Efficacy and Safety of LixiLan, a Titratable Fixed-Ratio Combination of Insulin Glargine Plus Lixisenatide in Type 2 Diabetes Inadequately Controlled on Basal Insulin and Metformin: The LixiLan-L Randomized Trial

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OBJECTIVE

This study was conducted to demonstrate the efficacy and safety of LixiLan (iGlarLixi), a novel, titratable, fixed-ratio combination of insulin glargine (iGlar) (100 units) and lixisenatide, compared with iGlar in patients with type 2 diabetes inadequately controlled on basal insulin with or without up to two oral glucose-lowering agents.

RESEARCH DESIGN AND METHODS

After a 6-week run-in when iGlar was introduced and/or further titrated, and oral antidiabetic drugs other than metformin were stopped, 736 basal insulin-treated patients (mean diabetes duration 12 years, BMI 31 kg/m^2) were randomized 1:1 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 dose of 60 units/day. The primary outcome was change in HbA_{1c} levels at 30 weeks.

RESULTS

HbA_{1c} decreased from 8.5% (69 mmol/mol) to 8.1% (65 mmol/mol) during the run-in period. After randomization, iGlarLixi showed greater reductions in HbA_{1c} from baseline compared with iGlar (–1.1% vs. –0.6%, $P < 0.0001$), reaching a mean final HbA_{1c} of 6.9% (52 mmol/mol) compared with 7.5% (58 mmol/mol) for iGlar. HbA_{1c} <7.0% (53 mmol/mol) was achieved in 55% of iGlarLixi patients compared with 30% on iGlar. Mean body weight decreased by 0.7 kg with iGlarLixi and increased by 0.7 kg with iGlar (1.4 kg difference, $P < 0.0001$). Documented symptomatic hypoglycemia (≤70 mg/dL) was comparable between groups. Mild gastrointestinal adverse effects were very low but more frequent with iGlarLixi.

CONCLUSIONS

Compared with iGlar, a substantially higher proportion of iGlarLixi-treated patients achieved glycemic targets with a beneficial effect on body weight, no additional risk of hypoglycemia, and low levels of gastrointestinal adverse effects in inadequately controlled, basal insulin-treated, long-standing type 2 diabetes.

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See accompanying article, p. 2026.

Recommendations from the American Diabetes Association and the European Association for the Study of Diabetes suggest that if HbA_{1c} targets are not achieved despite the addition of basal insulin in type 2 diabetes (1), treatment should be further advanced to combination injectable therapy with the progressive addition of prandial rapid-acting insulin or the addition of a glucagon-like peptide 1 receptor agonist (GLP-1 RA) (1,2).

Indeed, the combination of basal insulin with a GLP-1 RA has attracted significant interest recently, based on the complementary effects of these individual therapies and the potential for mitigating barriers to their individual use. Basal insulin therapy improves fasting plasma glucose (FPG) and nocturnal hypoglycemia (3), whereas GLP-1 RAs, especially the short-acting compounds, have a significant effect on postprandial plasma glucose (PPG) (4–9). When combined with basal insulin, GLP-1 RAs do not increase the risks of hypoglycemia and can mitigate the weight gain observed with insulin therapy (4,6–9); GLP-1 RAs do, however, present a risk of gastrointestinal adverse events (AEs), leading to frequent discontinuations (10).

Lixisenatide (Lixi) (Lyxumia; Sanofi, Paris, France) is a once-daily, prandial GLP-1 RA with a predominant PPG-lowering effect brought about mainly by delaying gastric emptying and reducing glucagon release (11). The complementary effects of Lixi administered with basal insulin as separate injections have been demonstrated in the GetGoal clinical trial program (7–9). In particular, in the GetGoal Duo-2 trial (12), which assessed patients with type 2 diabetes inadequately controlled on basal insulin, with or without 1–3 oral antidiabetic drugs (OADs), Lixi added to basal iGlar (100 units), with or without metformin, produced clinically meaningful improvements in glycemic control, with less hypoglycemia and weight gain compared with prandial insulin given as basal-plus or basal-bolus regimens.

iGlarLixi is a titratable, fixed-ratio combination of iGlar and Lixi delivered via a single, daily injection. In this trial, iGlarLixi was administered using two pens: one with a ratio of 2 units of iGlar to 1 μg of Lixi (pen A) and another with a ratio of 3 units of iGlar to 1 μg of Lixi (pen B), allowing for delivery of iGlar over a range of 10 to 60 units/day while ensuring that the Lixi dose did not exceed the recommended dose of 20 μg/day. In addition, the titratable combination allowed a gradual increase in dose of the Lixi component, offering the potential to attenuate the gastrointestinal AEs seen with GLP-1 RAs.

The LixiLan-L phase III trial described here compares the effects of the titratable, fixed-ratio combination iGlarLixi with iGlar in patients with type 2 diabetes inadequately controlled on basal insulin with up to two oral glucose-lowering agents.

RESEARCH DESIGN AND METHODS

Study Design

The LixiLan-L trial was an open-label, randomized, parallel-group, multinational, multicenter phase III clinical trial that was initiated on 27 January 2014 and ended on 9 July 2015. The trial 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.

Supplementary Figure 1 summarizes the trial design. Patients aged ≥18 years with type 2 diabetes diagnosed at least 1 year before screening were eligible to enroll. Patients had to have been treated with a basal insulin for at least 6 months before screening, with a stable regimen for at least 3 months. The total daily basal insulin dose was required to have been stable (± 20%) between 15 and 40 units/day for at least 2 months before the screening visit. The dose(s) of any oral glucose-lowering therapies must have been stable during the 3 months before the screening visit. The permitted OADs at screening were metformin (≥1,500 mg/day or maximal tolerated dose), a sulfonylurea, glinide, sodium–glucose cotransporter 2 inhibitor, or dipeptidyl peptide 4 inhibitor. The required FPG was ≤180 mg/dL (≤10 mmol/L) for patients receiving basal insulin in combination with two OADs or one OAD other than metformin, and ≤200 mg/dL (11.1 mmol/L) for patients on basal insulin with or without metformin.

Major exclusion criteria included the following: use of an oral or injectable glucose-lowering agent other than those stated above; history of hypoglycemia unawareness or metabolic acidosis, including diabetic ketoacidosis within 1 year before screening; patients who previously discontinued GLP-1 RAs because of poor safety, tolerability, or lack of efficacy; and previous use of nonbasal insulin (e.g., prandial or premixed insulin) in the year before screening, with the exception of treatment with nonbasal insulin for ≤10 days because of intercurrent illness. Also exclusionary were amylase and/or lipase levels >3 times the upper limit of the normal laboratory range or calcitonin ≥20 pg/mL (5.9 pmol/L).

Eligible patients entered a 6-week run-in phase during which any OAD other than metformin was stopped, patients were switched to iGlar (if they had previously been receiving another basal insulin), and the daily dose of iGlar was titrated and/or stabilized for all patients. At the end of the run-in phase, patients who had an HbA_{1c} level of 7–10% (53–86 mmol/mol), a mean fasting self-measured plasma glucose (SMPG) of ≤140 mg/dL (7.8 mmol/L), iGlar daily dose of 20–50 units (inclusive), calcitonin of ≤20 pg/mL (5.9 pmol/L), and amylase and/or lipase levels <3 times the upper limit of normal were randomized in a 1:1 ratio stratified by HbA_{1c} value (<8%, ≥8% [<64, ≥64 mmol/mol]) at week –1 and metformin use at screening (yes/no) to receive once-daily open-label treatment with iGlarLixi or iGlar for 30 weeks. An interactive voice/web response system generated the patient randomization list and allocated treatment centrally based on a randomization scheme provided by the study statistician.

Interventions

iGlarLixi was self-administered once daily within 60 min before breakfast using one of two SoloStar (Sanofi, Paris, France) pen injectors, according to the insulin dose required. Pen A, with a ratio of 2 units Glar:1 μg Lixi, delivered doses from 10 to 40 units, corresponding to delivered doses of iGlar/Lixi from 10 units:5 μg up to 40 units:20 μg. Pen B, with a ratio of 3 units iGlar:1 μg Lixi, delivered doses from 30 to 60 units, corresponding to doses of iGlar/Lixi of 30 units/10 μg up to 60 units/20 μg. The starting dose of iGlarLixi was determined from the last iGlar dose received before randomization, at the end of the run-in period, as follows: if, on the day

before randomization, the dose of iGlar was <30 units, the starting dose of iGlarLixi was 20 units:10 μg (given with pen A); however, if the dose was ≥30 units, the starting dose of iGlarLixi was 30 units:10 μg (given with pen B).

The starting dose was kept stable for 2 weeks, with subsequent titration once a week to reach and maintain a target fasting SMPG of 80–100 mg/dL (4.4–5.6 mmol/L) while avoiding hypoglycemia. Titration of iGlarLixi was based on the required dose of iGlar according to 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]). During the titration period, iGlarLixi was administered with pen A or pen B according to the required iGlarLixi daily dose. For a given dose of between 30 and 40 units, the pen that provided a higher dose of Lixi (i.e., pen A with a ratio of 2 units iGlar: 1 μg Lixi) was used as long as it was well tolerated.

iGlar was supplied in a prefilled disposable Lantus SoloStar (Sanofi U.S. LLC, Bridgewater, NJ) pen injector (100 units/mL). In the current study, the maximum iGlar once-daily dose was capped at 60 units. The iGlar injection time was at the discretion of patients and investigators but remained at about the same time each day throughout treatment. The initial daily dose of iGlar was the same dose as before randomization, and the titration regimen was the same as with iGlarLixi, capped also at 60 units.

Rescue medication in the form of a short/rapid-acting insulin (e.g., insulin glulisine) at the main meal was permitted if the study drug (and metformin, if taken) was insufficient to maintain glycemic control below predefined thresholds. The criteria for the use of rescue medication were as follows: if all fasting SMPG values on 3 consecutive days exceeded the specific limit, the patient contacted the investigator, and a central laboratory FPG measurement (and HbA_{1c} measurement after week 12) was performed.

The threshold values were defined as follows:

- from week 8 to week 12 (excluding the week 12 value): FPG >240 mg/dL (13.3 mmol/L),
- from week 12 to week 30 (including the week 30 value): FPG >200 mg/dL (11.1 mmol/L) or HbA_{1c} >8%.

If the FPG or HbA_{1c} values were above the predefined thresholds, the investigator had to ensure that no reasonable explanation existed for insufficient glucose control. If no reasons could be found, if appropriate actions failed, or if a dose of >60 units was necessary to decrease FPG and/or HbA_{1c} below the threshold values defined for rescue therapy, a short/rapid-acting insulin (insulin glulisine) was introduced as rescue therapy along with iGlarLixi or iGlar and metformin (if taken). This was started as a single daily administration at the main meal of the day (except breakfast in the iGlarLixi group). No other oral or injectable antidiabetic treatment was permitted as rescue medication in either treatment group.

All assessments originally planned for the end of treatment visit (visit 21) were performed before rescue therapy was initiated, including pharmacokinetic and antibody assessments. After these assessments were completed and rescue therapy had been initiated, the patient remained in the study according to the planned schedule and continued with study treatment (including metformin, if applicable). The standardized meal for the meal test consisted of one Boost Plus drink and one Boost High Protein drink (Nestlé, Vevey, Switzerland) at U.S. investigational sites, and two Ensure Plus drinks (Abbot, Lake Bluff, IL) at all other investigational sites.

Efficacy End Points

The primary efficacy end point was the change in HbA_{1c} from baseline to week 30. The percentage of patients reaching target HbA_{1c} <7.0% (53 mmol/mol) and ≤6.5% (48 mmol/mol) at week 30 and the change in 2-h PPG during the standardized liquid meal test were secondary end points. Other secondary end points were tested in the following prioritized order: change in 2-h PG excursion during a standardized liquid meal test, change in body weight, change in average 7-point SMPG profile, percentage of patients reaching HbA_{1c} <7% (53 mmol/mol) with no body weight gain at week 30, percentage of patients reaching HbA_{1c} <7% (53 mmol/mol) with no body weight gain at week 30 and no documented symptomatic hypoglycemia during treatment, iGlar daily dose, and FPG. Additional secondary end points included the percentage of patients reaching HbA_{1c} <7% (53 mmol/mol) at week 30 with no documented symptomatic hypoglycemia (PG ≤70 mg/dL [3.9 mmol/L]) during the 30-week randomized treatment period and the percentage of patients requiring rescue therapy during the 30-week randomized treatment period.

Safety End Points

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 an SMPG value of ≤70 mg/dL (≤3.9 mmol/L).

Safety end points of special interest included symptomatic hypoglycemia and gastrointestinal AEs. Allergic reactions, major cardiovascular events, and pancreatic events were adjudicated by specific independent committees, safety laboratory values, vital signs and physical examination, electrocardiogram (ECG), and anti-Lixi antibodies and/or anti-insulin antibodies.

Laboratory safety variables analyzed included hematology, clinical chemistry, lipid parameters, serum amylase, lipase, and calcitonin. Clinical safety was assessed by physical examination, systolic and diastolic blood pressure, heart rate, and ECG variables.

Committees and Blinding

The Data Monitoring Committee reviewed and analyzed safety data provided by an independent statistical group throughout the study. The Allergic Reaction Assessment Committee (ARAC) reviewed and adjudicated allergic reactions or allergy-like reactions after randomization. The Cardiovascular Events Adjudication Committee (CAC) reviewed and adjudicated major cardiovascular events after randomization. The Pancreatic Safety Assessment Committee (PSAC) reviewed and adjudicated selected pancreatic events (including pancreatitis, pancreatic neoplasms, and abnormal levels of amylase or lipase) after randomization.

The study was an open-label design. Therefore, data that could identify treatment were masked for data review and event adjudication, and thus the ARAC, CAC, and PSAC reviewed and adjudicated blinded data.

Statistical Methods

Enrolling 350 patients per group was required to detect a 0.4%, considered

clinically meaningful, mean difference in change in HbA_{1c} from baseline to week 30 between the iGlarLixi and the iGlar groups with at least 95% power (two-sided *t* test; 5% significance level; common SD of 1.1%).

Efficacy analyses were evaluated using a modified intent-to-treat (mITT) population of all randomized patients who had a baseline assessment and at least one postbaseline assessment of any primary or secondary efficacy variables, irrespective of compliance with the protocol and procedures. Analyses of the primary efficacy end point (change from baseline to week 30 in HbA_{1c}) were performed using the mITT population, using HbA_{1c} values obtained from the scheduled visits during the study, including those obtained after study drug discontinuation or rescue medication use. The statistical test was two-sided at the α level of 0.05. The primary efficacy end point was analyzed using a mixed-effect model with repeated measures (MMRM) 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 was the between-group difference and the 95% CI for the adjusted mean. This same MMRM method or ANCOVA was applied on continuous secondary efficacy end points, and the Cochran-Mantel-Haenszel method stratified by randomization strata was applied on categorical secondary efficacy end points. Secondary efficacy variables were tested in a prioritized order, and testing was stopped when an end point was found not to be statistically significant.

The safety population was defined as all randomized patients who received at least one dose of open-label iGlarLixi, or iGlar, 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 randomized.

RESULTS

Patient Disposition and Baseline Characteristics

A total of 736 patients were randomized at 187 centers in 18 countries, with 367 patients assigned to the iGlarLixi group and 369 to the iGlar group (Supplementary Fig. 2). At screening, 64.4% of patients were receiving iGlar, 21.5% NPH, and 14.1% insulin detemir as basal insulin. Demographics and baseline characteristics were similar across the two treatment groups (Table 1). Patients were a median age of 60.0 years, were primarily white (91.7%), were generally overweight or obese (mean BMI $\sim$31 kg/m^2), had a mean duration of diabetes of $\sim$12 years, and had a mean duration of prior basal insulin treatment of $\sim$3 years. In the iGlarLixi group, 43% of patients had previously received metformin plus another oral drug (discontinued at run-in start), and 46% had received only metformin. These proportions were similar in the iGlar group (38% and 52%, respectively).

Primary Efficacy End Point

During the run-in period of basal insulin (glargine) titration and stabilization, the mean HbA_{1c} level decreased overall from 8.5% (69 mmol/mol) at screening to 8.1% (65 mmol/mol) at baseline by the time of randomization. Statistical superiority of iGlarLixi over iGlar was demonstrated for the change in HbA_{1c} from baseline to week 30 (least-squares mean difference vs. iGlar –0.5%; 95% CI –0.6, –0.4; $P < 0.0001$). Mean HbA_{1c} levels were reduced more with iGlarLixi than with iGlar (–1.1% vs. –0.6%, respectively), achieving after 30 weeks of treatment final HbA_{1c} levels of 6.9% (52 mmol/mol) for iGlarLixi and 7.5% (58 mmol/mol) for iGlar (Fig. 1*A* and Table 2).

Secondary Efficacy End Points

A significantly greater proportion of patients treated with iGlarLixi had reached the HbA_{1c} targets of $<$7.0% (53 mmol/mol) (55% vs. 30%) and $\leq$6.5% (48 mmol/mol) (34% vs. 14%) compared with iGlar ($P < 0.0001$ in each case) at week 30 (Fig. 1*B* and Table 2). The improvement in HbA_{1c} was

Table 1—Demographics and baseline characteristics

	iGlarLixi (*n* = 367)	iGlar (*n* = 369)
Age, years	59.6 ± 9.4	60.3 ± 8.7
Female, %	55.0	51.5
Race, %		
White	92	92
Black	5	6
Other	3	2
Hispanic		
Yes	18	18
No	82	82
Body weight at baseline, kg	87.7 ± 14.5	87.1 ± 14.8
BMI at baseline, kg/m^2	31.3 ± 4.3	31.0 ± 4.2
Patients with BMI ≥30 kg/m^2, %	57.5	57.2
Duration of diabetes, years	12.0 ± 6.6	12.1 ± 6.9
Duration of basal insulin treatment, years	3.1 ± 3.1	3.3 ± 3.1
Basal insulin type at screening, %		
iGlar	64	65
Detemir	13	15
NPH	23	20
OAD use at screening, %		
None	5	5
Metformin	46	52
Sulfonylurea	4	4
DPP-4 inhibitor	1	1
Metformin + sulfonylurea	37	32
Metformin + DPP-4 inhibitor	5	5
Metformin + glinide	1	1
HbA_{1c}, %		
At screening*	8.5 ± 0.7	8.5 ± 0.7
At baseline†	8.1 ± 0.7	8.1 ± 0.7
FPG, mmol/L		
At screening*	7.9 ± 1.8	8 ± 1.8
At baseline†	7.3 ± 2.0	7.4 ± 2.1

Data are presented as the mean ± SD, or as indicated. DPP-4, dipeptidyl peptidase 4. Screening values are at week −6 or *week −8; †baseline values are at week −1.

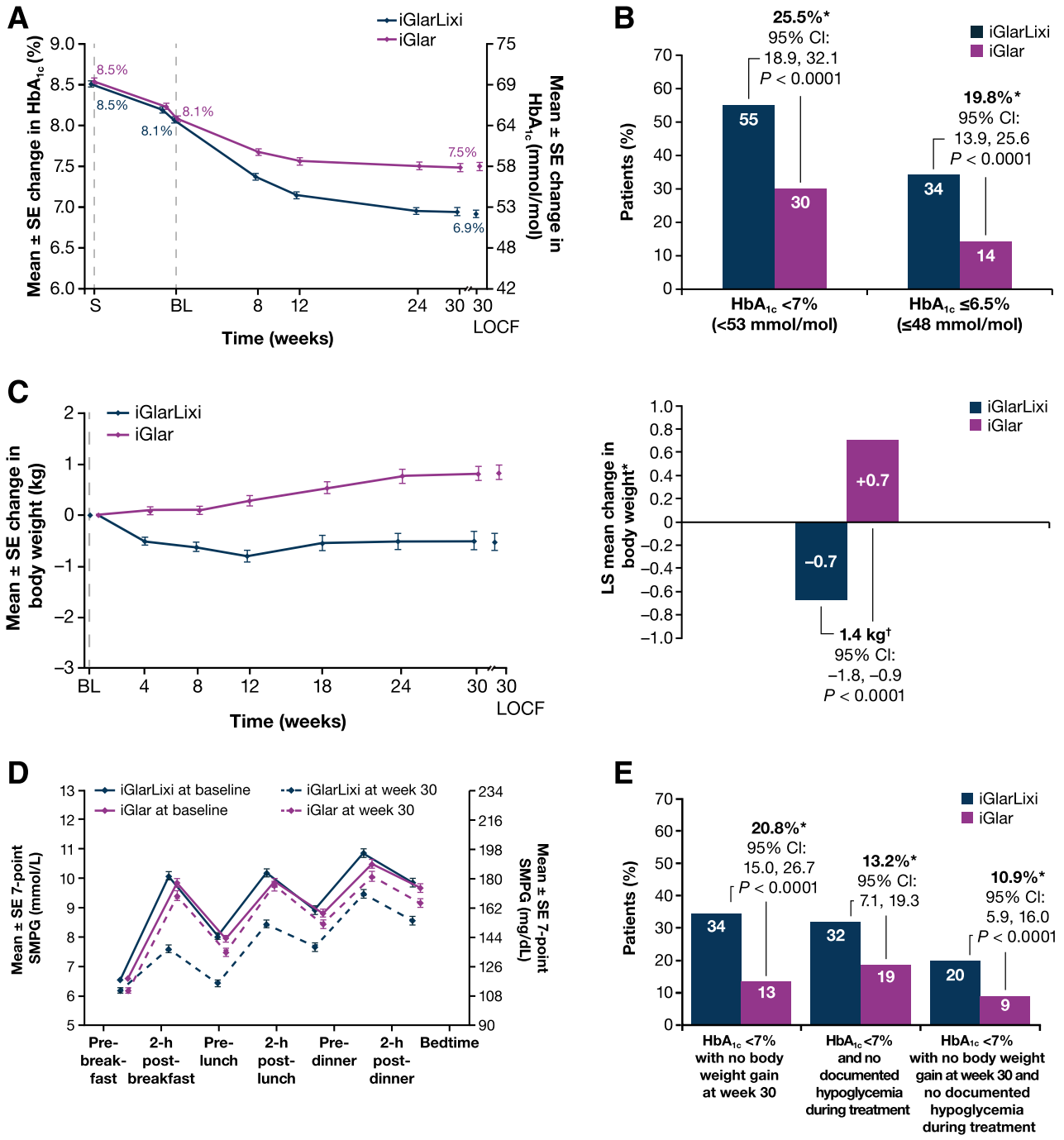

Figure 1—*A*: Change in HbA_{1c} over time (mean ± SE) (mITT population). *mITT/MMRM. *B*: Percentage of responders reaching HbA_{1c} at week 30 in the mITT population. *Weighted average of proportion difference between treatment groups. *C*: Mean ± SE and least squares (LS) mean change in body weight (mITT population). *mITT/MMRM; †LS mean difference vs. iGlar. *D*: Mean ± SE 7-point SMPG (mITT population). *E*: Patients achieving composite end points (mITT population). *Weighted average of proportion difference between treatment groups. BL, baseline; LOCF, last observation carried forward; S, screening.

accompanied by a significant difference of 1.4 kg in body weight change from baseline to week 30 favoring iGlarLixi compared with iGlar ($P < 0.0001$) (Fig. 1*C* and Table 2). Notably, a post hoc evaluation of the percentage of patients with no weight gain at week 30 showed that 54% of patients in the iGlarLixi group had no weight gain during the treatment period, whereas 62% of patients in the iGlar group gained weight.

Although the mean change in FPG was comparable for the two groups from baseline to week 30 (Table 2 and Supplementary Table 1), reflecting consistent titration of the basal insulin components, iGlarLixi compared with iGlar significantly improved postprandial glycemic control after a standardized liquid breakfast meal, as demonstrated by mean change in 2-h glucose excursion from baseline to week 30 (–62 mg/dL [–3.4 mmol/L] difference, $P < 0.0001$) and the 2-h PPG (–60 mg/dL [–3.3 mmol/L]

difference). Similarly, patients treated with iGlarLixi showed a significantly greater decrease in the average 7-point SMPG profiles compared with patients treated with iGlar (–16 mg/dL [–0.90 mmol/L] difference; $P < 0.0001$). After 30 weeks, values on the 7-point SMPG profiles were lower at all time points in the iGlarLixi group compared with iGlar, with the exception of similar fasting pre-breakfast values (Fig. 1*D*, Table 2, and Supplementary Table 1). These results are consistent with the comparable FPG levels observed between treatment groups.

A significantly higher percentage of patients reached the predefined composite end point of HbA_{1c} <7.0% (53 mmol/mol) with no body weight gain at week 30 in the iGlarLixi group (34%) compared with iGlar (13%; $P < 0.0001$) (Fig. 1*E* and Table 2) and reached the composite end point of HbA_{1c} <7.0% (53 mmol/mol) at week 30 with no documented symptomatic hypoglycemia during the treatment period with iGlarLixi (32%) than with iGlar (19%) (Table 2). In addition, a greater proportion reached HbA_{1c} <7.0% (53 mmol/mol) with no body weight gain at week 30 and with no documented symptomatic hypoglycemia during the treatment period with iGlarLixi (20%) than with iGlar (9%).

Insulin dose titration was initiated in the run-in period. To not exceed the highest recommended starting dose of 10 μg for Lixi, iGlarLixi treatment was initiated at a dose of 20 units with pen A or 30 units with pen B, depending on the patient's dose at the end of the run-in period. Therefore, although the insulin dose in the iGlarLixi group dropped at randomization, insulin doses were identical between the iGlarLixi and the iGlar treatment groups for most of the second half of the study and at week 30, reflecting basal insulin titration to similar final FPG levels. The mean final insulin dose was ~47 units, corresponding to a mean dose adjusted by body weight of 0.54 units/kg in both groups. The proportions of patients who required final insulin dose of 60 units were 27.1% in the iGlarLixi group and 30.7% in the iGlar group. The mean corresponding final Lixi dose was 17 μg in the iGlarLixi group. Rescue therapy with prandial insulin was required at the main meal in 10 patients (2.7%) in the iGlarLixi group and in 22 (6.0%) in the iGlar group.

Table 2—Response to therapy

Efficacy end point	iGlarLixi (*n* = 366)	iGlar (*n* = 365)
HbA_{1c}, % (mmol/mol)		
Baseline	8.1 ± 0.7 (65)	8.1 ± 0.7 (65)
Week 30	6.9 ± 0.9 (52)	7.5 ± 0.9 (58)
LS mean ± SE change from baseline*	−1.1 ± 0.06	−0.6 ± 0.06
LS mean ± SE difference vs. iGlar*	−0.5 ± 0.06	–
95% CI	−0.6, –0.4	–
P value	<0.0001	–
HbA_{1c} <7.0% (53 mmol/mol) at week 30		
n (%)	201 (54.9)	108 (29.6)
Difference from iGlar†, %	25.5	–
95% CI	18.9, 32.1	–
P value	<0.0001	–
HbA_{1c} ≤6.5% (48 mmol/mol) at week 30		
n (%)	124 (33.9)	52 (14.2)
Difference from iGlar†, %	19.8	–
95% CI	13.9, 25.6	–
P value	<0.0001	–
2-h plasma glucose excursion, mmol/L		
Baseline	7.0 ± 3.5	7.1 ± 3.1
Week 30 (LOCF)	3.1 ± 3.6	6.7 ± 3.3
LS mean ± SE change from baseline‡	−3.9 ± 0.3	−0.5 ± 0.3
LS mean ± SE difference vs. iGlar‡	−3.4 ± 0.3	–
95% CI	−3.9, –2.9	–
P value	<0.0001	–
2-h PPG, mmol/L		
Baseline	14.9 ± 3.8	15.0 ± 3.7
Week 30 (LOCF)	9.9 ± 3.9	13.4 ± 3.8
LS mean ± SE change from baseline‡	−4.7 ± 0.3	−1.4 ± 0.3
LS mean ± SE difference vs. iGlar‡	−3.3 ± 0.3	–
95% CI	−3.9, –2.8	–
FPG, mmol/L		
Baseline	7.3 ± 1.9	7.3 ± 2.1
Week 30	6.8 ± 2.3	6.7 ± 2.1
LS mean ± SE change from baseline*	−0.4 ± 0.1	−0.5 ± 0.1
LS mean ± SE difference vs. iGlar*	0.1 ± 0.2	–
95% CI	−0.2, 0.4	–
P value	0.495	–
Weight, kg		
Baseline	87.8 ± 14.4	87.1 ± 14.8
Week 30	87.5 ± 14.4	88.0 ± 15.1
LS mean ± SE change from baseline*	−0.7 ± 0.2	0.7 ± 0.2
LS mean ± SE difference vs. iGlar*	−1.4 ± 0.2	–
95% CI	−1.8, –0.9	–
P value	<0.0001	–
7-point SMPG, mmol/L		
Baseline	9.2 ± 1.6	9.1 ± 1.6
Week 30	7.8 ± 1.7	8.6 ± 1.7
LS mean ± SE change from baseline*	−1.5 ± 0.1	−0.6 ± 0.1
LS mean ± SE difference vs. iGlar*	−0.9 ± 0.1	–
95% CI	−1.2, –0.6	–
P value	<0.0001	–
HbA_{1c} <7.0% (53 mmol/mol)		
Without weight gain at week 30		
n (%)	125 (34.2)	49 (13.4)
Proportion difference vs. iGlar†, %	20.8	–
95% CI	15.0, 26.7	–
P value	<0.0001	–
Without documented symptomatic hypoglycemia		
n (%)	116 (31.7)	68 (18.6)
Proportion difference vs. iGlar†, %	13.2	–
95% CI	7.1, 19.3	–

Continued on p. 1978

Table 2—Continued

Efficacy end point	iGlarLixi (n = 366)	iGlar (n = 365)
Without weight gain and documented symptomatic hypoglycemia		
n (%)	73 (19.9)	33 (9.0)
Proportion difference vs. iGlar†, %	10.9	–
95% CI	5.9, 16.0	–
P value	<0.0001	–
Daily iGlar dose, units		
Start of run-in (SD)	27.3 (8.1)	27.7 (8.0)
Baseline	35.0 ± 9.2	35.2 ± 8.6
Week 30	46.7 ± 12.6	46.7 ± 12.5
LS mean ± SE change from baseline*	10.6 ± 0.6	10.9 ± 0.6
LS mean ± SE difference vs. iGlar*	−0.3 (0.8)	–
95% CI	−1.8, 1.3	–
P value	0.736	–

Data are presented as the mean ± SD, or as indicated. Data are provided in mg/dL in Supplementary Table 1. LOCF, last observation carried forward; LS, least squares. *Mixed-effect model with repeated measures; †Cochran-Mantel-Haenszel method; ‡ANCOVA model. The 2-h PG excursion = 2-h PPG – PG 30 min before the meal and before investigational medicinal product injection (only at week 30).

Safety Profile

Hypoglycemia

Comparable proportions of patients in the iGlarLixi (40.0%) and iGlar groups (42.5%) reported documented symptomatic hypoglycemia (PG ≤70 mg/dL [≤3.9 mmol/L]). The corresponding number of events per patient-year was lower in the iGlarLixi group than in the iGlar group (3.03 vs. 4.22). The percentage of patients with at least one severe symptomatic hypoglycemic event was low: four patients (1.1%) in the iGlarLixi group experienced five events, and one patient (0.3%) in the iGlar group experienced one event. In most of these cases, there were contributing circumstances that likely explained the event development, such as excessive exercise and diminished oral intake before the events.

Overall Safety

Both treatments were well tolerated. The safety profile of iGlarLixi generally reflected the established safety profiles of its components (Table 3). The most frequently reported AE was nausea in the iGlarLixi group and nasopharyngitis in the iGlar group. Gastrointestinal disorders were more common with iGlarLixi than with iGlar (Table 3), were generally mild to moderate, and led to treatment discontinuation in very few patients (1.1%). Few potential allergic events were sent to ARAC for adjudication, and none was adjudicated as an allergic reaction in the iGlarLixi group. Major cardiovascular AEs occurred in low and similar percentages of patients in both groups. There were no pancreatitis AE, and no pancreatic neoplasms were reported.

A similar proportion of serious AEs were reported with iGlarLixi and iGlar (Table 3). Three patients experienced at least one severe AE leading to death: one from the iGlarLixi group (pneumonia) and two from the iGlar group (gallbladder cancer and cardiopulmonary failure). A higher proportion of patients withdrew from treatment because of AEs in the iGlarLixi group than in the iGlar group. This difference was mainly because of gastrointestinal AEs (1.1%).

Generally, there was no substantial difference in the safety profiles of (anti-insulin and anti-Lixi) antibody-positive and antibody-negative populations. No clinically significant safety concerns were identified from a review of clinical laboratory parameters (including lipase and amylase), vital signs, physical examination, or ECGs.

Increased calcitonin, categorized as AEs, was confirmed in two patients in the iGlar group and in no patients in the iGlarLixi group. None of the events were serious or led to treatment discontinuation.

CONCLUSIONS

This study demonstrated that iGlarLixi, a novel, titratable, fixed-ratio combination of iGlar and Lixi was more effective in achieving meaningful improvements in glycemic control than iGlar alone, reaching a final mean HbA_{1c} of 6.9% (52 mmol/mol) for iGlarLixi, with beneficial effects on body weight and without increasing hypoglycemia risk, in a challenging population of patients with poorly controlled, basal-insulin treated, long-standing type 2 diabetes. Patients included in the study were overweight or obese, with a long duration of disease (mean diabetes duration of ~12 years) and a mean HbA_{1c} at screening of 8.5% despite treatment for several years with basal insulin plus OADs. The improvement with iGlar alone to an HbA_{1c} of 7.5% was consistent with several trials when the basal insulin is titrated robustly but not enough to reach HbA_{1c} targets (13) because further therapy is needed to address postprandial hyperglycemia. iGlarLixi was indeed successful in further improving HbA_{1c} to a meaningful 6.9% by addressing simultaneously fasting and postprandial hyperglycemia in a single injection formulation.

The improvement in HbA_{1c} was also supported by the significantly higher proportion of patients treated with iGlarLixi in this study who reached the HbA_{1c} targets of <7.0% (53 mmol/mol) (55% vs. 30%) and <6.5% (48 mmol/mol) (34% vs. 14%) compared with iGlar ($P <$ 0.0001 for both).

As observed with previous studies (14,15), the Lixi component of iGlarLixi appears to have mitigated the weight gain generally observed with basal insulin in this population, with a significant weight difference of 1.4 kg between the iGlarLixi and iGlar arms ($P < 0.0001$). The composite end points further confirm that the glycemic control achieved with iGlarLixi did not come at the cost of increased weight, because 34% of patients reached HbA_{1c} <7% (53 mmol/mol) with no weight gain for iGlarLixi compared with 13% for iGlar. Despite the meaningful improvements in glycemic control, the incidence of documented symptomatic hypoglycemia was similar in the iGlarLixi and iGlar treatment groups.

As expected, nausea and vomiting AEs were reported more frequently in the iGlarLixi group than in the iGlar group; however, nausea and vomiting incidences were much lower than those observed when Lixi is used as a standalone treatment, generally in the 25–30% range (7,9,12). Importantly, very few patients discontinued iGlarLixi because of nausea (1.1%) and none for vomiting. This is most likely because of the gradual

Table 3—AEs and hypoglycemic events

Patients (*n* [%]) with	iGlarLixi (*n* = 365)	iGlar (*n* = 365)
At least one TEAE		
Any TEAE	195 (53.4)	191 (52.3)
Serious TEAE	20 (5.5)	18 (4.9)
TEAE leading to death	1 (0.3)	2 (0.5)
TEAE leading to discontinuation	10 (2.7)	3 (0.8)
AE by organ class in ≥5% of patients		
Infections and infestations	98 (26.8)	112 (30.7)
Nervous system disorders	39 (10.7)	19 (5.2)
Gastrointestinal disorders (overall)	62 (17.0)	29 (7.9)
Nausea	38 (10.4)	2 (0.5)
Discontinuation due to nausea	4 (1.1)	0
Vomiting	13 (3.6)	2 (0.5)
Discontinuation due to vomiting	0	0
Diarrhea	16 (4.4)	10 (2.7)
Discontinuation due to diarrhea	0	0
Documented hypoglycemia		
Symptomatic*		
Patients with events, *n* (%)	146 (40.0)	155 (42.5)
Events per patient-year†, *n*	3.03	4.22
Severe‡		
Patients with events, *n* (%)	4 (1.1)	1 (0.3)
Events per patient-year†, *n*	0.02	<0.01
Event rate ratio (95% CI) vs. iGlar	0.77 (0.55–1.07)	–

Patient-years of exposure were calculated as the time from the first to the last injection of the investigational drug plus 1 day. Symptomatic hypoglycemia defined as symptomatic hypoglycemia recorded on the dedicated electronic case report form and meeting the protocol definition for severe or documented hypoglycemia. On-treatment period is 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. TEAE, treatment-emergent AE. *Defined as plasma glucose ≤70 mg/dL [≤3.9 mmol/L]). †Calculated as number of events divided by total patient-years of exposure. ‡In these cases, most had confounding circumstances that likely contributed to the development of the event, such as excessive exercise and diminished oral intake before the events.

increase of the Lixi dose that follows in parallel to the iGlar titration guided by FPGs and tolerance, which clearly mitigates the gastrointestinal AEs. This is a very relevant result given that gastrointestinal AEs were among the main reasons for discontinuation of GLP-1 RAs in a real-world patient survey (16).

Although an indirect comparison, these results compare favorably with those of the GetGoal Duo-2 trial (12), in which Lixi given sequentially as an add-on to basal insulin achieved HbA_{1c} levels of 7.2% in a similar population, and suggest that iGlar plus Lixi given simultaneously as iGlarLixi may be highly effective in a population requiring further treatment intensification despite prior basal insulin treatment.

Comparative benefits of combination of basal insulin with GLP-1 RA as a single injection versus iGlar titration in basal insulin–treated patients with type 2 diabetes have also been reported in the Dual Action of Liraglutide and Insulin Degludec (DUAL) V trial, which examined the efficacy of IDegLira, a single injection combination of insulin degludec and the GLP-1 RA liraglutide (17). In both LixiLan-L and DUAL V, greater HbA_{1c} reductions and a greater proportion of patients reaching glycemic targets were achieved with the combination of basal insulin with GLP-1 RA (iGlarLixi and IDegLira, respectively) compared with titration of iGlar. Consistent across both studies, the delivery of basal insulin with GLP-1 RA as a gradually titratable coformulation appears to confer advantages in weight reduction compared with iGlar titration and seems to be associated with less gastrointestinal intolerability than that typically seen with stepped titration of the GLP-1 RA.

One limitation of the study was its open-label design, which was necessary to account for differences in therapy administration between the groups. An additional limitation is the 30-week study duration. Longer trials will be needed to assess durability of the glucose-lowering effects.

In conclusion, in overweight patients with long-standing type 2 diabetes uncontrolled despite several years on basal insulin and up to two OADs, iGlarLixi achieved superior improvements in glycemic control, with beneficial effects on body weight, no additional risk of hypoglycemia compared with iGlar, and a low rate of gastrointestinal AEs compared with data from prior studies of lixisenatide. These findings further support the approach of using a titratable, fixed-ratio combination of basal insulin and a GLP-1 RA therapy in the same formulation to simplify and more effectively intensify basal insulin treatment in this challenging patient population with long-standing type 2 diabetes.

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participated in speakers' bureaus for Amgen, AstraZeneca, Boehringer Ingelheim, Eli Lilly, Janssen, MSD, Novo Nordisk, Sanofi, Stendhal, and Takeda. H.G. is a consultant for Sanofi. A.T., E.N., and E.S. are employees of and own stock/are shareholders in Sanofi. R.M.B. has served on a scientific advisory board, consulted, or performed clinical research with Abbott Diabetes Care, AstraZeneca, Bayer, Becton Dickinson, Boehringer Ingelheim, DexCom, Eli Lilly, Halozyme, Hygieia, Johnson & Johnson, Medtronic, Merck, Novo Nordisk, Roche, Sanofi, and Takeda. R.M.B.'s employer, the non-profit Park Nicollet Institute, contracts for his services, and no personal income goes to R.M.B. He has inherited Merck stock. No other potential conflicts of interest relevant to this article were reported.

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