Efficacy and Safety of 1:1 Fixed-Ratio Combination of Insulin Glargine and Lixisenatide Versus Lixisenatide in Japanese Patients With Type 2 Diabetes Inadequately Controlled on Oral Antidiabetic Drugs: The LixiLan JP-O1 Randomized Clinical Trial

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OBJECTIVE

To assess the efficacy and safety of a 1:1 fixed-ratio combination of insulin glargine and lixisenatide (iGlarLixi) versus lixisenatide (Lixi) in insulin-naive Japanese patients with type 2 diabetes mellitus (T2DM) inadequately controlled on oral antidiabetic drugs (OADs).

RESEARCH DESIGN AND METHODS

In this phase 3, open-label, multicenter trial, 321 patients with HbA_{1c} ≥7.5 to ≤10.0% (58–86 mmol/mol) and fasting plasma glucose (FPG) ≤13.8 mmol/L (250 mg/dL) were randomized 1:1 to iGlarLixi or Lixi for 52 weeks. The primary end point was change in HbA_{1c} at week 26.

RESULTS

Change in HbA_{1c} from baseline to week 26 was significantly greater with iGlarLixi (−1.58% [−17.3 mmol/mol]) than with Lixi (−0.51% [−5.6 mmol/mol]), confirming the superiority of iGlarLixi (least squares [LS] mean difference −1.07% [−11.7 mmol/mol], $P < 0.0001$). At week 26, significantly greater proportions of patients treated with iGlarLixi reached HbA_{1c} <7% (53 mmol/mol) (65.2% vs. 19.4%; $P < 0.0001$), and FPG reductions were greater with iGlarLixi than Lixi (LS mean difference −2.29 mmol/L [−41.23 mg/dL], $P < 0.0001$). Incidence of documented symptomatic hypoglycemia (≤3.9 mmol/L [70 mg/dL]) was higher with iGlarLixi (13.0% vs. 2.5%) through week 26, with no severe hypoglycemic events in either group. Incidence of gastrointestinal events through week 52 was lower with iGlarLixi (36.0% vs. 50.0%), and rates of treatment-emergent adverse events were similar.

CONCLUSIONS

This phase 3 study demonstrated superior glycemic control and fewer gastrointestinal adverse events with iGlarLixi than with Lixi, which may support it as a new treatment option for Japanese patients with T2DM that is inadequately controlled with OADs.

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The prevalence of type 2 diabetes mellitus (T2DM) in Japan is 12.1% and continues to rise (1). Uncontrolled T2DM worsens patient quality of life and general well-being and, in the long term, compromises multiple organ systems, leading to increased patient morbidity and mortality.

T2DM is characterized by a progressive decline in β-cell function and a reduction in the supply of endogenous insulin. In many patients, oral antidiabetic drugs (OADs) do not ameliorate this progression and gradually become ineffective at controlling glycemia, necessitating insulin replacement (2,3). Basal insulin is a common insulin regimen in patients with T2DM inadequately controlled on oral therapy, and it can effectively control fasting plasma glucose (FPG) by suppressing endogenous glucose production (2–4). However, this regimen is less effective at correcting postprandial glucose (PPG) excursions, which are physiologically controlled by glucose-stimulated, glucagon-like peptide 1 (GLP-1)–mediated rapid insulin secretion (3,5). GLP-1 regulates PPG spikes by a number of different mechanisms, including increased insulin secretion, reduced glucagon secretion, delayed gastric emptying, and modulation of feeding behavior (6,7). GLP-1 receptor agonists (RAs) provide an alternative treatment option for patients with T2DM (6). Short-acting GLP-1 RAs, in particular, appear to mimic the postprandial effects of endogenous GLP-1 (8).

The implications for the patient with poorly controlled plasma glucose are well documented. However, complicated treatment regimens, medication side effects, reluctance to initiate injection therapy, and issues with adherence often discourage patients and physicians from optimizing glycemic control (9,10). The failure to optimize therapy, which is often justified by the difficulty of using complex treatments or fear of adverse drug reactions, has been termed "clinical inertia" (11). In Japan, 45.9% patients with T2DM have suboptimal glycemic control and are therefore at high risk of potentially preventable diabetic complications (12). Treatment is escalated slowly. Mean duration of diagnosed diabetes is 11.3 years before the start of insulin therapy, and mean HbA$_{1c}$ is 9.8% (84 mmol/mol) at that point (13). Insulin treatment in Japan is particularly challenging because of the extreme sensitivity of Japanese patients to insulin. In Add-on Lantus to Oral Hypoglycemic Agents 2 (ALOHA-2), a postmarketing surveillance study of combination therapy with insulin glargine (iGlar) U100 and OAD in Japanese patients with T2DM, the mean initial and final insulin doses were 6.3 and 9.8 units/day, respectively (14). Patients' need for low iGlar doses and their sensitivity to increases in therapy are, thus, essential considerations in Japanese clinical practice. An effective, easy-to-manage therapeutic intervention that allows the use of small insulin doses with a low adverse event (AE) profile could improve clinical care and the acceptance of therapy.

Used together, basal insulin and a short-acting GLP-1 RA can effectively lower FPG and PPG in patients with T2DM (15,16). The combination of these agents has been included in guidelines by the American Diabetes Association, European Association for the Study of Diabetes, and Japan Diabetes Society (2,3,17). Currently available fixed-ratio combinations of basal insulin and a GLP-1 RA are iDegLira (insulin degludec [50 units] and the long-acting GLP-1 RA liraglutide [1.8 mg]), and iGlarLixi (iGlar U100 and the short-acting GLP-1 RA lixisenatide [Lixi] in a dose ratio of 2 units:1 μg or 3 units:1 μg).

In contrast to the United States and Europe, iGlarLixi in Japan is being developed at a dose ratio of 1 unit:1 μg. This difference reflects the lower insulin requirements in Japanese populations, who tend to have lower BMI, greater insulin sensitivity, and lower β-cell responsiveness than Western patients (18,19). In addition, Japanese patients appear to respond favorably to incretin-based therapy, such as dipeptidyl peptidase 4 (DPP-4) inhibitors and GLP-1 RAs (20,21). Studies have shown that healthy Japanese subjects have low GLP-1 levels at baseline and postprandially, which might contribute to their reduced capacity to secrete insulin (22). These findings may be partly due to the genetic variations found in Japanese patients with T2DM that are not found in Caucasians with T2DM (23). A 1:1 dose ratio in iGlarLixi allows the delivery of basal insulin with optimal doses of Lixi in the range expected to meet the needs of Japanese patients.

In a previous phase 3 study in 521 Japanese patients with T2DM (baseline mean age 59.7 years, BMI 26.0 kg/m², HbA$_{1c}$ 8.04% [64.4 mmol/mol]), treatment with iGlarLixi 1:1 led to a significantly greater reduction in HbA$_{1c}$ (−1.40% [−15.3 mmol/mol] vs. −0.76% [−8.3 mmol/mol]) and control of PPG (−4.26 vs. +0.19 mmol/L) without increased risk of symptomatic hypoglycemia (0.73 vs. 0.54 events per patient-year) or weight gain (+0.26 vs. +1.33 kg), compared with iGlar (24). The present phase 3 study evaluates the efficacy and safety of iGlarLixi in comparison with Lixi in Japanese patients with T2DM inadequately controlled on OADs.

RESEARCH DESIGN AND METHODS

Study Design and Patients

LixiLan JP-O1 (NCT02749890) was a 26-week, open-label, active-controlled, parallel-group, multicenter, phase 3 study followed by a 26-week extension safety period (Supplementary Fig. 1). Eligible patients were insulin-naïve Japanese adults with T2DM with HbA$_{1c}$ between 7.5% (58 mmol/mol) and 10% (86 mmol/mol) and FPG ≤13.8 mmol/L (250 mg/dL), who were inadequately controlled on one or two OADs (biguanides, thiazolidinediones, α-glucosidase inhibitors, sodium–glucose cotransporter 2 [SGLT2] inhibitors, sulfonylureas, glinides, or DPP-4 inhibitors) for at least 3 months prior to screening. Major exclusion criteria were use of any other glucose-lowering agents in the 3 months prior to screening; previous use of insulin except for short-term treatment including gestational diabetes; a history of discontinuation of GLP-1 RAs because of safety, lack of tolerability, or lack of efficacy; and pancreatic or liver enzymes greater than three times the upper limit of normal.

This study consisted of a 2-week screening period, a 26-week main treatment period for primary end point assessment, and a 26-week safety extension, resulting in a total of 52 weeks of treatment and 3 days of posttreatment safety follow-up. The maximum duration of the study was ~55 weeks (Supplementary Fig. 1). After the screening period, patients were randomized 1:1 to receive either iGlarLixi or Lixi, stratified by DPP-4 inhibitor use (yes, no) and HbA$_{1c}$ value (<8%, ≥8% [64 mmol/mol]) at screening. Patients were stratified by DPP-4 inhibitor use, as DPP-4 inhibitors are the most commonly used OAD (57%) in Japan (25). An interactive voice web response system was used for patient randomization.

The study was approved by the relevant institutional review boards and

conducted in accordance with the Declaration of Helsinki and Good Clinical Practices. All participants provided written informed consent prior to the study.

Treatment

iGlarLixi or Lixi was self-administered subcutaneously once daily within an hour before breakfast. The starting dose of iGlarLixi was 5 units/5 μg. Dose titration by 1 unit/1 μg once a week was recommended until the patient achieved a fasting self-monitored plasma glucose (SMPG) of ≥4.4 and ≤5.6 mmol/L (≥80 and ≤100 mg/dL) without hypoglycemia. The maximum iGlarLixi dose was 20 units/20 μg. For median fasting SMPG from the last three measurements of >7.8 mmol/L (140 mg/dL) and 5.6–7.8 mmol/L (100–140 mg/dL), the iGlarLixi dose was increased by +2 and +1 steps (unit/μg)/day, respectively. For fasting SMPG 3.3–4.4 mmol/L (60–80 mg/dL), the dose was decreased by −2, and if fasting SMPG was below 3.3 mmol/L (60 mg/dL), or if two or more symptomatic hypoglycemic episodes or one severe hypoglycemic episode (requiring assistance) were documented in the preceding week, the dose was decreased by −3 or more (Supplementary Table 1). The starting dose of Lixi was 10 μg with a maintenance dose of 20 μg. Lixi was titrated up by 5 μg/week until the patient reached the maintenance dose. iGlarLixi was administered via reusable pen injectors, and Lixi was administered using prefilled disposable pens.

DPP-4 inhibitors, if taken, were discontinued at randomization. Sulfonylureas, glinides, and SGLT2 inhibitors were to be decreased by 50% or discontinued at randomization if HbA$_{1c}$ at the screening visit was <8% (64 mmol/mol) to reduce the risk of hypoglycemic events. Otherwise, OADs were continued at minimum at the usual maintenance dose as taken before screening and at a stable dose during the screening and open-label treatment periods unless there was a safety issue.

Rescue therapy was recommended for HbA$_{1c}$ that exceeded the threshold value of 8.5% (69 mmol/mol) after week 12 or 8.0% (64 mmol/mol) after week 26 if no reasonable explanation existed for insufficient glucose control, appropriate actions failed, and/or a daily dose greater than 20 units/20 μg in the iGlarLixi group was necessary to decrease HbA$_{1c}$ below

the threshold. In such cases, the addition of a short-/rapid-acting insulin was recommended in the iGlarLixi group. In the Lixi group, this choice was left to the discretion of the investigator.

Assessments

Samples for HbA$_{1c}$ and FPG testing were obtained under fasting conditions before administration of the study drug. All laboratory tests were performed at a central laboratory.

The primary end point was the change in HbA$_{1c}$ from baseline to week 26. Secondary end points were evaluated at the end of week 26 and included the proportion of patients achieving HbA$_{1c}$ <7% (53 mmol/mol) or HbA$_{1c}$ ≤6.5% (48 mmol/mol), change in FPG, change in average seven-point SMPG, percentage of patients achieving HbA$_{1c}$ <7% (53 mmol/mol) without weight gain, and change in weight from baseline. All efficacy end points were also descriptively evaluated over 52 weeks.

Throughout the study, patients were monitored for hypoglycemia and other AEs. Hypoglycemia was categorized as severe (requiring assistance from another person), symptomatic (exhibiting symptoms of hypoglycemia concurrently with a plasma glucose ≤3.9 mmol/L [70 mg/dL]), or asymptomatic (plasma glucose ≤3.9 mmol/L [70 mg/dL] without the typical symptoms of hypoglycemia).

Statistical Methods

It was estimated that enrollment of 318 patients (159 per treatment group), assuming a 20% drop-out rate by week 26, would leave at least 127 evaluable patients per group, providing 95% power to detect a 0.5% (5.5 mmol/mol) difference in HbA$_{1c}$ between iGlarLixi and Lixi, 90% power to detect a 0.45% (4.9 mmol/mol) difference, and 82% power to detect a 0.4% (4.4 mmol/mol) difference, at week 26. These calculations assumed a common SD of 1.1% (12.0 mmol/mol) and a two-sided significance level of 5%.

Efficacy was assessed at weeks 26 and 52 for the modified intent-to-treat population, which was defined as all randomized patients who received at least one postbaseline primary or secondary end point assessment irrespective of compliance with the study protocol and procedures. Statistical testing was two-sided at a nominal significance level of 5%. ANCOVA was used to analyze change in HbA$_{1c}$ from baseline to week 26. Fixed

effects were the two treatment groups, randomization strata for HbA$_{1c}$ (<8% and ≥8% [64 mmol/mol]), and the use of a DPP-4 inhibitor at screening. The covariate was the baseline HbA$_{1c}$ value. The last observation carried forward (LOCF) method was applied using the last available postbaseline HbA$_{1c}$ measurement during the 26-week treatment period as the week 26 value.

The least squares (LS) mean change and the corresponding SE were estimated for the difference in HbA$_{1c}$ from baseline to week 26 for each treatment group and for the difference between treatment groups. The two-sided 95% CI was also calculated for the difference between treatment groups.

Similarly, ANCOVA was used to analyze and compare treatment groups for all continuous secondary efficacy end points. All categorical secondary efficacy end points were analyzed with the Cochran–Mantel–Haenszel method stratified on randomization strata, and the differences between the iGlarLixi and Lixi groups and associated two-sided 95% CI were analyzed. To control for type I errors, secondary efficacy end points were tested in the prioritized order: percentage of patients reaching HbA$_{1c}$ <7% (53 mmol/mol) at week 26, change in FPG, change in average seven-point SMPG, and percentage of patients achieving HbA$_{1c}$ <7% (53 mmol/mol) without weight gain. Testing was to be stopped when an end point was found not to be statistically significant at the 5% level.

Throughout the study, safety was analyzed for every randomized patient who received at least one injection of iGlarLixi or Lixi, regardless of the amount administered. Safety analyses were based on treatments actually received. All AEs were assessed with descriptive statistics. All summaries and statistical analyses were generated using SAS (version 9.4 or higher).

RESULTS

Patient Disposition and Baseline Characteristics

Of 399 patients screened, 321 were randomized at 61 participating centers in Japan; 161 to the iGlarLixi group and 160 to the Lixi group. The median duration of treatment in both groups was 365.0 days. More patients in the iGlarLixi group than in the Lixi group completed treatment at

week 26 (97.5% vs. 88.1%) and week 52 (93.8% vs. 83.8%) (Supplementary Fig. 2).

Demographics and baseline characteristics were comparable between treatment groups (Table 1).

Primary Efficacy End Point
At baseline, HbA$_{1c}$ levels were 8.39% and 8.38% ($\sim$68 mmol/mol) with iGlarLixi and Lixi, respectively. At week 26 (LOCF), these levels were 6.73% ($\sim$50 mmol/mol) and 7.79% ($\sim$62 mmol/mol), respectively. LS mean change in HbA$_{1c}$ from baseline to week 26 (LOCF) was -1.58% (-17.3 mmol/mol) with iGlarLixi and -0.51% (-5.6 mmol/mol) with Lixi. The LS mean difference was -1.07% (-11.7 mmol/mol, 95% CI -1.251 to -0.889% [~ -13.7 to ~ -9.7 mmol/mol]; $P < 0.0001$), confirming the superiority of iGlarLixi over Lixi (Fig. 1A and Table 2). In both groups, HbA$_{1c}$ decreased primarily during the first 20 weeks (with a greater decrease in the iGlarLixi group), and it remained stable thereafter until the end of the 52-week treatment period (Fig. 1B).

Secondary Efficacy End Points
At week 26, a significantly higher proportion of patients in the iGlarLixi group (65.2%) reached the target of HbA$_{1c}$ <7% (53 mmol/mol) than in the Lixi group (19.4%). The proportion difference was 45.9% ($P < 0.0001$). In addition, a substantially higher proportion of iGlarLixi patients reached HbA$_{1c}$ $\leq$6.5% (48 mmol/mol) (Fig.

1C and Table 2). Similar findings were observed at week 52 (LOCF) (Supplementary Table 2).

LS mean change in FPG from baseline to week 26 (LOCF) was significantly greater with iGlarLixi than with Lixi (LS mean difference -2.29 mmol/L [-41.23 mg/dL], 95% CI -2.663 to -1.915 mmol/L [-47.968 to -34.501 mg/dL], $P < 0.0001$) (Fig. 1D and Table 2). This outcome was also seen at week 52 (LOCF) (Supplementary Table 2).

LS mean change in average seven-point SMPG from baseline to week 26 was significantly greater with iGlarLixi than with Lixi (LS mean difference -1.94 mmol/L [-34.99 mg/dL], 95% CI -2.362 to -1.516 mmol/L [-42.604 to -27.372 mg/dL], $P < 0.0001$) (Fig. 1E and Table 2). With both treatments, the effects were most evident after breakfast compared with subsequent meals. Similar results were seen at week 52 (Supplementary Table 2).

At week 26, the proportions of patients achieving HbA$_{1c}$ <7% (53 mmol/mol) with no weight gain were significantly higher with iGlarLixi than with Lixi (29.8% vs. 17.5%, $P = 0.0089$) (Table 2). Similar findings were seen at week 52 (Supplementary Table 2).

LS mean change in body weight from baseline to week 26 (LOCF) was +0.62 kg for iGlarLixi and -1.32 kg for Lixi. The LS mean difference was +1.94 kg (95% CI 1.479–2.407 kg) (Table 2). Body weight changes were similar at week 52 (Supplementary Table 2).

From the starting dose of 5.00 units, the mean daily iGlar U100 dose in the iGlarLixi group was increased to 16.69 units at week 26 (LOCF) (Table 2). Similar dose usage was seen at week 52 (Supplementary Table 2). Insulin titration occurred primarily in the first 12 weeks of the study. In the Lixi group, 85.6% of patients were receiving the maintenance dose (20 μg) at week 26, and 86.3% were receiving it at week 52.

During the 26-week treatment period, rescue therapy was required for 1 of 161 patients (0.6%) in the iGlarLixi group and 19 of 160 patients (11.9%) in the Lixi group (Table 2); by 52 weeks, these numbers increased to three patients (1.9%) and 37 patients (23.1%), respectively (Supplementary Table 2).

Safety
The incidence of documented symptomatic hypoglycemia ($\leq$3.9 mmol/L [70 mg/dL]) was 13.0% in the iGlarLixi group and 2.5% in the Lixi group during the first 26 weeks; and 18.0% and 4.4%, respectively, over 52 weeks. The number of events per patient-year was 0.80 and 0.10 over 52 weeks, respectively. No severe hypoglycemia was reported in either treatment group (Table 3).

In both treatment groups, the majority of patients experienced at least one treatment-emergent AE (TEAE) during the study. Serious TEAEs were reported in five patients (3.1%) in the iGlarLixi group and four patients (2.5%) in the Lixi group by week 26, and in seven patients (4.3%) and 13 patients (8.1%), respectively, by week 52 (Supplementary Table 3). Four patients (2.5%) reported TEAEs leading to treatment discontinuation in the iGlarLixi group, and 17 (10.6%) in the Lixi group, during the first 26 weeks, and 4 (2.5%) and 20 (12.5%), respectively, by week 52. Nausea was the most frequent reason for discontinuation in both groups: two patients (1.2%) in the iGlarLixi group and eight patients (5.0%) in the Lixi group (Table 3).

During the study treatment period, one patient from the Lixi group died of congestive heart failure (considered by the investigator to be related to treatment) and pulmonary alveolar hemorrhage. No deaths occurred in the iGlarLixi group.

In the Lixi group, nausea usually occurred in the early weeks of administration. Nausea was less common in the iGlarLixi group (Supplementary Fig. 3).

Table 1—Patient characteristics

	iGlarLixi (n = 161)	Lixi (n = 160)
Age, years	58.3 ± 9.9	57.7 ± 11.5
Sex, female	57 (35.4)	58 (36.3)
BMI at baseline, kg/m^2	26.79 ± 4.44	26.85 ± 4.17
Patients with baseline BMI ≥30 kg/m^2	32 (19.9)	32 (20.0)
Duration of diabetes, years	8.12 ± 6.04	9.22 ± 6.39
Age at onset of T2DM, years	50.1 ± 10.0	48.5 ± 10.3
HbA$_{1c}$, % [mmol/mol]		
At screening*	8.43 ± 0.62 [69 ± 6.8]	8.42 ± 0.64 [69 ± 7.0]
At baseline	8.39 ± 0.64 [68 ± 7.0]	8.38 ± 0.63 [68 ± 6.9]
FPG at baseline, mmol/L	9.83 ± 1.61	9.62 ± 1.71
OAD use at screening*		
Metformin	88 (54.7)	83 (51.9)
Sulfonylurea	50 (31.1)	52 (32.5)
DPP-4 inhibitor	71 (44.1)	71 (44.4)
Number of OADs used at screening*		
One OAD	61 (37.9)	58 (36.3)
Two OADs	100 (62.1)	102 (63.8)

Data are shown as mean ± SD or n (%). *Screening values are at week −2.
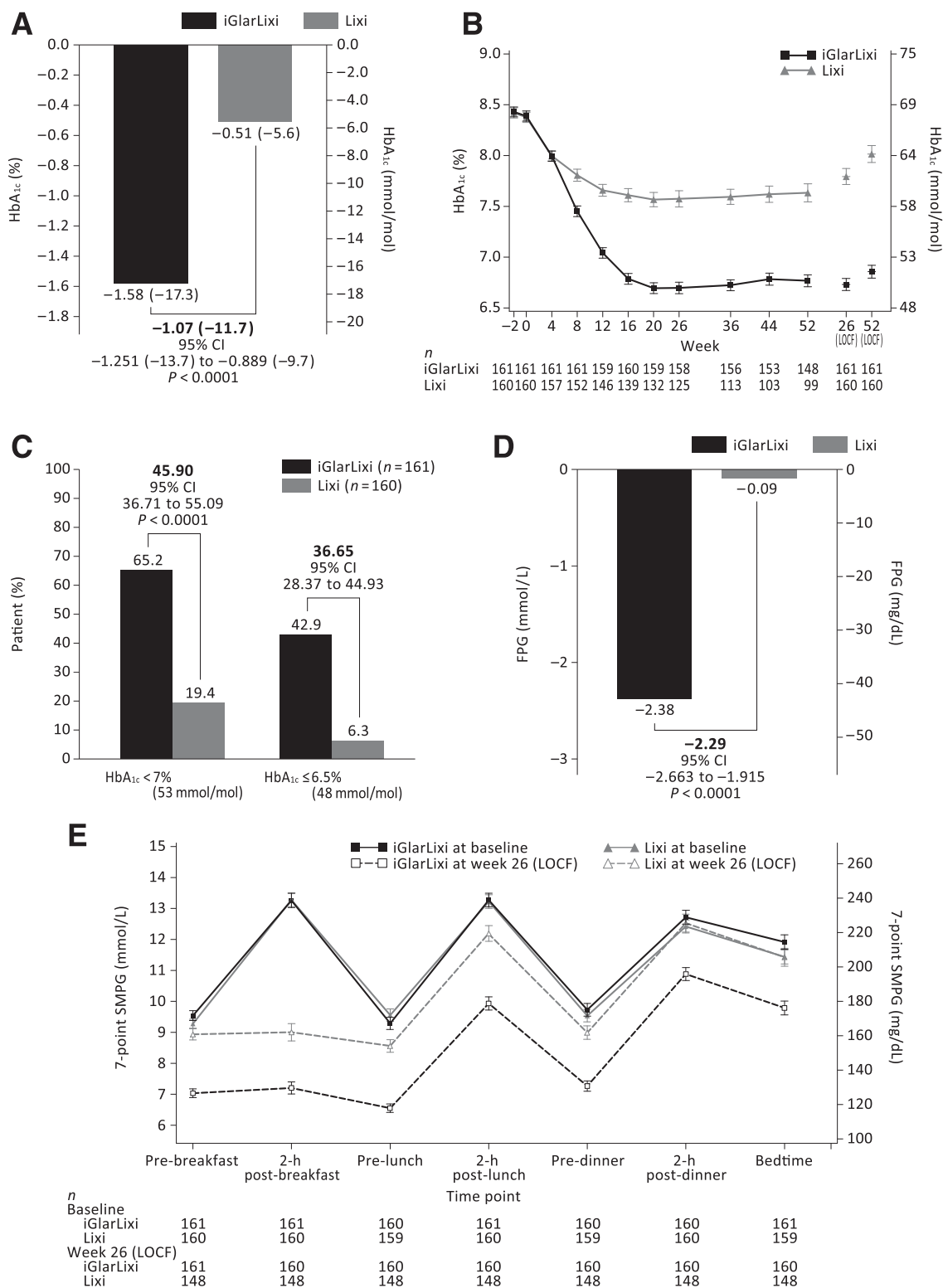
Figure 1—Efficacy end points. *A*: Total difference in HbA$_{1c}$ after 26 weeks of treatment; HbA$_{1c}$ (%) outside the parentheses, HbA$_{1c}$ (mmol/mol) inside the parentheses for LS mean change from baseline, LS mean difference between the two groups, and 95% CI. *B*: Time course of change in HbA$_{1c}$ throughout the 52-week treatment period. Values are presented as mean ± SE. *C*: Percentage of patients achieving HbA$_{1c}$ <7% (53 mmol/mol) and ≤6.5% (48 mmol/mol) in the 26-week treatment period. *D*: Change in FPG in the first 26-week treatment period. *E*: Changes in seven-point SMPG profile in the 26-week treatment period.

Table 2—Efficacy end points

Parameter	iGlarLixi (n = 161)	Lixi (n = 160)
HbA$_{1c}$, % [mmol/mol]		
Baseline	8.39 ± 0.64 [68 ± 7.0]	8.38 ± 0.63 [68 ± 6.9]
Week 26	6.73 ± 0.75 [50 ± 8.2]	7.79 ± 1.00 [62 ± 10.9]
LS mean change from baseline ± SE*	−1.58 ± 0.072 [−17.3 ± 0.8]	−0.51 ± 0.073 [−5.6 ± 0.8]
LS means difference ± SE vs. Lixi*	−1.07 ± 0.092 [−11.7 ± 1.0]	
95% CI	−1.251 to −0.889 [−13.7 to −9.7]	
P value	<0.0001	
HbA$_{1c}$ <7% [53 mmol/mol]		
Week 26	105 (65.2)	31 (19.4)
Proportion difference vs. Lixi, %†	45.90	
95% CI	36.71–55.09	
P value	<0.0001	
HbA$_{1c}$ ≤6.5% [48 mmol/mol]		
Week 26	69 (42.9)	10 (6.3)
Proportion difference vs. Lixi, %†	36.65	
95% CI	28.37–44.93	
FPG, mmol/L		
Baseline	9.83 ± 1.61	9.64 ± 1.71
Week 26	7.30 ± 1.71	9.48 ± 2.10
LS mean change from baseline ± SE*	−2.38 ± 0.143	−0.09 ± 0.146
LS means difference ± SE vs. Lixi*	−2.29 ± 0.190	
95% CI	−2.663 to −1.915	
P value	<0.0001	
Average seven-point SMPG, mmol/L		
Baseline	11.38 ± 1.98	11.19 ± 1.97
Week 26	8.36 ± 1.60	10.23 ± 2.38
LS mean change from baseline ± SE*	−2.88 ± 0.160	−0.94 ± 0.168
LS means difference ± SE vs. Lixi*	−1.94 ± 0.215	
95% CI	−2.362 to −1.516	
P value	<0.0001	
Body weight, kg		
Baseline	72.26 ± 14.80	72.99 ± 14.88
Week 26	72.91 ± 15.02	71.70 ± 15.06
LS mean change from baseline ± SE*	0.62 ± 0.177	−1.32 ± 0.180
LS means difference ± SE vs. Lixi*	1.94 ± 0.236	
95% CI	1.479–2.407	
HbA$_{1c}$ <7% with no weight gain		
Week 26	48 (29.8)	28 (17.5)
Proportion difference vs. Lixi, %†	12.39	
95% CI	3.36–21.43	
P value	0.0089	
Daily iGlar dose, units‡		
Day 1	5.00 ± 0.00	
Week 26	16.69 ± 4.19	
Change from day 1	11.69 ± 4.19	
Patients requiring rescue therapy		
Week 26	1 (0.6)	19 (11.9)
Proportion difference vs. Lixi, %†	−11.21	
95% CI	−16.46 to −5.96	

Data are shown as mean ± SD or n (%) unless otherwise indicated. Includes only patients for whom both baseline and week 26 (LOCF) measurements are available for continuous end points. Patients were treated as nonresponders if they had no assessments at week 26 (LOCF) for categorical end points. Analysis included measurements obtained before the introduction of rescue medication and up to day 14 for HbA$_{1c}$, day 1 for FPG, day 0 for average seven-point SMPG and iGlar dose, and day 3 for body weight after the last injection of open-label study drug before or at week 26 visit (or day 183 if week 26 visit was missing). Number of patients analyzed: n (iGlarLixi) = 161 and n (Lixi) = 157 for FPG; n (iGlarLixi) = 160 and n (Lixi) = 148 for average seven-point SMPG; n (iGlarLixi) = 161, n (Lixi at baseline) = 160 and n (Lixi at week 26) = 157 for body weight. *ANCOVA model with treatment groups, randomization strata of HbA$_{1c}$ (<8.0%, ≥8.0% [64 mmol/mol]) at week −2, and randomization strata for DPP-4 inhibitor use at screening (yes, no) as fixed effects, and with each baseline value as a covariate. †Weighted average of proportion difference between treatment groups using the Cochran–Mantel–Haenszel method with randomization strata of HbA$_{1c}$ (<8.0%, ≥8.0%) at week −2 and randomization strata of DPP-4 inhibitor use at screening (yes, no). ‡Dose of first injection of open-label study drug was considered as average daily insulin dose at day 1. Since iGlarLixi contains a 1:1 fixed-ratio combination of iGlar (units) and Lixi (μg), results in iGlarLixi group are considered as results of Lixi dose (μg).

Table 3—Summary of AEs

	iGlarLixi ($n = 161$)		Lixi ($n = 160$)	
	Week 26	Week 52	Week 26	Week 52
At least one TEAE				
Any TEAE	109 (67.7)	129 (80.1)	122 (76.3)	139 (86.9)
Serious TEAE	5 (3.1)	7 (4.3)	4 (2.5)	13 (8.1)
TEAE leading to death	0	0	1 (0.6)	1 (0.6)
TEAE leading to discontinuation	4 (2.5)	4 (2.5)	17 (10.6)	20 (12.5)
TEAE by organ class in PT in ≥5% of patients*				
Infections and infestations (overall)	62 (38.5)	79 (49.1)	63 (39.4)	88 (55.0)
Nasopharyngitis	38 (23.6)	47 (29.2)	35 (21.9)	53 (33.1)
Gastrointestinal disorders (overall)	47 (29.2)	58 (36.0)	68 (42.5)	80 (50.0)
Nausea	23 (14.3)	24 (14.9)	43 (26.9)	45 (28.1)
Discontinuation due to nausea	2 (1.2)	2 (1.2)	8 (5.0)	8 (5.0)
Vomiting	9 (5.6)	10 (6.2)	8 (5.0)	8 (5.0)
Discontinuation due to vomiting	0	0	1 (0.6)	1 (0.6)
Diarrhea	8 (5.0)	13 (8.1)	10 (6.3)	11 (6.9)
Discontinuation due to diarrhea	0	0	1 (0.6)	1 (0.6)
Constipation	2 (1.2)	4 (2.5)	9 (5.6)	10 (6.3)
Discontinuation due to constipation	0	0	1 (0.6)	1 (0.6)
Dyspepsia	4 (2.5)	5 (3.1)	9 (5.6)	9 (5.6)
Discontinuation due to dyspepsia	0	0	1 (0.6)	1 (0.6)
Hypoglycemia				
Symptomatic†				
Patients with events	21 (13.0)	29 (18.0)	4 (2.5)	7 (4.4)
Number of events per patient-year‡		0.80		0.10
Severe				
Patients with events	0	0	0	0

Data are shown as n (%). Table shows time from first injection of open-label study drug up to 3 days (1 day for hypoglycemia) after the last injection of open-label study drug regardless of introduction of rescue therapy. For 26-week treatment period, last injection of open-label study drug was at or before week 26 visit (or day 183 if week 26 visit was missing). PT, preferred term. *Based on Medical Dictionary for Regulatory Activities Version 20.1. †Defined as plasma glucose ≤3.9 mmol/L (70 mg/dL). ‡Calculated as number of events divided by total patient-years of exposure.

CONCLUSIONS

In Japanese patients with T2DM inadequately controlled on one or two OADs, iGlarLixi (1 unit:1 μg ratio) provided clinically significant reduction in HbA$_{1c}$ (-1.58% [-17.3 mmol/mol]), statistically greater than with Lixi alone (-0.51% [-5.6 mmol/mol]) after 26 weeks of treatment. At week 26, mean HbA$_{1c}$ levels were 6.73% (~50 mmol/mol) with iGlarLixi and 7.79% (~62 mmol/mol) with Lixi. The improvement in HbA$_{1c}$ with iGlarLixi, compared with Lixi, remained consistent throughout the study; at week 26, the proportion of patients who achieved HbA$_{1c}$ <7% (53 mmol/mol) was 65.2% with iGlarLixi vs. 19.4% with Lixi. At week 52, these proportions were 61.5% and 15.6%, respectively.

Decreases in FPG were also significantly greater with iGlarLixi than with Lixi at weeks 26 and 52. Although FPG reduction is predominantly driven by the action of iGlar, Lixi may also decrease FPG in a dose-dependent manner (6,26). However, the major mechanism of action of Lixi is on PPG reduction, as previously demonstrated in patients with T2DM (27). Consistent with the complementary and dose-dependent effects of iGlar and Lixi on fasting and PPG (28), in the current study, iGlarLixi lowered the daily plasma glucose profile, reducing both HbA$_{1c}$ levels and glycemic variability. These effects persisted throughout the 52 weeks.

Body weight increased only slightly with iGlarLixi (+0.62 kg) and decreased with Lixi (-1.32 kg). This finding is supported by our previous 26-week phase 3 study comparing iGlarLixi (+0.26 kg) with iGlar (+1.33 kg) alone in Japanese patients (24). The weight gain associated with iGlar thus appears to be mitigated by the weight-reducing effects of Lixi.

At week 26, the proportion of patients who achieved HbA$_{1c}$ <7% (53 mmol/mol) without weight gain was 29.8% for the iGlarLixi group versus 17.5% for the Lixi group, which is consistent with the complementary actions of iGlar and Lixi and the findings above. All efficacy results at week 52 were similar to those at week 26, supporting the sustained efficacy of iGlarLixi over Lixi alone.

Treatment with iGlarLixi was well tolerated, and no new or unexpected safety issues were observed. As expected with insulin-based treatment, the incidence of hypoglycemia was higher in the iGlarLixi group than in the Lixi group, but no severe hypoglycemic events occurred in either group. The difference in the incidence of hypoglycemic events was attributed to the effect of iGlar and is consistent with findings in previous studies of GLP-1 RAs given concomitantly with long-acting insulins (26,29). In addition, the Japan-specific fixed-ratio combination ratio of 1 unit:1 μg for iGlarLixi used in this study was specifically developed to meet the pathophysiology of Japanese patients with T2DM. The efficacy and safety of that ratio was proven in this analysis.

The results of this study suggest that the 1 unit:1 μg combination of a relatively small (by Western standards) dose of basal insulin with a maximal or near-maximal dose of GLP-1 RA, which is postprandially active, provides a highly effective and well-tolerated therapeutic intervention for Japanese patients with T2DM inadequately controlled on OADs. Japanese patients on average require only 0.154 units/kg/day of insulin (30) and respond better to GLP-1 RAs than Caucasian patients who, in contrast, require 0.44 units/kg/day of insulin on average (31). iGlarLixi 1:1 may thus allow more Japanese patients with T2DM to achieve and maintain optimal glycemic control, and lead to decreased morbidity and mortality in this population. The same benefits may be seen in other sensitive populations. Whether these results can be translated to other Asian populations remains to be investigated.

The incidence of TEAEs was similar in both groups. However, the percentage of patients who discontinued due to TEAEs was lower with iGlarLixi than with Lixi. Discontinuations due to nausea were less frequent with iGlarLixi than with Lixi (1.2% vs. 5.0%). Consistent with previous findings, gastrointestinal symptoms were less frequent with iGlarLixi than with Lixi (32). Nausea events in the Lixi group were particularly frequent during the initial period of administration. No such trend was seen in the iGlarLixi group. A possible explanation for the lower incidence of nausea in the iGlarLixi group is the smaller starting dose and the much slower uptitration of Lixi in this group. More patients in the iGlarLixi

group than in the Lixi group completed treatment at week 26 (97.5% vs. 88.1%) and week 52 (93.8% vs. 83.8%) (Supplementary Fig. 2). This is most likely related to the slower uptitration and the lower final dose of Lixi in the iGlarLixi group. Simultaneous use of both drugs in the form of iGlarLixi provided more effective glycemic control at lower doses of therapy, mitigating the side effects of both therapies.

Potential limitations of this study include the use of an open-label design. However, a double-blind design would have required a dummy injection in both treatment groups, for a total of two injections/day, which would have imposed an additional burden for the patients. The findings of this specific fixed-ratio combination, although highly relevant to Japanese and other East Asian populations who respond favorably to incretin-based therapy, may be less applicable to non–East Asian populations. Nevertheless, fixed-ratio combinations of iGlar and Lixi are available in other parts of the world and our observations on effectiveness and complementary mechanisms of action are validated by findings from other regions. In addition, this study excluded patients with HbA$_{1c}$ >10%, FPG >250 mg/dL, and those previously showing a lack of efficacy with a GLP-1 RA. Our results may therefore not be applicable to these patients, and further real-world studies will need to be conducted to validate effectiveness in a broader population.

In conclusion, in Japanese patients with T2DM inadequately controlled on OADs, iGlarLixi in a 1 unit:1 μg ratio significantly improved glycemic control compared with Lixi. iGlarLixi demonstrated a more favorable safety profile than Lixi, with considerably fewer gastrointestinal events. iGlarLixi at a 1 unit:1 μg dose ratio represents an important therapeutic treatment option in Japanese patients with T2DM uncontrolled with OADs.

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