears to differ between patient groups and may be dependent on the pathophysiology of the disease. PPG control has particular significance in East Asians with type 2 diabetes because of the prominence of β-cell dysfunction and reduced insulin secretion compared with Caucasians, who are characterized by increased insulin resistance and obesity[10,11]. A study using continuous glucose monitoring in drug-naive Japanese patients with type 2 diabetes demonstrated a positive correlation between HbA1c values and the range of postprandial increases after breakfast and dinner; furthermore, peak PPG levels were higher in patients with a 'high' median HbA1c (8.8%) than in patients with a 'low' median HbA1c (6.8%)[12].

The importance of PPG as a therapeutic target is well recognized in Japan; dipeptidyl peptidase-4 (DPP-4) inhibitors are the most frequently prescribed oral anti-diabetes drugs (OAD)[13,14] and the first-line drug of choice[13,15,16]. In Japan, 44–57% of patients with type 2 diabetes are on DPP-4 inhibitors while only 11–17% are on biguanides[13,16]. This is in marked contrast to the UK, Europe, and the USA, where guidance and clinical practice identify the biguanide metformin as the initial OAD of choice, often initiated at the point of diagnosis[1,17].

East Asians, including the Japanese, seem to be very sensitive to incretin therapies, e.g., DPP-4 inhibitors[18], possibly due to the unique pathophysiology of East Asians' type 2 diabetes primarily characterized by impaired β-cell function rather than insulin resistance[11,19]. However, treatment with DPP-4 inhibitors is insufficient for some patients to achieve or maintain glycemic control[20,21]. These patients may require treatment escalation, which has been traditionally either monotherapy with basal insulin or a glucagon-like peptide-1 receptor agonist (GLP-1 RA). However, real-world evidence suggests that these agents alone are relatively ineffective at bringing patients to target, with only 38% of patients on basal insulin and 21% patients on a GLP-1 RA achieving HbA1c <7% within 1 year[22,23].

Recent guidance (American Diabetes Association/European Association for the Study of Diabetes) has suggested that the combination of insulin and a GLP-1 RA should be considered as initial therapy in patients with HbA1c >10 or 2% above target, or in patients not achieving target with a single injectable agent[1].

A fixed-ratio combination (FRC) of a GLP-1 RA with basal insulin has been gaining much attention recently. FRC offers an incretin-based intervention to enhance insulin secretion and to lower PPG levels, combined with insulin that primarily reduces FPG. In Japan, IDegLira, a formula of an insulin degludec:liraglutide ratio of 1 unit (U) insulin degludec and 0.036 mg liraglutide, which is the same ratio as that approved in the USA and EU[24,25], is available. However, optimal basal insulin doses for Japanese patients with type 2 diabetes may be lower than those for Caucasians[11]. Therefore, an FRC of insulin glargine 100 U/mL (iGlar) and lixisenatide (Lixi) has been developed in Japan at a unique ratio of 1 U:1 μg (20 μg Lixi with 20 U iGlar 100 U/mL) to allow effective GLP-1 RA dosing with basal insulin doses appropriate for Japanese patients with type 2 diabetes.

In phase 3 trials in Japanese patients with type 2 diabetes, iGlarLixi with a ratio of 1 U iGlar:1 μg Lixi demonstrated significantly greater reductions in HbA1c than those observed with either Lixi (LixiLan JP-O1 trial)[26] or iGlar (LixiLan JP-O2 and JP-L trials)[27,28]. As treatment with a GLP-1 RA can improve postprandial hyperglycemia and thereby residual hyperglycemia and HbA1c, this *post-hoc* analysis of the LixiLan JP-L trial adds to the findings of the original study by comparing the effect of iGlarLixi with iGlar on the specific subpopulation of Japanese patients with type 2 diabetes who experienced residual hyperglycemia.

METHODS

LixiLan JP-L trial design and *post-hoc* analysis

The design of LixiLan JP-L (NCT02752412), a randomized, open-label, multicenter trial of iGlarLixi vs iGlar in Japanese patients with type 2 diabetes uncontrolled on basal insulin and OADs, has been described previously[27]. In summary, Japanese adult patients who had been diagnosed with type 2 diabetes for >1 year and had HbA1c ≥7.5% and ≤9.5% despite using basal insulin and one or two OADs entered an initial 12-week run-in period where all OADs except metformin were discontinued, metformin therapy was initiated if not already being administered, and existing treatment with basal insulin was continued or switched to iGlar and optimized to reach fasting self-monitored plasma glucose (SMPG) levels ≤160 mg/dL. At the end of the run-in period, patients with average doses of iGlar 5–14 U/day, metformin ≥750 mg/day, and no signs of pancreatic disease were randomly assigned to iGlarLixi or iGlar for a 26-week treatment period. iGlarLixi was administered before breakfast. iGlar was administered before breakfast or at bedtime (at about the same time every day), in line with the summary of product characteristics[29] for iGlar, and as part of the agreed protocol for the main study on which the *post-hoc* analysis was based. The study was approved by the appropriate institutional

review board at each study center and was carried out in accordance with the Declaration of Helsinki and Good Clinical Practice. Written informed consent was provided in advance by all participants.

This *post-hoc* analysis assessed outcomes at week 26 in patients with residual hyperglycemia at baseline, including the variables of weight, HbA1c, FPG, 2-h PPG (during a standardized meal test), change in 7-point SMPG, and the daily dose of iGlar. PPG and plasma glucose excursions were assessed during a standardized meal test. Glycemic control categories were adapted from Raccah *et al.*[30]: hyperglycemia: HbA1c ≥7% and FPG ≥130 mg/dL; residual hyperglycemia: HbA1c ≥7% and FPG <130 mg/dL; and HbA1c at target: HbA1c <7% and FPG <130 mg/dL or ≥130 mg/dL. The proportion of patients in each glycemic category (hyperglycemia, residual hyperglycemia, and HbA1c at target) at baseline and other time points throughout the treatment period was assessed for each treatment arm.

Statistical methods

All statistical tests were performed for descriptive purposes only; *P* values were without multiplicity adjustment and should be considered nominal. *Post-hoc* analyses were based upon the modified intent-to-treat (mITT) population, defined as all randomized patients who received at least one dose of study treatment and had both a baseline assessment and at least one post-baseline assessment of any primary or secondary efficacy variables. Week 26 data were based on the last available post-baseline measurements (last observation carried forward [LOCF]). The least squares (LS) mean difference between the groups and corresponding standard error (SE) and 95% confidence interval (CI) for the efficacy variables were estimated using analysis of covariance with treatment groups, randomization strata of HbA1c (<8 and ≥8%) at the end of the run-in period and randomization strata of metformin use at screening as fixed effects, and baseline value as a covariate. Documented symptomatic hypoglycemia (plasma glucose <70 mg/dL) was compared between the groups using the Cochran–Mantel–Haenszel method stratified by randomization strata of HbA1c (<8 and ≥8%) at the end of the run-in period and randomization strata of metformin use at screening.

RESULTS

Patient disposition and baseline characteristics

All randomized patients qualified for the mITT population. Of the 255 patients randomized to iGlarLixi and the 257 randomized to iGlar (the overall study populations), similar proportions in the two treatment groups had residual hyperglycemia at baseline (iGlarLixi, *n* = 83 [32.5%] and iGlar, *n* = 79 [30.7%]) (Figure 1). Among patients with baseline residual hyperglycemia, baseline characteristics between the treatment groups were similar with the exception of metformin use at screening, which was higher in the iGlarLixi group than in the iGlar group (83.1 vs 70.9%) (Table 1). The body mass index (BMI; kg/m^2) of patients with residual hyperglycemia was numerically lower than that of patients in the overall study population (mean [standard deviation]; 23.49 [3.47] vs 25.32 [4.18] for iGlarLixi; 23.78 [4.13] vs 24.88 [3.85] for iGlar).

Residual hyperglycemia over 26 weeks

In the overall study population, the proportion of patients with residual hyperglycemia at week 26 (LOCF) decreased to 15.7% in the iGlarLixi group and increased to 36.9% in the iGlar group, while the proportion of patients with hyperglycemia decreased to 32.3% and 47.1%, respectively (Figure 1). The proportion of patients with HbA1c at target increased from 0.0% in both groups at baseline to 52.0 and 16.1%, respectively, at week 26 (LOCF). In the iGlarLixi group, there was a decrease after week 8 of treatment, and the proportion appeared to be stable from week 20 (Figure 2). In the iGlar group, the proportion increased at week 8 and remained higher than in the iGlarLixi group through to the end of treatment (Figure 2). Of the original 83 patients in the iGlarLixi group who had residual hyperglycemia at baseline, 15 (18.1%) had residual hyperglycemia at week 26 (LOCF); of the 79 patients in the iGlar group, 42 (53.2%) still had residual hyperglycemia at week 26 (LOCF) (Table 2).

Weight, glycemic parameters, and insulin dose over 26 weeks in patients with residual hyperglycemia at baseline

At week 26, iGlarLixi treatment in patients with residual hyperglycemia resulted in significantly greater reductions in HbA1c, body weight, and 2-h PPG when compared with iGlar treatment (Table 3). The HbA1c change (SD) was –1.17% (0.87%) and –0.44% (0.73%) in the iGlarLixi and iGlar arms, respectively (LS mean difference [SE] –0.72% [0.128]; $P < 0.0001$). The mean change (SD) in body weight among patients taking iGlarLixi was −0.40 (2.17) kg vs an increase of 0.57 (1.69) kg in those taking iGlar (LS mean difference [SE] –0.97 [0.317] kg; $P = 0.0025$). The mean (SD) 2-h PPG changes were −111.19 (71.34) mg/dL among patients taking iGlarLixi and −23.54 (55.32) mg/dL among patients taking iGlar (LS mean difference [SE] −90.65 (9.110) mg/dL; $P < 0.0001$).

The FPG increased in both treatment groups. Although the increase was higher in the iGlarLixi group, the difference between the groups was not statistically significant (Table 3). The mean (SD) FPG at baseline increased by 14.93 (41.92) mg/dL to 122.96 (38.74) mg/dL at week 26 (LOCF) for patients who received iGlarLixi, and by 6.35 (30.46) mg/dL to 115.67 (28.12) mg/dL at week 26 (LOCF) for patients who received iGlar (LS mean difference for change [SE] 7.33 [5.485] mg/dL; $P = 0.1834$). iGlarLixi demonstrated lower mean values than iGlar for 7-point SMPG profiles across all time points except pre-breakfast (Figure S1).

There was no significant difference between the iGlarLixi and iGlar groups in the change of average daily dose of insulin from baseline to week 26 (LS mean difference [SE] −0.51 [0.565]; $P = 0.3640$).

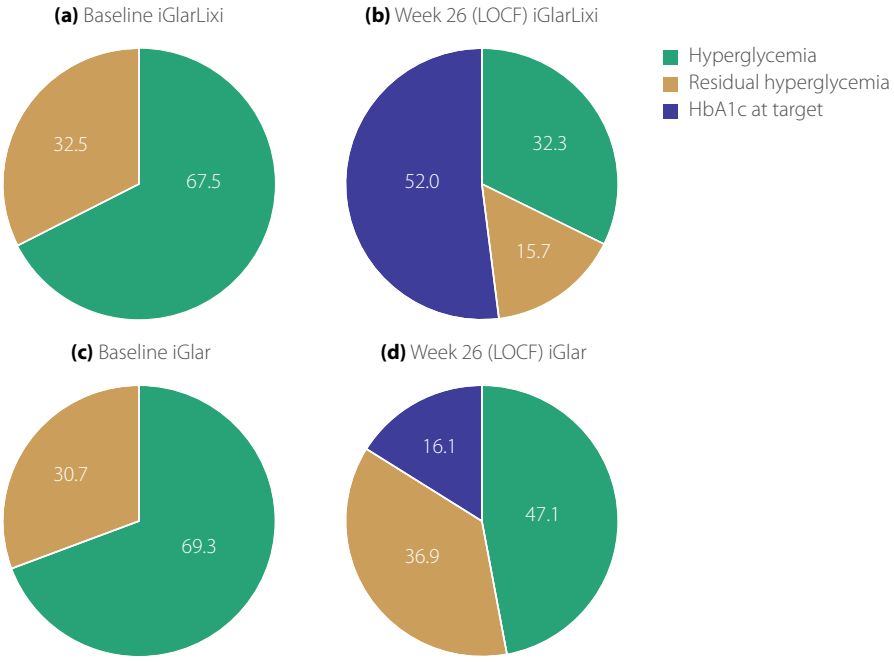


Figure 1 | Proportion of patients in each glycemic category at baseline and week 26 among patients treated with (a) and (b) fixed-ratio combination of insulin glargine and lixisenatide (iGlarLixi) or (c) and (d) insulin glargine 100 U/mL (iGlar). Data are the proportions of all patients in the modified intent-to-treat population in the overall study population. Week 26 data are based on last observation carried forward (LOCF). Hyperglycemia is defined as glycated hemoglobin (HbA1c) ≥7% and fasting plasma glucose (FPG) ≥130 mg/dL; residual hyperglycemia is defined as HbA1c ≥7% and FPG <130 mg/dL; and HbA1c at target is defined as HbA1c <7% and FPG <130 mg/dL or ≥130 mg/dL.

Table 1 | Baseline demographics and disease characteristics of patients with residual hyperglycemia at baseline

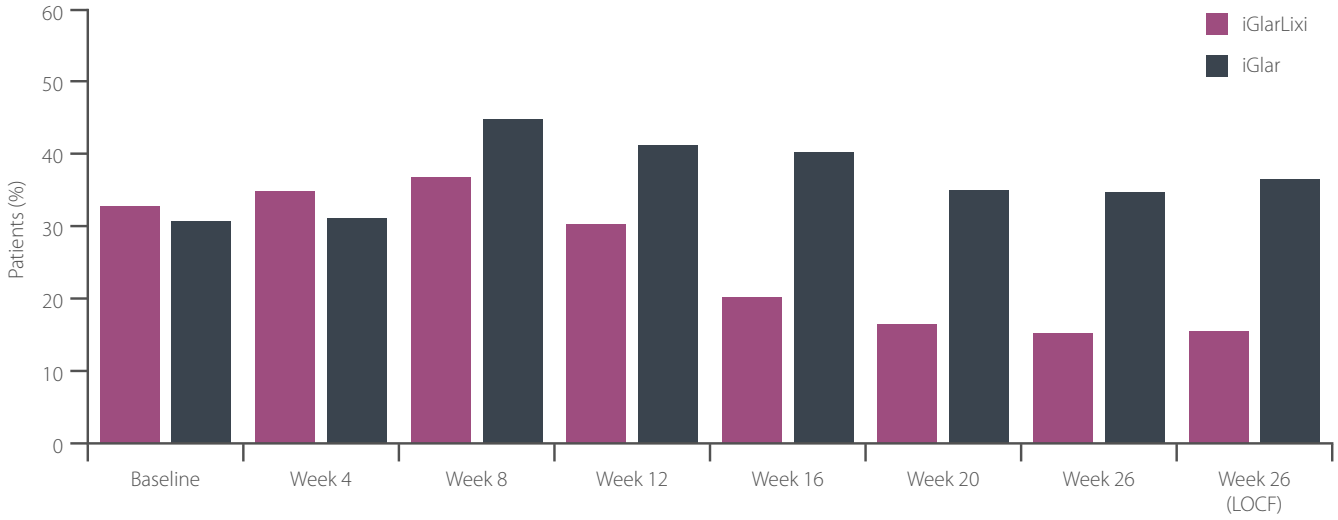
Characteristic	iGlarLixi (n = 83)	iGlar (n = 79)
Age, years	60.4 (9.9)	59.9 (10.9)
Duration of diabetes, years	12.70 (8.21)	12.93 (7.47)
Body weight, kg	61.65 (12.05)	63.39 (15.03)
BMI, kg/m^2	23.49 (3.47)	23.78 (4.13)
HbA1c, %	8.22 (0.53)	8.20 (0.48)
FPG, mg/dL	108.11 (14.90)	109.32 (14.93)
2-h PPG, mg/dL	254.27 (53.34)	260.63 (62.37)
Duration of diabetes, years	12.70 (8.21)	12.93 (7.47)
Duration of prior basal insulin treatment, years	2.44 (1.77)	2.87 (2.92)
Average daily dose of iGlar, U[†]	11.73 (2.80)	11.20 (3.15)
OAD use at screening, n (%)		
Metformin	69 (83.1)	56 (70.9)
Other[‡]	46 (55.4)	44 (55.7)

Data are mean (standard deviation) at baseline for the modified intent-to-treat population, unless otherwise stated. [†]Averaged daily dose for the 3 days before randomization. [‡]Other classes were as follows: alpha-glucosidase inhibitor, sodium glucose co-transporter 2 inhibitor, sulfonylurea, glinide, and dipeptidyl peptidase-4 inhibitor. BMI, body mass index; FPG, fasting plasma glucose; HbA1c, glycated hemoglobin; iGlar, insulin glargine 100 U/mL; iGlarLixi, fixed-ratio combination of insulin glargine and lixisenatide; OAD, oral antidiabetic drug; PPG, postprandial plasma glucose.

No significant differences were seen in the proportion of patients experiencing documented symptomatic hypoglycemia, defined as a plasma glucose of <70 mg/dL (22.9% and 25.3% of patients in the iGlarLixi and iGlar arms, respectively).

DISCUSSION

This *post-hoc* analysis of the LixiLan JP-L trial demonstrated that following a run-in period of 12 weeks, when the insulin dose was titrated to a target SMPG level of 160 mg/dL,



Number	255	257	253	254	250	251	247	244	246	239	245	234	241	229	254	255
n (%)	83 (32.5)	79 (30.7)	88 (34.8)	80 (31.5)	92 (36.8)	115 (45.8)	75 (30.4)	106 (43.4)	50 (20.3)	103 (43.1)	40 (16.3)	90 (38.5)	37 (15.4)	89 (38.9)	40 (15.7)	94 (36.9)
Difference	1.81%		3.29%		−9.02%		−13.08%		−22.77%		−22.14%		−23.51%		−21.11%	
95% CI	−6.25, 9.87		−4.90, 11.48		−17.60, −0.43		−21.54, −4.62		−30.81, −14.73		−29.90, −14.37		−31.29, −15.73		−28.54, −13.69	

Figure 2 | Proportion of patients with residual hyperglycemia over time. CI, confidence interval; iGlar, insulin glargine; iGlarLixi, fixed-ratio combination of insulin glargine and lixisenatide; LOCF, last observation carried forward.

Table 2 | Status of patients by glycemic control categories at week 26 (LOCF) according to baseline category

Status	iGlarLixi (*n* = 255)	iGlar (*n* = 257)
Baseline hyperglycemia, *n* (%)	172 (67.5)	178 (69.3)
Of whom status at week 26 (LOCF), *n* (%)		
Hyperglycemia	60 (34.9)	99 (55.6)
Residual hyperglycemia	25 (14.5)	52 (29.2)
HbA1c at target	87 (50.6)	25 (14.1)
Missing	0	2 (1.1)
Baseline residual hyperglycemia, *n* (%)	83 (32.5)	79 (30.7)
Of whom status at week 26 (LOCF), *n* (%)		
Hyperglycemia	22 (26.5)	21 (26.6)
Residual hyperglycemia	15 (18.1)	42 (53.2)
HbA1c at target	45 (54.2)	16 (20.3)
Missing	1 (1.2)	0

Data are from the modified intent-to-treat population. HbA1c, glycated hemoglobin; iGlar, insulin glargine 100 U/mL; iGlarLixi, fixed-ratio combination of insulin glargine and lixisenatide; LOCF, last observation carried forward.

approximately one-third of patients had baseline residual hyperglycemia. At week 26 (LOCF), treatment with iGlarLixi reduced this proportion of patients by more than half to 15.7%, whereas the proportion of patients with residual hyperglycemia in the iGlar group increased to 36.9%. The iGlarLixi treatment resulted in a higher proportion of patients with residual hyperglycemia at baseline attaining HbA1c <7% at week 26 when compared with iGlar treatment, with greater mean reductions in HbA1c. These findings add to the data from the LixiLan JP-L trial and increase our understanding of the treatment of Japanese patients with type 2 diabetes who experience residual hyperglycemia. In the iGlar group, the proportion of patients with residual hyperglycemia increased at week 8 and remained higher than in the iGlarLixi group through to the end of treatment (Figure 2); this suggests that the lack of effect on PPG with continued effects on basal glucose results in an increased

Table 3 | Changes in weight, glucose parameters, and insulin dose from baseline to week 26 in patients with residual hyperglycemia at baseline

Parameter	iGlarLixi (n = 83)	iGlar (n = 79)	LS mean difference (SE) (95% CI) P-value
Body weight (kg, mean [SD])			
Baseline	61.61 (12.11)	63.39 (15.03)	
Week 26 (LOCF)	61.21 (12.47)	63.96 (15.28)	
Change	−0.40 (2.17)	0.57 (1.69)	−0.97 (0.317) (−1.600, −0.347) P = 0.0025
HbA1c (%, mean [SD])			
Baseline	8.22 (0.53)	8.20 (0.48)	
Week 26 (LOCF)	7.05 (0.87)	7.75 (0.84)	
Change	−1.17 (0.87)	−0.44 (0.73)	−0.72 (0.128) (−0.967, −0.463) P < 0.0001
FPG (mg/dL, mean [SD])[†]			
Baseline	108.04 (14.98)	109.32 (14.93)	
Week 26 (LOCF)	122.96 (38.74)	115.67 (28.12)	
Change	14.93 (41.92)	6.35 (30.46)	7.33 (5.485) (−3.504, 18.164) P = 0.1834
2-h PPG (mg/dL, mean [SD])[‡]			
Baseline	252.80 (51.16)	256.86 (61.85)	
Week 26 (LOCF)	141.61 (55.92)	233.32 (61.55)	
Change	−111.19 (71.34)	−23.54 (55.32)	−90.65 (9.110) (−108.654, −72.646) P < 0.0001
Average daily dose of iGlar (U, mean [SD])			
Baseline	11.73 (2.80)	11.20 (3.15)	
Week 26 (LOCF)	15.59 (4.03)	15.67 (4.49)	
Change	3.85 (3.88)	4.47 (3.08)	−0.51 (0.565) (−1.629, 0.601) P = 0.3640
Patients with documented symptomatic hypoglycemia[§] (≤70 mg/dL), n (%)	19 (22.9)	20 (25.3)	Proportional difference (95% CI): −4.68% (−18.31, 8.95) P = 0.4995

Data are from the modified intent-to-treat population. The difference is calculated as values for iGlarLixi minus values for iGlar. Patients with both baseline and week 26 (LOCF) measurements are included in the analysis. [†]n = 82 patients in the iGlarLixi group. [‡]n = 79 patients in the iGlarLixi group and n = 72 patients in the iGlar group. [§]Hypoglycemia occurring during the period defined as the time from the first injection of open-label study drug up to 1 day after the last injection of open-label study drug, regardless of the introduction of rescue therapy. CI, confidence interval; FPG, fasting plasma glucose; HbA1c, glycated hemoglobin; iGlar, insulin glargine 100 U/mL; iGlarLixi, fixed-ratio combination of insulin glargine and lixisenatide; LOCF, last observation carried forward; LS, least squares; PPG, postprandial plasma glucose; SD, standard deviation; SE, standard error.

differential effect between basal glucose and PPG, which increases the number of patients with residual hyperglycemia when treated with iGlar alone. These effects were demonstrated despite there being no differences in the increase in insulin dose over 26 weeks between the treatments, and despite comparable numbers of documented symptomatic hypoglycemic episodes. The incidence of treatment-emergent adverse events (TEAEs) in the overall population was similar in the iGlarLixi and iGlar arms (61.2 and 58.0%, respectively)[27]; a summary of TEAEs has been provided in Table S1. The proportion of patients with documented symptomatic hypoglycemia in the current analysis (plasma glucose ≤70 mg/dL) was 22.9% with iGlarLixi and 25.3% with iGlar compared with 18.8% with iGlarLixi and 16.7% with iGlar in the overall population (plasma glucose ≤70 mg/dL)[27].

The control of postprandial hyperglycemia is a major unmet need for patients with type 2 diabetes and is a limiting factor in the long-term success of insulin-based therapies[31]. High

baseline rates of residual hyperglycemia in patients entering the LixiLan JP-L trial underscore the need for a therapeutic strategy that targets both FPG and PPG in Japanese patients. This therapeutic need is also evidenced by the high rate of residual hyperglycemia observed at the endpoint of randomized controlled trials of basal insulin worldwide, with rates exceeding 40% in a review of Asia-Pacific trials[9].

The effect of the FRC iGlarLixi in reducing the rate of residual hyperglycemia observed in this *post-hoc* analysis is consistent with the complementary mechanism of action of the GLP-1 RA Lixi and basal insulin[32–34]. Although Lixi improves glycemic control irrespective of β-cell function, the proportion of patients with type 2 diabetes and reduced β-cell function reaching HbA1c <7% was low despite a substantial reduction in PPG, suggesting the importance of combining Lixi with basal insulin in some populations[32,33,35]. Combining the GLP-1 RA Lixi with basal insulin provides benefits, as demonstrated in the present analysis by the improvement in residual hyperglycemia observed with iGlarLixi compared with iGlar, despite both iGlar and iGlarLixi having the same dose of insulin (Table 3). Among patients with residual hyperglycemia at baseline, the mean HbA1c at week 26 was 7.05% with iGlarLixi and 7.75% with iGlar, while the average daily dose of iGlar at week 26 was 15.59 U with iGlarLixi and 15.67 U with iGlar. This demonstrates the significant contribution of the GLP-1 RA Lixi in improving HbA1c by controlling PPG in patients with residual hyperglycemia, as indicated by their 7-point SMPG profiles.

The benefits of iGlarLixi in reducing the rates of residual hyperglycemia have previously been demonstrated for non-Japanese patients in a *post-hoc* analysis of the LixiLan-L trial[36,37]. That study used formulations of iGlarLixi containing iGlar to Lixi ratios of 2 U:1 μg and 3 U:1 μg. The data presented here confirm the effect of iGlarLixi on residual hyperglycemia in Japanese patients with type 2 diabetes using a Lixi: insulin ratio of 1:1, in keeping with the lower typical insulin requirements in this population.

Similar effects on residual hyperglycemia have been described in both the USA and EU using iGlarLixi formulations at 2:1 and 3:1[36–39]. This substudy confirms that the 1:1 unique formulation available in Japan delivers similar therapeutic benefits at lower insulin doses that are commonly seen in real-world practice[40].

In this analysis, patients with residual hyperglycemia at baseline had a numerically lower BMI than the overall study population. In a Caucasian population a lower BMI would theoretically indicate a population more responsive to insulin. However, this relationship is not evident in Japanese patients, in whom type 2 diabetes is frequently observed in patients without obesity[41]. The BMI was identical between the treatment groups in this analysis, indicating that the greater glycemic benefits of FRC therapy vs insulin were not due to baseline differences in potential responsiveness. Furthermore, the treatment effect of iGlarLixi was not dependent on BMI in previous investigations; in a subgroup analysis of the LixiLan-O trial, the glycemic effect of iGlarLixi was not affected by BMI[42]. In this trial of insulin-naive patients with type 2 diabetes, iGlarLixi led to greater reductions in HbA1c and a higher proportion of patients achieving HbA1c <7% at week 30, when compared with iGlar or Lixi given alone irrespective of a baseline BMI <30 kg/m^2 or ≥30 mg/m^2 [42].

It is known that glycemic fluctuations lead to the deterioration of pancreatic β-cell function (such as reduced insulin secretory capacity) in Japanese patients, whose β-cells are more vulnerable to hyperglycemia compared with those of Caucasians[43–45]. Glucose fluctuations have been reported to induce excessive formation of reactive oxygen species, inflammatory cytokines, and oxidative stress, contributing to the apoptosis of β-cells[46]. In addition, the fact that glycemic fluctuations may lead to the development of atherosclerosis and subsequent, potentially serious cardiovascular conditions has drawn much attention[47,48]. Therefore, it is possible that substantially reducing residual hyperglycemia using iGlarLixi would have additional beneficial effects in the face of the deterioration of β-cell function and the development of atherosclerosis in the long term, particularly in Japanese patients with type 2 diabetes. Needless to say, further study with a much larger population would be necessary to address this point.

It is important to note several limitations of the current analyses. *Post-hoc* analyses and sub-analyses are inherently entirely dependent on the design of the primary trial. Therefore, the sample size and power calculation for the primary endpoint may not have been applicable to these analyses, particularly as patient numbers were considerably reduced in the subgroups. For these reasons, *P* values should be considered nominal. Additionally, some outcomes of LixiLan JP-L may potentially have been influenced by the trial's open-label design, which was necessitated by distinctly different administration devices. Although not related to these sub-analyses, it is also important to note that the LixiLan JP trials had a relatively short duration (26 weeks; the JP-O1 trial had an extension to 52 weeks for safety follow-up), and studies with longer treatment/follow-up periods are needed to assess long-term efficacy and safety. As with all clinical trials and associated *post-hoc* analyses, real-world studies are needed to confirm the findings of the current analyses.

In conclusion, in this *post-hoc* analysis of the LixiLan JP-L trial, a titratable 1:1 FRC of iGlarLixi was more effective than iGlar in reducing the overall rate of residual hyperglycemia in Japanese patients with type 2 diabetes over 26 weeks, and it was also more effective in reducing HbA1c in those patients with residual hyperglycemia.

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DISCLOSURE

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Data Availability

Qualified researchers may request access to data and analytic methods through the Clinical Study Data Request platform (www.clinicalstudydatarequest.com).

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SUPPORTING INFORMATION

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

Figure S1 | Changes in 7-point SMPG profile (mean ± SE).
Table S1 | TEAEs in the overall population[27].