Benefits of LixiLan, a Titratable Fixed-Ratio Combination of Insulin Glargine Plus Lixisenatide, Versus Insulin Glargine and Lixisenatide Monocomponents in Type 2 Diabetes Inadequately Controlled on Oral Agents: The LixiLan-O Randomized Trial

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OBJECTIVE

To evaluate efficacy and safety of LixiLan (iGlarLixi), a novel titratable fixed-ratio combination of insulin glargine (iGlar) and lixisenatide (Lixi), compared with both components, iGlar and Lixi, given separately in type 2 diabetes inadequately controlled on metformin with or without a second oral glucose-lowering drug.

RESEARCH DESIGN AND METHODS

After a 4-week run-in to optimize metformin and stop other oral antidiabetic drugs, participants (*N* = 1,170, mean diabetes duration ~8.8 years, BMI ~31.7 kg/m^2) were randomly assigned to open-label once-daily iGlarLixi or iGlar, both titrated to fasting plasma glucose <100 mg/dL (<5.6 mmol/L) up to a maximum insulin dose of 60 units/day, or to once-daily Lixi (20 μg/day) while continuing with metformin. The primary outcome was HbA_{1c} change at 30 weeks.

RESULTS

Greater reductions in HbA_{1c} from baseline (8.1% [65 mmol/mol]) were achieved with iGlarLixi compared with iGlar and Lixi (−1.6%, −1.3%, −0.9%, respectively), reaching mean final HbA_{1c} levels of 6.5% (48 mmol/mol) for iGlarLixi versus 6.8% (51 mmol/mol) and 7.3% (56 mmol/mol) for iGlar and Lixi, respectively (both *P* < 0.0001). More subjects reached target HbA_{1c} <7% with iGlarLixi (74%) versus iGlar (59%) or Lixi (33%) (*P* < 0.0001 for all). Mean body weight decreased with iGlarLixi (−0.3 kg) and Lixi (−2.3 kg) and increased with iGlar (+1.1 kg, difference 1.4 kg, *P* < 0.0001). Documented symptomatic hypoglycemia (≤70 mg/dL) was similar with iGlarLixi and iGlar (1.4 and 1.2 events/patient-year) and lower with Lixi (0.3 events/patient-year). iGlarLixi improved postprandial glycemic control versus iGlar and demonstrated considerably fewer nausea (9.6%) and vomiting (3.2%) events than Lixi (24% and 6.4%, respectively).

CONCLUSIONS

iGlarLixi complemented iGlar and Lixi effects to achieve meaningful HbA_{1c} reductions, close to near normoglycemia without increases in either hypoglycemia or weight, compared with iGlar, and had low gastrointestinal adverse effects compared with Lixi.

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**A complete list of the LixiLan-O principal investigators can be found in the Supplementary Data online.*

See accompanying article, p. 1972.

The most recent American Diabetes Association/European Association for the Study of Diabetes recommendations suggest that if the individualized HbA_{1c} target is not achieved with lifestyle modifications and metformin, a combination of metformin with any one of six options should be considered, including the choice of injectable basal insulin or a GLP-1 receptor agonist (RA) (1). However, most clinicians and patients prefer to choose dual or even triple oral therapy before deciding between injectable basal insulin and a GLP-1 RA to reach the patient's individualized glycemic target.

Numerous reports have established the value of basal insulin in achieving HbA_{1c} targets. Targets can be met with basal insulin in 50–60% of people with type 2 diabetes uncontrolled with oral agents if the basal insulin is properly titrated and especially when it is initiated during the early stages of diabetes in combination with metformin (2). Basal insulin therapy improves glycemic control primarily by reducing nocturnal and fasting plasma glucose (FPG) (3). Postprandial plasma glucose (PPG) excursions cannot be normalized or considerably improved with basal insulin alone. Thus, those 40–50% with type 2 diabetes who are unable to achieve their individualized glycemic targets with basal insulin alone (4–6) can benefit from the addition of PPG-lowering agents.

GLP-1 RAs stimulate postprandial insulin secretion and suppress glucagon release in a glucose-dependent fashion, and short-acting agents like exenatide and lixisenatide (Lixi) have a pronounced effect on delaying gastric emptying, resulting in a robust lowering of PPG (7). Numerous reports have confirmed the HbA_{1c}-lowering capabilities of GLP-1 RAs when added to oral agents in uncontrolled type 2 diabetes alongside a low risk of hypoglycemia and potential for weight reduction, similar to basal insulin.

However, clinical inertia and aversion to injectable therapy remain barriers for the use of basal insulin and/or GLP-1 RAs in type 2 diabetes. More specifically, concerns about hypoglycemia risk and weight gain (8,9) often delay insulin initiation for many years, and gastrointestinal adverse events (GI AEs) such as nausea and vomiting make GLP-1 RA intolerable for some patients, prompting low adherence and frequent drug discontinuation (10).

Lixi (Lyxumia; Sanofi, Paris, France) is a once-daily, prandial GLP-1 RA with a predominant PPG-lowering effect mainly through delayed gastric emptying and reduction of glucagon release (11). Lixi and insulin glargine (iGlar) 100 units have similar physicochemical features, allowing both components to be mixed as a defined fixed-ratio iGlar:Lixi formulation (iGlarLixi or LixiLan) and delivered through a single daily injection. iGlarLixi can deliver iGlar over a range of 10–60 units/day in steps of 1 unit in a 2:1 or a 3:1 ratio with Lixi. For example, 2 units iGlar will deliver 1 μg Lixi for pen A, whereas for pen B, the 3:1 ratio results in 3 units iGlar to 1 μg Lixi. The fixed-ratio combination limits Lixi to a maximum dose of 20 μg/day and allows a slow increase in the Lixi dose that follows the basal insulin titration.

The clinical rationale for the combination of basal insulin with a short-acting GLP-1 RA is based on the complementary effects of the two agents and on the potential for mitigating barriers to their individual use; iGlar improves FPG, and Lixi decreases PPG without increasing hypoglycemia risk and may attenuate the risk of weight gain experienced with iGlar alone (3,12–16). In addition, the known GI AEs of Lixi can potentially be mitigated by the gradual Lixi dose increments that follow iGlar titration, which is guided solely by the FPG level response and by hypoglycemia and GI tolerance (1).

In a proof-of-concept study, iGlarLixi (2 units iGlar to 1 μg Lixi) achieved robust HbA_{1c} reductions, with weight loss and no increased hypoglycemia compared with iGlar, as well as a very low frequency of GI AEs in patients with type 2 diabetes inadequately controlled on metformin (17). The main objective of the LixiLan-O (Efficacy and Safety of Insulin Glargine/Lixisenatide Fixed Ratio Combination Compared to Insulin Glargine Alone and Lixisenatide Alone on Top of Metformin in Patients With T2DM) study (NCT02058147) was to further those findings by comparing the effects of the titratable fixed-ratio combination of LixiLan (iGlarLixi) with iGlar or Lixi alone on glycemic control in a population of insulin-naive patients with type 2 diabetes inadequately controlled on metformin with or without another glucose-lowering agent, which was discontinued at run-in.

RESEARCH DESIGN AND METHODS

Study Design

The LixiLan-O study was an open-label, randomized, parallel-group, multinational, multicenter phase III clinical trial initiated (first patient enrolled) on 12 February 2014 and ending (last patient completed) on 17 June 2015. Supplementary Fig. 1 summarizes the study design. Patients (aged ≥18 years) with type 2 diabetes diagnosed at least 1 year before screening were eligible if they showed inadequate glycemic control despite being treated for at least 3 months with metformin with or without a second oral glucose-lowering therapy. Inadequate glycemic control was defined as HbA_{1c} ≥7.5% and ≤10.0% (58–86 mmol/mol) for patients treated with metformin alone and ≥7.0% and ≤9.0% (53–75 mmol/mol) for those previously treated with metformin and a second oral glucose-lowering therapy, namely a sulfonylurea, glinide, sodium-glucose cotransporter 2, or dipeptidyl peptidase 4 inhibitor.

Major exclusion criteria were use of an oral agent other than the aforementioned during the 3 months before screening, previous treatment with insulin (except short-term treatment due to intercurrent illness, including gestational diabetes mellitus), and previous discontinuation of a GLP-1 RA due to safety, tolerability, or lack of efficacy. Additional exclusion criteria were amylase and/or lipase more than three times the upper limit of normal or calcitonin ≥20 pg/mL (5.9 pmol/L).

Eligible patients entered a 4-week run-in phase during which those receiving metformin plus another oral glucose-lowering therapy at screening were required to stop the second oral agent at the start of the run-in. For all patients, the dose of metformin was titrated to at least 2,000 mg/day or to the maximum tolerated dose, which had to be ≥1,500 mg/day. At the end of the run-in phase, patients with an HbA_{1c} ≥7.0% and ≤10.0% (53–86 mmol/mol), and an FPG ≤250 mg/dL (≤13.9 mmol/L) were randomly assigned in a 2:2:1 ratio to receive iGlarLixi, iGlar, or Lixi, respectively, for 30 weeks, stratified by HbA_{1c} (<8%, ≥8% [<64, ≥64 mmol/mol]) and for second oral

glucose-lowering therapy use at screening (yes, no). An interactive voice/Web response system generated patient randomization. The study was designed and monitored in accordance with Good Clinical Practice, the International Conference on Harmonization, and the Declaration of Helsinki. Institutional review boards or ethics committees at each study site approved the protocol. Each patient gave written informed consent.

Interventions

iGlarLixi was administered once daily using one of two SoloSTAR (Sanofi) pen injectors: pen A, with a 2:1 ratio of 2 units iGlar to 1 μg Lixi, delivers corresponding insulin doses from 10 to 40 units, allowing administration of iGlarLixi doses from 10 units/5 μg up to 40 units/20 μg, and pen B, with a 3:1 ratio of 3 units iGlar to 1 μg Lixi, delivers corresponding insulin doses from 30 to 60 units, allowing administration of iGlarLixi doses from 30 units/10 μg up to 60 units/20 μg. All patients were started on pen A at 10 units (10 units/5 μg) and continued on the same pen A up to a dose of 40 units. When patients required doses >40 units (40 units/20 μg), they were switched to pen B. Only the window for the insulin dose was visible in both pens. Treatment was titrated once a week to reach and maintain a self-measured FPG of 80–100 mg/dL (4.4–5.6 mmol/L) while avoiding hypoglycemia. Titration for iGlarLixi and iGlar by only 2–4 units weekly was similarly guided only by the required dose for iGlar on the basis of the following algorithm: +2 units (if FPG was >100 and ≤140 mg/dL [>5.6 and ≤7.8 mmol/L]) or +4 units (if FPG was >140 mg/dL [>7.8 mmol/L]). The use of the two pens allowed doses of the component iGlar to be between 10 and 60 units/day while always limiting the Lixi component to a maximum of 20 μg/day regardless of the pen used. iGlarLixi was self-administered once daily 0–60 min before breakfast.

iGlar was supplied in a prefilled disposable Lantus SoloSTAR (Sanofi U.S. LLC, Bridgewater, NJ) pen injector (100 units/mL). The pen can deliver doses from 1 to 80 units in steps of 1 unit. In the current study, the maximum iGlar once-daily dose allowed was 60 units. Injection time was at the discretion of patients and investigators but remained at about the same time throughout treatment. The initial daily dose of iGlar during the first week of treatment was 10 units, and the titration regimen was the same as for iGlarLixi.

Lixi was supplied in disposable prefilled pens containing 50 μg/mL for the starting dose of 10 μg for the first 2 weeks and a different pen containing 100 μg/mL for the 20 μg maintenance dose during the remainder of the study. Lixi was self-administered once daily, 0–60 min before breakfast or the evening meal at the discretion of patients and investigators but remained at about the same time throughout treatment.

Efficacy End Points

The primary efficacy end point was change in HbA_{1c} from baseline to week 30. Changes in the following continuous secondary efficacy end points from baseline to week 30 were assessed: 2-h PPG levels during a standardized meal test, body weight, seven-point self-measured plasma glucose (SMPG) profiles, and FPG.

Categorical secondary efficacy end points at week 30 included percentages of patients reaching HbA_{1c} <7% (53 mmol/mol) and ≤6.5% (48 mmol/mol), composite end points of HbA_{1c} <7% (53 mmol/mol) with no body weight gain, HbA_{1c} <7% (53 mmol/mol) with no documented symptomatic hypoglycemia (≤70 mg/dL [3.9 mmol/L]) during treatment, and HbA_{1c} <7% (53 mmol/mol) with no body weight gain and with no documented symptomatic hypoglycemia. For seven-point SMPG profiles, the average daily change from baseline to week 30 and the change from baseline to week 30 for each of the seven points were evaluated.

Safety End Points

The safety end points assessed were symptomatic hypoglycemia and AEs, including allergic reactions, major cardiovascular events, and pancreatic events, adjudicated by specific independent committees. Severe symptomatic hypoglycemia was defined as requiring another person's assistance to actively administer carbohydrate, glucagon, or other resuscitative actions. Documented symptomatic hypoglycemia was defined as typical symptoms of hypoglycemia accompanied by a measured plasma glucose concentration of ≤70 mg/dL (3.9 mmol/L).

Laboratory safety variables analyzed were hematology; clinical chemistry; lipid parameters; serum amylase, lipase, and calcitonin levels; and urine albumin-to-creatinine ratio. Clinical safety was assessed by physical examination, systolic and diastolic blood pressure, heart rate, and electrocardiographic variables. Anti-Lixi antibodies and/or anti-insulin antibodies were measured at day 1 and at week 30 at centralized laboratories using validated assay methodologies.

Statistical Methods

Enrolling 450 patients in each of the iGlarLixi and iGlar groups would provide >95% power to show noninferiority of the iGlarLixi group to the iGlar group in the HbA_{1c} change from baseline to week 30 on the basis of a true difference between the two groups of zero and a noninferiority upper margin of 0.3% (SD 1.1%, 2.5% significance level one-sided *t* test). A sample size of 450 patients in the iGlarLixi group and 225 patients in the Lixi group would provide >95% power to detect a difference of 0.4% in the HbA_{1c} change from baseline to week 30 between the groups (SD 1.1%, 5% significance level two-sided *t* test).

Efficacy analyses were evaluated with a modified intent-to-treat (mITT) population of all randomly assigned patients who had a baseline assessment and at least one postbaseline assessment of any primary or secondary efficacy variables. The primary efficacy end point was analyzed by a mixed-effect model with repeated measures that included the treatment groups, randomization strata, visit, treatment-by-visit interaction, and country as fixed-effect factors and the baseline HbA_{1c}-by-visit interaction as covariates. The adjusted mean change in HbA_{1c} from baseline to week 30 for each treatment group was estimated as well as the between-group difference and the 95% CI for the adjusted mean. A similar mixed-effect model with repeated measures or ANCOVA was applied for continuous secondary efficacy end points, and Cochran-Mantel-Haenszel method stratified by randomization strata was applied on categorical efficacy end points.

The coprimary hypotheses of statistical superiority of iGlarLixi to Lixi alone and noninferiority of iGlarLixi to iGlar alone

were tested for the primary efficacy end point. Both coprimary hypotheses were required to be established for the primary efficacy end point before the step-down testing procedure for the secondary efficacy end points, and a test of superiority of iGlarLixi over iGlar alone was performed at an α-level of 0.05 (two-sided).

An estimate of the composite end point of HbA_{1c} <7% (53 mmol/mol) at week 30 with no documented symptomatic hypoglycemia in the iGlarLixi group versus iGlar or Lixi was made. This exploratory composite end point was not included in the testing order.

The safety population was defined as all randomly assigned patients who received at least one dose of open-label iGlarLixi, iGlar, or Lixi regardless of the amount of treatment administered. Patients were analyzed for safety according to the treatment received rather than the group to which they were assigned.

RESULTS

Patient Disposition and Baseline Characteristics

A total of 1,170 patients were randomly assigned at 240 centers in 23 countries, with 469 patients assigned to the iGlarLixi group, 467 to the iGlar group, and 234 to the Lixi group (Supplementary Fig. 2). The mITT and safety populations included 1,167 and 1,169 patients, respectively. Demographics and baseline characteristics were similar across the treatment groups (Table 1). Patients had an average age of 58 years, were predominantly Caucasian (~90%), were overweight or obese (BMI ~32 kg/m^2), and had a mean duration of diabetes of ~9 years.

Table 1—Baseline demographics and clinical characteristics (randomized population)

	iGlarLixi (*n* = 469)	iGlar (*n* = 467)	Lixi (*n* = 234)	All (*N* = 1,170)
Age (years)	58.2 ± 9.5	58.3 ± 9.4	58.7 ± 8.7	58.4 ± 9.3
Sex				
Male	222 (47.3)	237 (50.7)	133 (56.8)	592 (50.6)
Female	247 (52.7)	230 (49.3)	101 (43.2)	578 (49.4)
Race				
Caucasian	417 (88.9)	421 (90.1)	216 (92.3)	1,054 (90.1)
Black	33 (7.0)	33 (7.1)	12 (5.1)	78 (6.7)
Asian/Oriental	8 (1.7)	7 (1.5)	3 (1.3)	18 (1.5)
Other	11 (2.3)	6 (1.3)	3 (1.3)	20 (1.7)
Ethnicity				
Hispanic	85 (18.1)	87 (18.6)	51 (21.8)	223 (19.1)
Non-Hispanic	384 (81.9)	380 (81.4)	183 (78.2)	947 (80.9)
Duration of diabetes (years)	8.9 ± 5.5	8.7 ± 5.6	8.9 ± 6.3	8.8 ± 5.7
Baseline BMI (kg/m^2)	31.6 ± 4.4	31.7 ± 4.5	32.0 ± 4.4	31.7 ± 4.4
Patients with BMI ≥30 kg/m^2	62.9	61.7	67.9	63.4
HbA_{1c} at screening				
%	8.2 ± 0.7	8.2 ± 0.7	8.3 ± 0.7	8.2 ± 0.7
mmol/mol	66	66	67	66
HbA_{1c} at baseline				
%	8.1 ± 0.7	8.1 ± 0.7	8.1 ± 0.7	8.1 ± 0.7
mmol/mol	65	65	65	65
Patients with HbA_{1c} ≥8% (64 mmol/mol)	55.9	55.7	56.0	55.8
Baseline FPG (mmol/mol)	9.9 ± 2.4	9.8 ± 2.3	9.8 ± 2.2	9.8 ± 2.3
Baseline metformin dose (mg)	2,246 ± 457	2,245 ± 445	2,267 ± 427	2,250 ± 446
Second oral glucose-lowering therapy use at screening				
Yes	58.4	57.8	56.8	57.9
Sulfonylurea	55.2	53.3	52.6	53.9
Glinide	0.6	2.1	2.1	1.5
SGLT-2 inhibitor	0.4	0.4	0	0.3
DPP-4 inhibitor	2.6	2.4	2.1	2.4

Data are mean ± SD, *n* (%), or %. Screening values are at week −6; baseline values are at week −1. DPP-4, dipeptidyl peptidase 4; SGLT-2, sodium-glucose cotransporter 2.

Primary Efficacy End Point

Baseline HbA_{1c} was 8.1% (65 mmol/mol) in all three groups. Mean HbA_{1c} levels achieved at week 30 were 6.5% (48 mmol/mol) for iGlarLixi, 6.8% (51 mmol/mol) for iGlar, and 7.3% (56 mmol/mol) for Lixi (Fig. 1*A*). The least squares (LS) mean changes from baseline to week 30 in HbA_{1c} were −1.63% for iGlarLixi, −1.34% for iGlar, and −0.85% for Lixi (Table 2 and Fig. 1*B*).

Statistical superiority of iGlarLixi over Lixi was demonstrated for the change in HbA_{1c} from baseline to week 30 (LS mean difference vs. Lixi −0.8% [−8.5 mmol/mol] [95% CI −0.9 to −0.7% (−9.8 to −7.3 mmol/mol)], $P < 0.0001$). The LS mean HbA_{1c} difference at week 30 between iGlarLixi and iGlar (−0.3% [−3.2 mmol/mol] [95% CI −0.4 to −0.2% (−4.2 to −2.1 mmol/mol)], $P < 0.0001$) met noninferiority of iGlarLixi compared with iGlar and demonstrated superiority for this primary efficacy end point ($P < 0.0001$) on the basis of the step-down testing procedure.

Secondary Efficacy End Points

A significantly higher proportion of patients in the iGlarLixi group (74%) reached the HbA_{1c} target of <7% (53 mmol/mol) compared with patients receiving iGlar (59%) or Lixi (33%), or the HbA_{1c} target of ≤6.5% (48 mmol/mol) ($P < 0.0001$ for all comparisons) (Table 2). Body weight increased in the iGlar group (+1.1 kg) and decreased in the iGlarLixi (–0.3 kg) and Lixi (–2.3 kg) groups. A significant difference of 1.4 kg in body weight change from baseline to week 30 was found between the iGlarLixi and iGlar groups ($P < 0.0001$) (Table 2 and Fig. 1*C*).

The LS mean reduction from baseline to week 30 in FPG was similar in the iGlarLixi and iGlar groups, reflecting similar basal insulin titration in both groups, but was smaller with Lixi (Table 2 and Fig. 1*D*). In addition, iGlarLixi substantially improved 2-h PPG compared with iGlar after a standardized breakfast (Table 2 and Fig. 1*E*).

Patients treated with iGlarLixi had a significantly greater decrease in average seven-point SMPG profile compared with those treated with iGlar (LS mean difference −12.5 mg/dL [−0.69 mmol/L] [95% CI −16.1 to −8.9 mg/dL (−0.89 to −0.50 mmol/L)], $P < 0.0001$) and Lixi (−25.2 mg/dL [−1.40 mmol/L] [95%

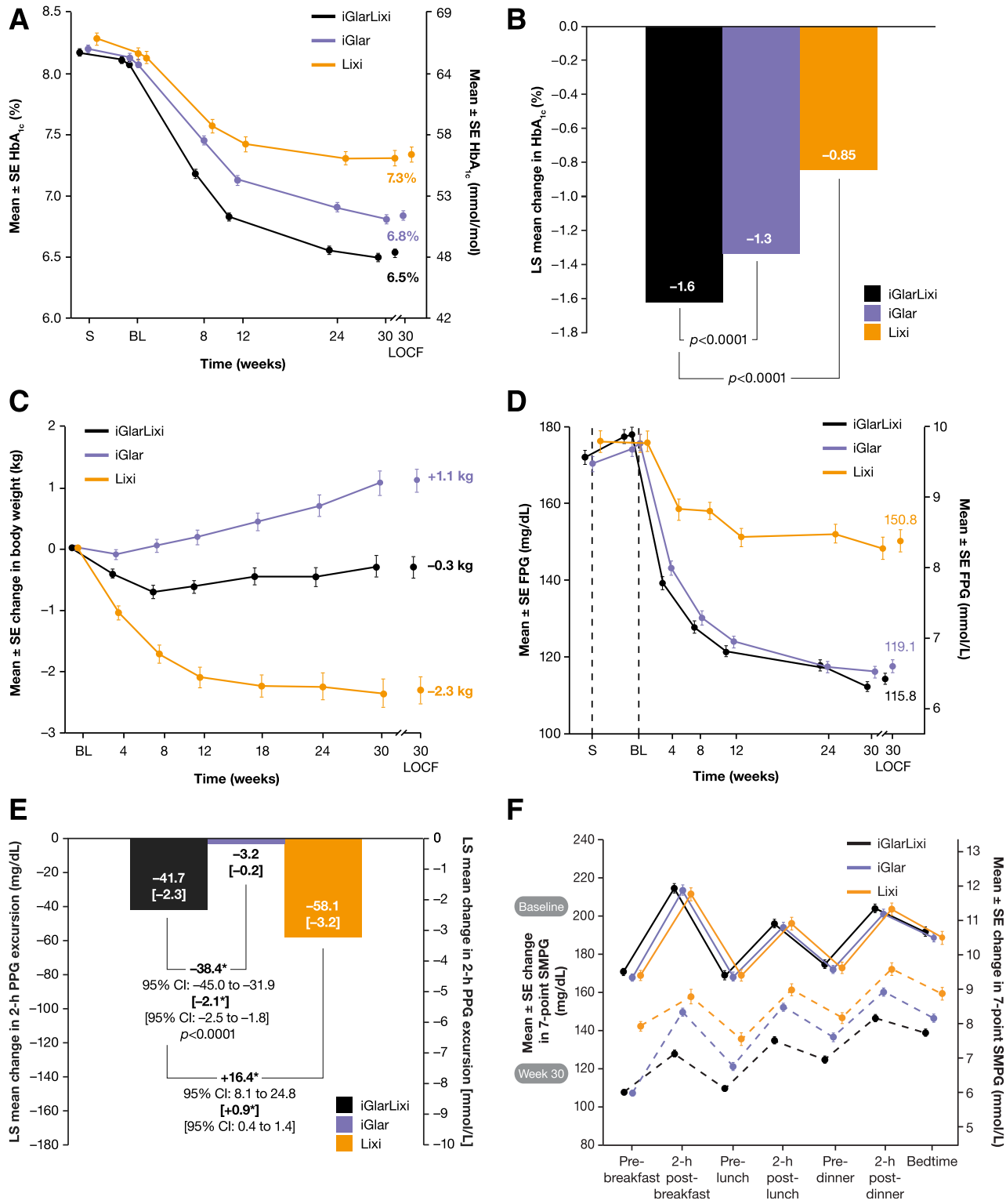

Figure 1—HbA_{1c} by study visit (observed cases) (*A*), LS mean change in HbA_{1c} (*B*), body weight by study visit (*C*), FPG by study visit (*D*), LS mean change in 2-h PPG excursion during a standardized meal test, all from baseline to week 30 (*E*), and change in seven-point SMPG profiles at baseline and week 30 (*F*). Data are mean ± SD. *LS mean difference vs. iGlar or Lixi (mITT; ANCOVA). BL, baseline; LOCF, last observation carried forward.

CI −29.6 to −20.9 mg/dL (−1.65 to −1.16 mmol/L)], $P < 0.0001$). After 30 weeks, mean values at all time points for the seven-point SMPG profiles were lower in the iGlarLixi group than in the iGlar and Lixi groups with the exception of the prebreakfast value, which was similar for iGlarLixi and iGlar (Fig. 1*F*).

As shown in Table 2, higher proportions of patients in the iGlarLixi group than in the iGlar or Lixi groups, reached at week 30 the predefined composite end points of HbA_{1c} <7.0% (53 mmol/mol) with no body weight gain in the iGlarLixi group and HbA_{1c} <7.0% (53 mmol/mol)

with no body weight gain and with no documented symptomatic hypoglycemia (≤70 mg/dL [3.9 mmol/L]) during the study. By week 30, a higher proportion of patients receiving iGlarLixi also reached the composite end point of HbA_{1c} <7% (53 mmol/mol) with no documented symptomatic hypoglycemia (54% for iGlarLixi vs. 44% and 31% for iGlar and Lixi, respectively).

The final mean basal insulin daily dose was similar between the iGlarLixi group (39.8 ± 14.9 units) and the iGlar group (40.3 ± 14.9 units) determined by the FPG titration. The analysis of the percentage of patients by average daily iGlar dose category at week 30 showed that the proportion of patients per dose category was generally similar between the two treatment groups. The majority of patients in both treatment groups had a final daily insulin dose ≥30 units and ≤60 units (71% in the iGlarLixi group, 70% in the iGlar group) with 44% and 45% receiving >40 to ≤60 units; only 16% and 20% received the maximum permissible dose of 60 units of insulin, respectively.

Table 2—Results (mITT population)

Efficacy end point	iGlarLixi (*n* = 468)	iGlar (*n* = 466)	Lixi (*n* = 233)
HbA_{1c} (%) (mmol/mol)			
Baseline	8.1 ± 0.7 (65)	8.1 ± 0.7 (65)	8.1 ± 0.7 (65)
Week 30	6.5 ± 0.8 (48)	6.8 ± 0.8 (51)	7.3 ± 0.9 (56)
LS mean ± SE change from baseline*	−1.6 ± 0.04	−1.3 ± 0.04	−0.9 ± 0.05
LS mean ± SE difference vs. iGlar*	−0.3 ± 0.05		
95% CI	−0.4 to −0.2		
P value	<0.0001		
LS mean ± SE difference vs. Lixi*	−0.8 ± 0.06		
95% CI	−0.9 to −0.7		
P value	<0.0001		
HbA_{1c} ≤6.5% (48 mmol/mol) at week 30			
n (%)	261 (55.8)	184 (39.5)	45 (19.3)
Difference from iGlar (%)†	16.4		
95% CI	10.1 to 22.6		
P value	<0.0001		
Difference from Lixi (%)†	36.4		
95% CI	29.8 to 43.0		
P value	<0.0001		
HbA_{1c} <7.0% (53 mmol/mol) at week 30			
n (%)	345 (73.7)	277 (59.4)	77 (33.0)
Difference from iGlar (%)†	14.3		
95% CI	8.4 to 20.3		
P value	<0.0001		
Difference from Lixi (%)†	40.6		
95% CI	33.6 to 47.6		
P value	<0.0001		
2-h PPG (mmol/L)			
Baseline	15.2 ± 3.6	14.6 ± 3.6	14.7 ± 3.3
Week 30 (LOCF)	9.2 ± 3.2	11.4 ± 3.1	10.0 ± 3.9
LS mean ± SE change from baseline‡	−5.7 ± 0.2	−3.3 ± 0.2	−4.6 ± 0.2
LS mean ± SE difference vs. iGlar‡	−2.4 ± 0.2		
95% CI§	−2.8 to −2.0		
LS mean ± SE difference vs. Lixi‡	−1.1 ± 0.3		
95% CI§	−1.6 to −0.6		
FPG (mmol/L)			
Baseline	9.9 ± 2.3	9.8 ± 2.3	9.8 ± 2.2
Week 30 (LOCF)	6.3 ± 1.5	6.5 ± 1.8	8.3 ± 2.2
LS mean ± SE change from baseline*	−3.5 ± 0.1	−3.3 ± 0.1	−1.5 ± 0.1
LS mean ± SE difference vs. iGlar*	−0.2 ± 0.1		
95% CI	−0.4 to 0.04		
P value	0.1		
LS mean ± SE difference vs. Lixi*	−2.0 ± 0.1		
95% CI	−2.2 to −1.7		
P value	<0.0001		
Body weight (kg)			
Baseline	89.4 ± 17.2	89.8 ± 16.3	90.8 ± 16.3
Week 30	89.2 ± 17.3	90.7 ± 16.0	88.6 ± 16.2
LS mean ± SE change from baseline*	−0.3 ± 0.2	1.1 ± 0.2	−2.3 ± 0.3
LS mean ± SE difference vs. iGlar*	−1.4 ± 0.3		
95% CI	−1.9 to −0.9		
P value	<0.0001		
LS mean ± SE difference vs. Lixi*	2.0 ± 0.3		
95% CI§	1.4 to 2.6		
HbA_{1c} <7.0% (53 mmol/mol) without weight gain at week 30			
n (%)	202 (43.2)	117 (25.1)	65 (27.9)
Difference vs. iGlar (%)†	18.1		
95% CI	12.2 to 24.0		
P value	<0.0001		
Difference vs. Lixi (%)†	15.2		
95% CI§	8.1 to 22.4		

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Safety Profile

Hypoglycemia

The incidence of symptomatic documented hypoglycemia (≤70 mg/dL) was similar with iGlarLixi and iGlar (26% and 24%, respectively) (Table 3). The corresponding number of events per patient-year was generally low and comparable between the two groups (1.4 and 1.2 for iGlarLixi and iGlar, respectively). The incidence and event rates were lower in the Lixi group (6%, 0.3 events/patient-year). One severe symptomatic hypoglycemic episode was reported, which occurred in the iGlar group.

Overall Safety

All treatments were well tolerated. The safety profile of iGlarLixi reflected the established safety profiles of its components except for considerably fewer GI AEs compared with Lixi (Table 3). Most AEs were considered mild or moderate in intensity. Nausea (9.6%, 24.0%) and diarrhea (both 9.0%) were the most frequent GI AEs associated with the iGlarLixi and Lixi groups, respectively; these subsided over time (Supplementary Fig. 3). Vomiting was

Table 2—Continued

Efficacy end point	iGlarLixi (*n* = 468)	iGlar (*n* = 466)	Lixi (*n* = 233)
HbA_{1c} <7.0% (53 mmol/mol) at week 30 and no documented symptomatic hypoglycemia			
n (%)	251 (53.6)	207 (44.4)	71 (30.5)
Difference vs. iGlar (%)†	9.3		
95% CI§	3.0 to 15.6		
Difference vs. Lixi (%)†	23.1		
95% CI§	15.8 to 30.3		
HbA_{1c} <7.0% (53 mmol/mol), no weight gain at week 30 and no documented symptomatic hypoglycemia			
n (%)	149 (31.8)	88 (18.9)	61 (26.2)
Difference vs. iGlar (%)†	13.0		
95% CI	7.5 to 18.5		
P value	<0.0001		
Difference vs. Lixi (%)†	5.6		
95% CI§	−1.3 to 12.6		

Data are mean ± SD unless otherwise indicated. LOCF, last observation carried forward. *Mixed-effect model with repeated measures with treatment groups, randomization strata of HbA_{1c} (<8.0%, ≥8.0%), randomization strata of second oral glucose-lowering therapy use at screening, visit, treatment-by-visit interaction, and country as fixed effects and baseline outcome measure value by visit as a covariate. †Weighted average of proportion difference between treatment groups from each strata (randomization strata of HbA_{1c} [<8.0%, ≥8.0%], randomization strata of second oral glucose-lowering therapy use at screening [yes, no]) using Cochran-Mantel-Haenszel weights. Proportion difference = difference of the proportions of patients achieving HbA_{1c} target. ‡ANCOVA model with treatment groups, randomization strata of HbA_{1c} (<8.0%, ≥8.0%), randomization strata of second oral glucose-lowering therapy use at screening, and country as fixed effects and baseline 2-h PPG excursion value as a covariate. §No *P* value because the comparison was specified in the step-down testing procedure.

also less common with iGlarLixi than with Lixi (3.2% vs. 6.4%). Adjudicated allergic reactions and major cardiovascular events occurred in low percentages of patients in all three treatment groups. No events were adjudicated as pancreatitis in any treatment group. One patient in the iGlar group had pancreatic cancer.

A similar proportion of patients reported serious AEs across the three treatment groups (Table 3). A higher proportion of patients withdrew from the Lixi group (9.0%) due to AEs than from the iGlarLixi (2.6%) or iGlar (1.9%) groups. A higher proportion of withdrawals followed GI AEs in the Lixi group than in the iGlarLixi and iGlar groups (Table 3).

The proportions of patients with any AEs adjudicated as allergic reactions were low and similar among groups (1.3%, 0.6%, and 0.9% in the iGlarLixi, iGlar, and Lixi groups, respectively). In the iGlarLixi group, three cases (0.6%) of urticaria were adjudicated as possibly related to study drug, and three cases (0.6%) of angioedema were adjudicated as not related. In the iGlar group, no event was adjudicated as related, and in the Lixi group, one case of urticaria (0.4%) and one case of anaphylaxis (0.4%) were classified as possibly related to study drug. With regard to positively adjudicated cardiovascular events, two patients experienced events in the iGlarLixi group (one cardiovascular death and one unstable angina), seven in the iGlar group (two cardiovascular deaths; two hospitalizations for heart failure; and one each of nonfatal stroke, unstable angina, and coronary revascularization procedure), and two in the Lixi group (one cardiovascular death and one nonfatal stroke). No clinically significant safety issues were identified on the basis of a review of clinical laboratory parameters (including lipase, amylase, and calcitonin) (Supplementary Table 1), vital signs, physical examinations, electrocardiograms, and antibody levels or compared with AEs in antibody-positive and antibody-negative populations (data not shown).

CONCLUSIONS

This study demonstrates that LixiLan (iGlarLixi), a novel titratable fixed-ratio combination of iGlar and Lixi, is more effective in achieving meaningful improvements in glycemic control than iGlar or Lixi alone, reaching a near-normal HbA_{1c} level of 6.5%, which was attained with no weight gain and without increasing the risk of hypoglycemia, thus contrasting with the known outcomes in insulin-naive patients with type 2 diabetes initiating basal insulin treatment. Most treat-to-target trials using basal insulin in insulin-naive patients have achieved HbA_{1c} levels in the 7.0–7.3% range (53–56 mmol/mol) (18–20), have reported weight gain, and, depending on the type of insulin and HbA_{1c} achieved, most found significant rates of hypoglycemia. Of note, the iGlar group in the current trial achieved an unusual HbA_{1c} level of 6.8% (51 mmol/mol), attesting to a well-conducted study with insulin optimization, but still, iGlarLixi achieved further HbA_{1c} reductions. Moreover, iGlarLixi was not associated with the weight gain often seen with the initiation of insulin therapy and showed no increased risk of hypoglycemia despite the lower HbA_{1c} levels compared with iGlar, while being associated with considerably fewer nausea and vomiting events than Lixi. The improvement in HbA_{1c} was also reflected in the substantially higher proportion of iGlarLixi-treated patients (74%) reaching the HbA_{1c} target of <7.0% versus patients in the iGlar (59%) and Lixi (33%) groups.

Fear of weight gain and hypoglycemia are some of the reasons why insulin-naive patients and their physicians may resist initiating insulin treatment despite poor glycemic control (13). In the current study, the Lixi component of iGlarLixi prevented the potential for weight gain classically seen with the introduction of insulin, with a significant weight difference of 1.4 kg between the iGlarLixi and iGlar arms ($P < 0.0001$). The composite end points further confirmed that the glycemic control achieved with iGlarLixi did not come with the burden of increased body weight: 43% of patients achieved HbA_{1c} <7% with no weight gain. Glycemic control with iGlarLixi was also achieved without increasing the risk of hypoglycemia compared with iGlar: the number of documented symptomatic hypoglycemia events per patient-year was generally low and comparable between iGlarLixi and iGlar (1.4 and 1.2, respectively), and no severe hypoglycemic events occurred in the iGlarLixi group.

Most notably, iGlarLixi had markedly lower rates of nausea (9.6%) and vomiting (3.2%) than Lixi (nausea 24.0%,

Table 3—Safety

Patients with	iGlarLixi (*n* = 469)	iGlar (*n* = 467)	Lixi (*n* = 233)
At least one treatment-emergent AE			
Any AE	267 (56.9)	227 (48.6)	157 (67.4)
Serious AE	18 (3.8)	19 (4.1)	9 (3.9)
AE leading to death*	2 (0.4)	3 (0.6)	1 (0.4)
AE leading to discontinuation	12 (2.6)	9 (1.9)	21 (9)
AE by organ class			
Gastrointestinal disorders (overall)	102 (21.7)	59 (12.6)	86 (36.9)
Nausea	45 (9.6)	17 (3.6)	56 (24.0)
Discontinuation due to nausea	2 (0.4)	0	6 (2.6)
Vomiting	15 (3.2)	7 (1.5)	15 (6.4)
Discontinuation due to vomiting	2 (0.4)	0	4 (1.7)
Diarrhea	42 (9.0)	20 (4.3)	21 (9.0)
Discontinuation due to diarrhea	1 (0.2)	0	2 (0.9)
Hypoglycemia			
Documented symptomatic hypoglycemia (plasma glucose ≤70 mg/dL [3.9 mmol/L])			
Patients with events	120 (25.6)	110 (23.6)	15 (6.4)
Number of events per patient-year†	1.4	1.2	0.3
Documented symptomatic hypoglycemia (plasma glucose <60 mg/dL [3.3 mmol/L])			
Patients with events	66 (14.1)	50 (10.7)	6 (2.6)
Number of events per patient-year†	0.5	0.3	0.1
Severe symptomatic hypoglycemia			
Patients with events	0	1 (0.2)	0
Number of events per patient-year†	0	<0.01	0

Data are *n* (%) unless otherwise indicated. *See Supplementary Data. †Calculated as number of events divided by total patient-years of exposure. Patient-years of exposure calculated as time from the first to the last injection of investigational drug plus 1 day. Documented symptomatic hypoglycemia = typical symptoms of hypoglycemia accompanied by a measured plasma glucose concentration of ≤70 mg/dL (3.9 mmol/L) or <60 mg/dL (3.3 mmol/L). Severe symptomatic hypoglycemia = requiring another person's assistance to actively administer carbohydrate, glucagon, or other resuscitative actions. On-treatment period defined as the time from the first injection of investigational drug up to 1 day for symptomatic hypoglycemia after the last injection of investigational drug, regardless of the introduction of rescue therapy.

vomiting 6.4%), leading to fewer permanent treatment discontinuations and better tolerance. The rate of nausea in the iGlarLixi group was also lower than that observed in previous studies where Lixi was coadministered with basal insulin as a separate injection (25–27% and 8–9%, respectively) (14,15,21). These findings are likely a result of the gradual small increases of the Lixi dose parallel to the iGlar titration according to fasting glucose targets, mitigating the risk of GI AEs seen when Lixi is administered separately in a fixed-dose fashion. This low frequency of GI AEs confirms the findings of the iGlarLixi proof-of-concept study in which the rates of nausea and vomiting were 7.5% and 2.5%, respectively (17).

The current study did not compare the efficacy of the fixed-ratio combination with that of a regimen consisting of basal insulin with a GLP-1 RA added as a separate injection. However, a cautious indirect comparison suggests that the sequential administration of basal insulin given first followed by the addition of a GLP-1 RA in insulin-naive patients with type 2 diabetes on metformin does not appear to achieve the same robust improvements in glycemic control as the simultaneous administration of both components demonstrated in this study. Perhaps, to support the hypothesis that simultaneous administration with iGlarLixi is more effective and better tolerated than sequentially adding Lixi to basal insulin, the findings of the GetGoal-Duo 1 study may provide some valid hints. Although not directly comparable, in part due to no capping (free titration) of iGlar dose, the GetGoal-Duo 1 study in a similar patient population, which started basal iGlar first and then added Lixi 3 months later in those whose HbA_{1c} was >7%, achieved a final HbA_{1c} of 7.0%, and 56% of participants reached HbA_{1c} <7% by using the sequential regimen (10). In the current study, however, the final HbA_{1c} was 6.5%, and 74% of patients reached the goal of HbA_{1c} <7%. A head-to-head trial comparing the efficacy of iGlarLixi with that of a sequential basal insulin-GLP-1 RA approach has not been conducted and would be needed to determine any additional benefit of the fixed-ratio combination. Nevertheless, the LixiLan-O data challenge the current treatment paradigm of type 2 diabetes, which continues to rely on the sequential addition of therapies to control blood glucose levels, and provide evidence for the value of a titratable fixed-ratio combination of injectable agents with complementary actions to achieve stronger efficacy and potentially better compliance (1).

Studies of other fixed-ratio combinations of basal insulin and a GLP-1 RA have produced fairly similar results. The DUAL 1 study (NCT01336023) showed that a fixed-ratio combination of basal insulin degludec and the GLP-1 RA liraglutide (IDegLira) substantially improved glycemic control compared with each of its components. After 26 weeks, mean HbA_{1c} decreased from a baseline of 8.3% (67 mmol/mol) to 6.4% (46 mmol/mol) with IDegLira, compared with 6.9% (52 mmol/mol) with insulin degludec and 7.0% (53 mmol/mol) with liraglutide. As in the current study, GI AEs developed in a lower proportion of patients receiving the fixed-ratio combination compared with those receiving liraglutide alone (22). However, the GLP-1 RA component of IDegLira has a different mode of action from that of iGlarLixi in that liraglutide potentiates the FPG control of degludec, whereas Lixi targets postprandial glucose levels.

Limitations of the current study include its open-label design. However, the differences in administration patterns of the injectable interventions meant that a double-blind study design would have been impractical. An additional limitation is the 30-week study duration; longer trials will be needed to assess durability of the glucose-lowering effects.

The 2015 American Diabetes Association/European Association for the Study of Diabetes position statement suggested that injectable therapies, such

as basal insulin or a GLP-1 RA, are appropriate as add-on therapies in patients with type 2 diabetes inadequately controlled on metformin alone or in combination with other oral agents (1). Considerable time and energy have been devoted to debating the decision-making process for selecting the first injectable agent, weighing the pros and cons of basal insulin or a GLP-1 RA for achieving individualized glycemic targets limited both by specific barriers and by misconceptions, safety profiles, and clinical inertia. The use of titratable fixed-ratio formulations of basal insulin with a GLP-1 RA proposes a new treatment paradigm that takes advantage of the complementary action of these two therapies while mitigating AEs, in a majority of patients, reaching robust HbA_{1c} reductions to levels previously unattainable with any of the individual therapies.

In conclusion, insulin-naive patients with uncontrolled type 2 diabetes randomly assigned to LixiLan (iGlarLixi) achieved near-normoglycemic control with modest weight loss (mitigating the weight gain observed with iGlar alone), saw no increase in hypoglycemia risk compared with iGlar, and had low levels of GI AEs compared with Lixi. These findings support revisiting the treatment paradigm and, potentially, moving away from the sequential addition of injectable therapies toward the use of a titratable fixed-ratio combination of basal insulin and GLP-1 RA therapy in the same formulation.

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