Switching to iGlarLixi Versus Continuing Daily or Weekly GLP-1 RA in Type 2 Diabetes Inadequately Controlled by GLP-1 RA and Oral Antihyperglycemic Therapy: The LixiLan-G Randomized Clinical Trial

https://doi.org/10.2337/dc19-1357

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OBJECTIVE

Fixed-ratio combinations of basal insulin plus glucagon-like peptide 1 receptor agonist (GLP-1 RA) allow concomitant administration of two proven complementary injectable therapies for type 2 diabetes. This study investigated switching to a titratable fixed-ratio combination of insulin glargine plus lixisenatide (iGlarLixi) in patients with type 2 diabetes receiving daily or weekly GLP-1 RA therapy.

RESEARCH DESIGN AND METHODS

LixiLan-G, a randomized, open-label, 26-week trial, comparing switching to iGlarLixi versus continuing prior GLP-1 RA in patients with type 2 diabetes and HbA_{1c} 7–9% (53–75 mmol/mol) taking maximum tolerated doses of a GLP-1 RA daily (60% on liraglutide once daily or exenatide twice daily) or weekly (40% on dulaglutide, exenatide extended release, or albiglutide) with metformin with or without pioglitazone and with or without sodium–glucose cotransporter 2 inhibitors. Adherence to randomized treatment was closely monitored throughout the study.

RESULTS

iGlarLixi ($n = 257$) reduced HbA_{1c} more than continued GLP-1 RA therapy ($n = 257$) from a baseline 7.8% (62 mmol/mol) in both to 6.7% (50 mmol/mol) and 7.4% (57 mmol/mol), respectively, at 26 weeks (least squares mean difference −0.6%; $P < 0.0001$). More iGlarLixi patients achieved HbA_{1c} <7% (53 mmol/mol) (62% vs. 26%; $P < 0.0001$) and the composite of HbA_{1c} <7% without documented symptomatic hypoglycemia (<54 mg/dL). Nausea and vomiting rates as well as numbers of documented symptomatic hypoglycemia events per patient-year were generally low but greater with iGlarLixi versus continued GLP-1 RA therapy.

CONCLUSIONS

Switching to iGlarLixi improves glucose control for patients with type 2 diabetes insufficiently controlled on a maximum tolerated dose of a GLP-1 RA plus oral antihyperglycemic agents.

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Received 9 July 2019 and accepted 26 August 2019

Clinical trial reg. no. NCT02787551, clinicaltrials.gov

This article contains Supplementary Data online at http://care.diabetesjournals.org/lookup/suppl/doi:10.2337/dc19-1357/-/DC1.

Lasting glycemic control can be difficult to achieve for patients with type 2 diabetes, often requiring multiple concomitant therapies to achieve and maintain glycemic control. The last consensus statement released by the American Diabetes Association and European Association for the Study of Diabetes in 2018 recommended glucagon-like peptide 1 receptor agonists (GLP-1 RAs) as preferred initial injectable therapy in most patients inadequately controlled despite dual or triple oral therapy, with individualized options for incorporation of basal insulin therapy as required (1,2).

Multiple studies have demonstrated the effectiveness of combining a GLP-1 RA with basal insulin as separate injectable therapies administered sequentially (3,4). Fixed-ratio combinations (FRCs) of basal insulin plus a GLP-1 RA represent a further advance to facilitate management, with one single injection offering concomitant administration of two effective injectable therapies with complementary modes of action to treat type 2 diabetes. Currently, titratable FRCs of liraglutide and insulin degludec (IDegLira) and of the short-acting GLP-1 RA lixisenatide and insulin glargine (iGlarLixi) are available. The short-acting GLP-1 RA exerts insulin-stimulating and glucagon-suppressing effects while also slowing gastric emptying, resulting in blunted postprandial glucose excursions with a greater effect after the meal following the injection time and a residual glucose lowering effect after the next meal (5). The concomitant use of insulin glargine provides control of basal glucose levels. iGlarLixi has been shown to be efficacious and well tolerated in patients with type 2 diabetes uncontrolled by oral antihyperglycemic drugs (OADs) in the LixiLan-O trial (6) or by basal insulin in the LixiLan-L trial (7).

No prior studies have evaluated the efficacy and safety of treatment intensification to iGlarLixi in previously GLP-1 RA–treated patients. Thus, the objective of the LixiLan-G trial was to evaluate the efficacy and safety of switching to iGlarLixi versus continuing treatment with prior GLP-1 RA therapy. This was examined over 26 weeks, monitoring adherence in both arms, in patients with insufficiently controlled type 2 diabetes despite receiving the maximum tolerated dose of a daily or weekly GLP-1 RA in combination with OADs.

RESEARCH DESIGN AND METHODS

Study Design

LixiLan-G was a randomized, open-label, active-controlled, parallel-group, phase 3, 26-week treatment duration study followed by a single-arm, 26-week extension for iGlarLixi (to be reported separately) (Supplementary Fig. 1). The trial was initiated on 6 July 2016, and the randomized 26-week period ended on 25 May 2018. The study was designed and monitored in accordance with Good Clinical Practice guidelines, the International Conference on Harmonization, and the Declaration of Helsinki. Institutional review boards or ethics committees at each study site approved the protocol. Each participant provided written informed consent.

Eligible patients were adults with type 2 diabetes diagnosed for at least 1 year before screening, with HbA_{1c} $\geq$7% to $\leq$9% (53–75 mmol/mol), treated with the maximum tolerated dose of a GLP-1 RA. Specific criteria for different formulations of GLP-1 RAs included $\geq$4 months of treatment with a stable dose for $\geq$3 months before screening with liraglutide once daily or exenatide twice daily, or $\geq$6 months of treatment before screening with a stable dose of exenatide extended release once weekly, albiglutide once weekly, or dulaglutide once weekly. Patients had taken GLP-1 RAs in combination with metformin with or without pioglitazone with or without sodium–glucose cotransporter 2 (SGLT2) inhibitors, all at a stable dose for $\geq$3 months.

Major exclusion criteria included a BMI $\leq$20 or $>$40 kg/m^2 at screening, a history of hypoglycemia unawareness (on the basis of the medical history collected by the investigator and documented in the patients' medical files), previous treatment with insulin in the year before the screening visit (with the exception of short-term treatment [$\leq$10 days] as a result of intercurrent illness), or treatment with antidiabetes drugs within 3 months other than those described above, including sulfonylureas. Laboratory exclusion criteria at screening included amylase and/or lipase levels more than three times the upper limit of normal or calcitonin $\geq$20 pg/mL (5.9 pmol/L).

After a screening period of $\leq$2 weeks, patients were randomized in a 1:1 ratio stratified by HbA_{1c} value ($<$8% [$<$64 mmol/mol], $\geq$8% [$\geq$64 mmol/mol]) and GLP-1 RA subtype (once-daily/twice-daily or once-weekly formulations), either to continue with their current treatment with a GLP-1 RA or to switch from their current GLP-1 RA to iGlarLixi for 26 weeks. In both groups, existing therapies with oral agents were continued without modification. An interactive response technology system generated the patient randomization list and allocated treatment centrally on the basis of a randomization scheme provided by the study statistician.

Interventions

iGlarLixi was to be self-administered daily before breakfast using one of two SoloSTAR (Sanofi, Paris, France) pen injectors differentiated by the iGlar:Lixi ratio according to the insulin dose required. The first pen, with a ratio of 2 units iGlar:1 μg Lixi, was used to deliver doses from 10 to 40 units (10 units iGlar/5 μg Lixi up to 40 units iGlar/20 μg Lixi). The second pen, with a ratio of 3 units iGlar:1 μg Lixi, was used to deliver doses from 30 to 60 units (30 units iGlar/10 μg Lixi up to 60 units iGlar/20 μg Lixi). Treatment was initiated at a dose of 10 units (10 units iGlar/5 μg Lixi [first pen]) and then titrated to reach and maintain a fasting self-monitored plasma glucose (SMPG) target between 80 and 100 mg/dL, with the patient switching to the second, 30–60-unit pen if necessary (Supplementary Table 1). During the first 8 weeks of treatment, titration was performed twice weekly, and evaluated at least once a week afterward. The detailed titration algorithm is shown in Supplementary Table 1. Treatment compliance was estimated on the basis of patient diary review and visual check of returned pens. Patients in both treatment groups measured fasting SMPG once daily from randomization to week 8 inclusive, at least three times per week from week 9 until the end of the randomized treatment period, and whenever the patient experienced hypoglycemia signs or symptoms.

GLP-1 RA comparator therapy was administered subcutaneously as per local labeling, with patients continuing the same dose regimen as before randomization. For all patients not taking the maximum approved dose of the respective GLP-1 RA, investigators confirmed that it was because the maximum dose was not tolerated.

If HbA_{1c} was $>$8% (64 mmol/mol) at week 12 or later, and as confirmed by a retest, rescue therapy was to be

considered according to the investigator's clinical judgment. In the iGlarLixi arm, rescue therapy was recommended only if further dose titration was not possible (if already at the maximum daily dose of 60 units); rapid-acting insulin (insulin glulisine when available) was suggested and recommended to be started as a single daily administration at the main meal of the day (excluding breakfast). Basal insulin was not allowed as rescue therapy in the iGlarLixi arm. In the GLP-1 RA arm, suggested rescue therapy was basal insulin at the investigator's discretion.

Efficacy End Points

The primary end point was HbA_{1c} change from baseline to week 26. Secondary and additional end points included the proportion of patients reaching HbA_{1c} (<7% [<53 mmol/mol] and ≤6.5% [≤48 mmol/mol]) targets at week 26, fasting plasma glucose (FPG) change from baseline to week 26, change in 7-point SMPG profiles from baseline to week 26 (each time point and average daily value), change in 2-h postprandial plasma glucose (PPG) and blood glucose excursion during a standardized meal test from baseline to week 26, change in body weight from baseline to week 26, and iGlarLixi dose at week 26 in the iGlarLixi group. The standardized liquid meal contained ~600 kcal and was composed of 50–55% carbohydrate, 15–20% protein, and 25–30% fat. iGlarLixi or exenatide twice daily were injected 30 min before the start of the standardized meal. Patients taking weekly GLP-1 RAs injected their medication per their usual weekly schedule. The meal test was performed preferably within 3 days after the injection of the weekly GLP-1 RA.

Additional assessments included the composite end point of percentage of patients achieving target HbA_{1c} (<7% [53 mmol/mol]) while remaining free of documented symptomatic hypoglycemia (using thresholds of 70 and 54 mg/dL) over the 26-week treatment period and proportions of patients requiring rescue therapy. Safety assessments included documented symptomatic hypoglycemia; the occurrence of adverse events (AEs) that developed, worsened, or became serious during treatment; safety laboratory values; vital signs; and electrocardiogram results. Severe symptomatic hypoglycemia was defined as an event requiring the assistance of another person to actively administer carbohydrate, glucagon, or other resuscitative actions.

Committees and Blinding

The Allergic Reaction Assessment Committee reviewed and adjudicated allergic reactions or allergy-like reactions after randomization. The Pancreatic Safety Assessment Committee reviewed and adjudicated selected pancreatic events after randomization. The study was an open-label design, but data that could identify treatment were masked for event adjudication by both committees. The investigator and the sponsor remained masked to the HbA_{1c} primary efficacy end point until the end of the 26-week randomized comparative study period. However, if HbA_{1c} was >8% at or after week 12, the investigator received an alert issued by the central laboratory for the purposes of determining whether rescue therapy was necessary, as described earlier.

Statistical Methods

Sample-size calculations were based on the primary efficacy variable (change in HbA_{1c} from baseline to week 26 and intention-to-treat [ITT] analysis), a common SD of 1.1%, a 0.4% mean difference between iGlarLixi and GLP-1 RA in change in HbA_{1c} from baseline to week 26, and an estimated dropout rate of 20% and a *t* test at a two-sided 5% significance level with at least 90% power. On the basis of these assumptions, 500 patients (250 per group) were needed for this study. Efficacy analyses were evaluated using a modified ITT (mITT) population, which included all randomized patients with a baseline assessment and at least one postbaseline assessment of any primary or secondary efficacy variables, irrespective of compliance with the protocol and procedures and regardless of whether patients had received rescue therapy or discontinued the trial. The primary efficacy end point was analyzed using a mixed-effects model with repeated measures (MMRM) under the missing-at-random framework (additional details on MMRM analyses in Supplementary Table 2). The adjusted mean change in HbA_{1c} from baseline to week 26 for each treatment group was estimated in the framework of this model as well as the between-group difference in least squares (LS) means and the corresponding 95% CIs.

This same MMRM approach with the corresponding baseline value-by-visit interaction as a covariate to compare iGlarLixi with GLP-1 RA was used to analyze continuous secondary efficacy end points, except for 2-h PPG and glucose excursion. Two-hour PPG and glucose excursion (for each of which only one postbaseline assessment was scheduled) were analyzed using ANCOVA with the missing data at week 26 imputed by last observation carried forward to compare iGlarLixi with GLP-1 RA.

All categorical secondary efficacy end points defined were analyzed by a Cochran-Mantel-Haenszel method stratified by the randomization strata. The proportion in each treatment group was provided as were the differences in proportions between groups with associated two-sided 95% CIs.

A stepdown testing procedure was applied to control type I error. Testing was performed in the following order: HbA_{1c} change from baseline to week 26 (the primary end point), the percentage of patients reaching HbA_{1c} <7% (53 mmol/mol) at week 26, FPG, average 7-point SMPG, 2-h PPG, and/or glucose excursion (all from baseline to week 26). Testing was stopped when an end point was not statistically significant at the 0.05 level.

Safety population descriptive analyses included all randomized patients who received at least one dose of open-label investigational medicinal product, regardless of the amount of treatment administered. Patients were analyzed according to the treatment actually received.

RESULTS

Patient Disposition and Baseline Characteristics

Overall, 514 patients were randomized at 112 centers in nine countries (Canada, Estonia, Germany, Israel, Italy, Romania, Slovakia, Spain, and U.S.), with 257 randomized to each treatment arm (Supplementary Fig. 2). Of these, 252 and 253 patients comprised the mITT populations of the iGlarLixi and GLP-1 RA treatment arms, respectively.

The demographics and patient characteristics at screening or baseline were fairly similar between the treatment groups (Table 1). Median age was 60.0 years, mean BMI was ~33 kg/m^2, and ~73% of the patients had a BMI

value ≥30 kg/m^2. At screening, overall mean HbA_{1c} was 7.9%, with ~58% of patients having a value <8%. Patients had been taking a GLP-1 RA for slightly <2 years in both groups; 59.7% of patients were receiving a GLP-1 RA administered once or twice daily, while 40.3% were taking a GLP-1 RA once weekly. The most common GLP-1 RAs received were liraglutide (54.5%) and dulaglutide (20.4%). Dose levels are shown in Supplementary Table 2. According to the protocol, all patients were taking metformin at screening; 10.1% were on an SGLT2 inhibitor, and 6.6% were on pioglitazone.

In the iGlarLixi and GLP-1 RA arms, respectively, 230 (91%) and 246 (97%) patients in the mITT population completed the 26-week treatment period. The treatment compliance range was 80–100% in 98.4% and 99.6% in the iGlarLixi and GLP-1 RA groups, respectively.

Primary Efficacy End Point

In the mITT population, which included patients regardless of whether they had received rescue therapy or discontinued treatment, HbA_{1c} reductions from comparable baseline levels of 7.8% to week 26 were −1.0% for the iGlarLixi group and −0.4% for the GLP-1 RA group, reaching mean values of 6.7% and 7.4% at week 26, respectively (LS mean difference vs. continued GLP-1 RA −0.6% [95% CI −0.8%, −0.5%]; $P < 0.0001$) (Fig. 1*A* and *B* and Table 2). These results were robust across various sensitivity analyses, including an on-treatment analysis, an analysis of 26-week completers (patients who completed the 26-week randomized treatment period and did not start any rescue therapy during this time), an analysis to assess the impact of rescue medication, and an analysis with multiple imputations for missing values at week 26.

Secondary and Additional Efficacy End Points

Significantly greater proportions of patients in the iGlarLixi arm achieved HbA_{1c} targets of <7% or ≤6.5% at week 26: 62% and 40.5%, respectively, in the iGlarLixi arm vs. 26% and 10%, respectively, in the GLP-1 RA arm ($P < 0.0001$ for both comparisons) (Fig. 1*C* and Table 2). Starting from slightly different baseline levels (163 mg/dL [9.1 mmol/L] for iGlarLixi and 170 mg/dL [9.5 mmol/L] for GLP-1 RA), the reduction in FPG was significantly greater in the iGlarLixi group compared with the GLP-1 RA group (between-group difference −30 mg/dL [−1.7 mmol/L; $P < 0.0001$], reaching 124 mg/dL [6.9 mmol/L] and 156 mg/dL [8.7 mmol/L] at week 26, respectively) (Fig. 1*D* and Table 2). Moreover, in the iGlarLixi group, after the switch from the pretrial GLP-1 RA, no relevant increase in mean fasting (prebreakfast) SMPG values was observed during the first 4 weeks of treatment. The improvements in FPG in the iGlarLixi group were related to a steady increase in the mean daily insulin dose over the treatment period, reaching a mean value of 43.5 units (0.46 units/kg) at week 26. Most patients (80%) had final insulin daily doses of ≥30 to ≤60 units, with 67 patients (26%) receiving the maximum daily dose of 60 units. For the subgroup reaching the

Table 1—Demographics and baseline and disease characteristics in the randomized population

	iGlarLixi (n = 257)	GLP-1 RA (n = 257)
Age (years)	59.2 ± 9.6	60.0 ± 10.3
Female	131 (51.0)	113 (44.0)
Race		
Asian	3 (1.2)	4 (1.6)
Black	12 (4.7)	7 (2.7)
White	241 (93.8)	244 (94.9)
Other*	1 (0.4)	2 (0.8)
Hispanic or Latino	27 (10.5)	26 (10.1)
HbA_{1c} at visit 1 (week –2) (%)	7.9 ± 0.6	7.9 ± 0.5
Randomization strata of HbA_{1c} at visit 1 (week –2) (%)		
<8 (<64 mmol/mol)	149 (58.0)	147 (57.2)
≥8 (≥64 mmol/mol)	108 (42.0)	110 (42.8)
Baseline BMI (kg/m^2)	32.8 ± 4.4	33.0 ± 4.4
Duration of diabetes (years)	11.2 ± 7.4	11.0 ± 6.1
Duration of GLP-1 RA treatment (years)	1.9 ± 1.8	1.9 ± 1.9
GLP-1 RA use by type at screening		
Once-daily/twice-daily formulation	153 (59.5)	154 (59.9)
Once-weekly formulation	104 (40.5)	103 (40.1)
Liraglutide at baseline	135 (52.5)	145 (56.4)
Exenatide at baseline	18 (7.0)	9 (3.5)
Dulaglutide at baseline	54 (21.0)	51 (19.8)
Exenatide extended release at baseline	45 (17.5)	48 (18.7)
Albiglutide at baseline	5 (1.9)	4 (1.6)
Pioglitazone use at screening	12 (4.7)	22 (8.6)
SGLT2 inhibitor use at screening	26 (10.1)	26 (10.1)
Duration of metformin treatment (years)	7.2 ± 5.3	8.1 ± 5.2
Daily dose of metformin at baseline (mg)	1,966.9 ± 434.6	2,030.7 ± 497.2

Data are mean ± SD or *n* (%). *Includes multiracial patients, and race unknown or not reported. Also includes one patient in the iGlarLixi group identified as Native Hawaiian or other Pacific Islander.

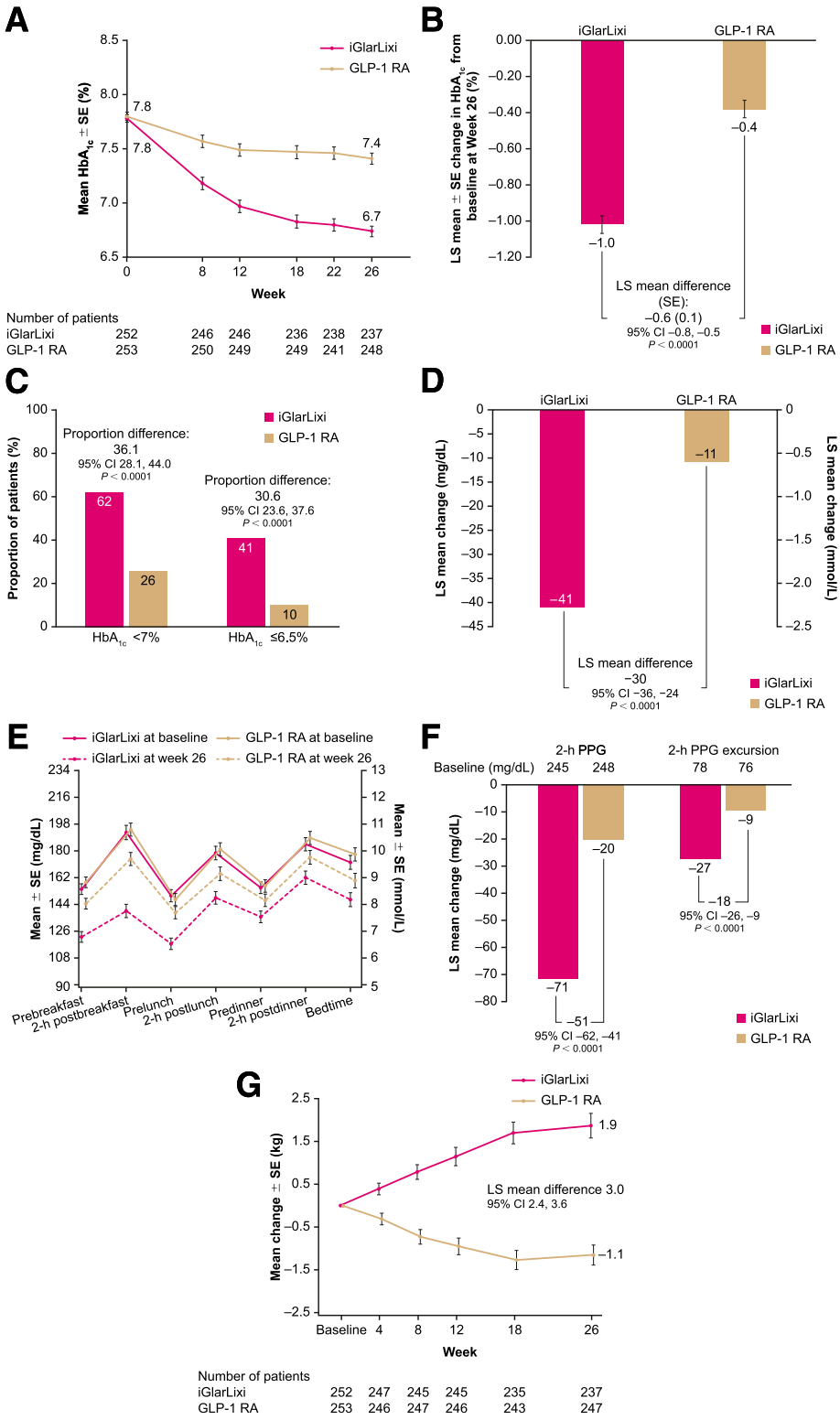

Figure 1—Efficacy over the 26-week randomized treatment period. *A*: Mean HbA_{1c} by visit. *B*: Change in mean HbA_{1c} from baseline at week 26. *C*: Patients at target HbA_{1c}. *D*: FPG. *E*: Seven-point SMPG at baseline and study end (week 26). *F*: PPG. *G*: Change in mean weight from baseline at week 26.

maximum dose, the mean HbA_{1c} at week 26 was 6.9% compared with 6.7% for those receiving a final dose <60 units. In the subgroup reaching the maximum FRC dose, 51% of the patients had an HbA_{1c} <7% at week 26 vs. 66% for the subgroup receiving a final dose <60 units. At week 26, the mean daily dose of the lixisenatide component was 16.6 μg/day, and most patients (75%) had a final dose of ≥15 to ≤20 μg, with 30% receiving the maximum dose of 20 μg.

Patients in the iGlarLixi group reported significantly greater decreases in the average 7-point SMPG profile from baseline to week 26 compared with patients in the GLP-1 RA group ($P < 0.0001$). Seven-point SMPG profiles showed that values

Table 2—Efficacy over 26 weeks (mITT population)

	iGlarLixi (n = 252)		GLP-1 RA (n = 253)
HbA_{1c} (primary end point)			
Baseline			
%	7.8 ± 0.6		7.8 ± 0.6
mmol/mol	62		62
Week 26			
%	6.7 ± 0.8		7.4 ± 0.8
mmol/mol	50		57
LS mean change ± SE	−1.0 ± 0.05		−0.4 ± 0.05
LS mean difference ± SE		−0.6 ± 0.07	
95% CI		−0.8, −0.5	
P value		<0.0001	
Reached target HbA_{1c} <7% (53 mmol/mol)			
n (%)	156 (62)		65 (26)
Proportion difference		36.1	
95% CI		28.1, 44.0	
P value		<0.0001	
Reached target HbA_{1c} ≤6.5% (48 mmol/mol)			
n (%)	102 (41)		25 (10)
Proportion difference		30.6	
95% CI		23.6, 37.6	
P value		<0.0001	
FPG (mg/dL)			
Baseline	163 ± 38		170 ± 35
Week 26	124 ± 30		156 ± 36
LS mean change ± SE	−41 ± 2		−11 ± 2
LS mean difference ± SE		−30 ± 3	
95% CI		−36, −24	
P value		<0.0001	
FPG (mmol/L)			
Baseline	9.1 ± 2.1		9.5 ± 1.9
Week 26	6.9 ± 1.7		8.7 ± 2.0
LS mean change ± SE	−2.3 ± 0.12		−0.6 ± 0.12
LS mean difference ± SE		−1.7 ± 0.17	
95% CI		−2.0, −1.3	
P value		<0.0001	
2-h PPG during standardized meal test (mg/dL)			
Baseline	245 ± 60		248 ± 58
Week 26 (LOCF)	174 ± 56		227 ± 59
LS mean change (LOCF) ± SE	−71 ± 4		−20 ± 4
LS mean difference ± SE		−51 ± 5	
95% CI		−61, −41	
P value		<0.0001	
2-h PPG during standardized meal test, mmol/L			
Baseline	13.6 ± 3.3		13.8 ± 3.3
Week 26 (LOCF)	9.7 ± 3.1		12.6 ± 3.3
LS mean change (LOCF) ± SE	−4.0 ± 0.2		−1.1 ± 0.2
LS mean difference ± SE		−2.9 ± 0.29	
95% CI		−3.4, −2.3	
P value		<0.0001	
HbA_{1c} <7% (53 mmol/mol) with no documented (≤70 mg/dL) symptomatic hypoglycemia, *n* (%)	109 (43.3)		64 (25.3)
HbA_{1c} <7% (53 mmol/mol) with no documented (<54 mg/dL) symptomatic hypoglycemia, *n* (%)	143 (56.7)		64 (25.3)

Data are mean ± SD unless otherwise indicated. LOCF, last observation carried forward.

at all time points through week 26 were notably reduced from baseline in the iGlarLixi group and were always lower in the iGlarLixi group compared with the GLP-1 RA group (Fig. 1*E*).

Treatment with iGlarLixi significantly improved prandial glycemic control after a standardized meal test compared with GLP-1 RA, as shown by the greater LS mean change in both 2-h PPG and 2-h PPG excursion (2-h PPG value − preprandial value) in the iGlarLixi group versus the GLP-1 RA group. LS mean differences between the treatment groups for 2-h PPG and 2-h PPG excursion, respectively, were −51 mg/dL (−2.9 mmol/L) and −18 mg/dL (−1.0 mmol/L; $P < 0.0001$ for both) (Fig. 1*F*).

A greater proportion of patients treated with iGlarLixi achieved the composite end point of HbA_{1c} <7% without

documented symptomatic hypoglycemia (<70 mg/dL) (43% in the iGlarLixi arm vs. 25% in the GLP-1 RA arm). The difference was even greater (57% vs. 25%, respectively) when the hypoglycemia threshold of <54 mg/dL was used (Table 2). Over 26 weeks of treatment, body weight increased in the iGlarLixi group and decreased in the GLP-1 RA group, with an LS mean change from baseline of 1.9 kg and −1.1 kg, respectively (LS mean difference vs. continued GLP-1 RA 3.0 kg [95% CI 2.42, 3.64 kg]) (Fig. 1*G*). Body weight changes over the randomized treatment period are shown in Supplementary Fig. 3. The percentage of patients who required rescue therapy was lower in the iGlarLixi group (5%) compared with the GLP-1 RA group (15%).

In the iGlarLixi group, the mean ± SD daily dose of insulin glargine at week 26 was 43.5 ± 15.1 units (0.46 ± 0.16 units/kg). The mean ± SD daily dose of lixisenatide was 16.6 ± 3.8 μg.

Safety Profile

Hypoglycemia

As expected when comparing an insulin-based therapy with continued GLP-1 RA, more patients in the iGlarLixi group experienced at least one documented hypoglycemic event regardless of whether the threshold used was ≤70 mg/dL (3.9 mmol/L; 27.8% vs. 2.3% of patients, respectively) or 54 mg/dL (<3.0 mmol/L; 9.4% vs. 0.4% of patients, respectively) (Table 3), but only one case of severe symptomatic hypoglycemia was reported in the iGlarLixi group. Although generally low in both groups, the number of events per patient-year was also higher in the iGlarLixi group compared with the GLP-1 RA group: 1.54 vs. 0.08 events/patient-year with plasma glucose ≤70 mg/dL (≤3.9 mmol/L) and 0.25 vs. <0.01 events/patient-year with plasma glucose <54 mg/dL (<3.0 mmol/L). Among the 71 patients treated with iGlarLixi who experienced documented symptomatic hypoglycemia with plasma glucose ≤70 mg/dL, approximately one-half of patients (47.9%; *n* = 34) reported only one episode; of the six patients in the GLP-1 RA group, 66.7% (*n* = 4) reported only one episode.

Overall Safety

During the 26-week randomized treatment period, the percentage of patients who had at least one AE was higher in the iGlarLixi group (63.9%) compared with the GLP-1 RA group (47.3%) (Table 3). The majority of patients across both treatment groups had AEs that were considered mild or moderate in intensity. The most commonly reported AEs were nasopharyngitis, nausea, and diarrhea. In patients who had been taking once- or twice-daily GLP-1 RA formulations, nausea was reported in 10.5% (*n* = 16 of 152) in the iGlarLixi group and 2.6% (*n* = 4 of 153) in the GLP-1 RA group. In patients taking once-weekly formulations, nausea was reported in 5.8% (*n* = 6 of 103) in the iGlarLixi group and 1.9% (*n* = 2 of 103) in the GLP-1 RA group. Serious AEs were reported by similar percentages of patients in both treatment groups (3.9% in the iGlarLixi group and 3.5% in the GLP-1 RA group).

Overall, the percentage of patients who permanently discontinued the randomized study drug because of an AE was low, with a higher percentage of patients in the iGlarLixi group (3.5% [*n* = 9 of 255], including 2% [*n* = 5 of 255] because of gastrointestinal AEs) compared with no discontinuations in the GLP-1 RA group. Nausea and vomiting led to permanent treatment discontinuation in three patients (1.2%) and one patient (0.4%), respectively, in the iGlarLixi group.

Table 3—AEs* and hypoglycemic events in the safety population

	iGlarLixi (n = 255)	GLP-1 RA (n = 256)
Patients with any AE	163 (63.9)	121 (47.3)
Patients with any serious AE	10 (3.9)	9 (3.5)
Patients with any AE leading to death	0	0
Patients with any AE leading to permanent treatment discontinuation	9 (3.5)	0
AE by organ class (≥3% in any treatment group)		
Infections and infestations	78 (30.6)	68 (26.6)
Influenza	11 (4.3)	6 (2.3)
Nasopharyngitis	25 (9.8)	23 (9.0)
Upper respiratory tract infection	9 (3.5)	12 (4.7)
Nervous system disorders	30 (11.8)	13 (5.1)
Headache	10 (3.9)	6 (2.3)
Gastrointestinal disorders	55 (21.6)	26 (10.2)
Diarrhea	14 (5.5)	6 (2.3)
Nausea	22 (8.6)	6 (2.3)
Vomiting	8 (3.1)	2 (0.8)
Documented (≤70 mg/dL [≤3.9 mmol/L]) symptomatic hypoglycemia	71 (27.8)	6 (2.3)
Documented (≤70 mg/dL [≤3.9 mmol/L]) symptomatic hypoglycemia (events/patient-year)	1.54	0.08
Documented (<54 mg/dL [<3.0 mmol/L]) symptomatic hypoglycemia	24 (9.4)	1 (0.4)
Documented (<54 mg/dL [<3.0 mmol/L]) symptomatic hypoglycemia (events/patient-year)	0.25	<0.01

Data are *n* (%) unless otherwise indicated. *AEs listed are treatment-emergent AEs.

CONCLUSIONS

The LixiLan-G trial provides evidence for the efficacy and safety of switching from GLP-1 RA therapy to the FRC iGlarLixi in patients with type 2 diabetes insufficiently controlled with once-/twice-daily or once-weekly GLP-1 RA and OADs. iGlarLixi improved overall glycemic control, as reflected by a significantly greater HbA_{1c} reduction and a higher proportion of patients reaching the HbA_{1c} target of <7% (53 mmol/mol), as well as significantly reduced FPG, 2-h PPG, 2-h glucose excursions, and average 7-point SMPG compared with patients continuing GLP-1 RA. Numerically more patients treated with iGlarLixi reached the composite HbA_{1c} target of <7% without documented hypoglycemia. Notably, these results were obtained in a population with a substantial duration of type 2 diabetes who had taken GLP-1 RAs for a mean of 1.9 years and were at the maximum tolerated doses and yet not at an HbA_{1c} <7%.

The safety profile of iGlarLixi reflected those of its components, without new or unexpected findings compared with what has been observed previously (6,7). Patients treated with iGlarLixi gained a modest amount of weight and experienced more level 1 (≤70 mg/dL [3.9 mmol/L]) or level 2 (54 mg/dL [<3.0 mmol/L]) hypoglycemic episodes (8) versus unchanged GLP-1 RA therapy; these results are consistent with previous findings on GLP-1 RA intensification with insulin-containing therapy in similar populations (9,10). In this study, the number of hypoglycemic events per patient-year (defined as plasma glucose <54 mg/dL) was higher in the iGlarLixi group compared with the GLP-1 RA group (0.25 vs. <0.01, respectively). In a previous trial that evaluated treatment with IDegLira (the DUAL III trial) in a similar patient population, the number of hypoglycemic events per patient-year (defined as plasma glucose ≤56 mg/dL) was also higher in the IDegLira group compared with the GLP-1 RA group (2.82 vs. 0.12, respectively, in the overall population and 1.75 vs. 0, respectively, in nonsulfonylurea-treated patients) (9). In a study of insulin degludec versus placebo added to GLP-1 RA treatment, the number of hypoglycemic events per patient-year (defined as plasma glucose <56 mg/dL) was 0.57 for the insulin degludec group and 0.12 for the placebo group (10). In a study comparing two basal insulins over 6 months in insulin-naïve patients using OADs, rates of hypoglycemia (defined as plasma glucose <54 mg/dL) were 6.4 events/patient-year with insulin glargine 300 units/mL and 8.5 events/patient-year for glargine 100 units/mL (7). The modest increase in body weight seen with FRC therapy in this patient population (on baseline GLP-1 RA therapy) is in contrast to the small weight loss or weight neutrality experienced by patients on oral agents or basal insulin whose therapy is intensified with an FRC.

The incidence of nausea, vomiting, and diarrhea, although low in both treatment groups, was higher in the iGlarLixi group (8.6%, 3.1%, and 5.5%, respectively) compared with the GLP-1 RA group (2.3%, 0.8%, and 2.3%, respectively). In the iGlarLixi group, three (1.2%) patients discontinued because of nausea and one (0.4%) because of vomiting; none treated with continued GLP-1 RA therapy discontinued because of an AE. The difference might be linked to the comparison of initiation of a different type of GLP-1 RA (lixisenatide) versus continuation of a GLP-1 RA regimen that had been stable for at least 3–6 months. Nausea was also reported more frequently in patients switched to iGlarLixi who had been taking once- or twice-daily GLP-1 RA formulations (10.5%) than in those who had been taking once-weekly formulations (5.8%).

Adherence and persistence are significant obstacles to the success of GLP-1 RA therapy. A multinational survey found that among patients who discontinued GLP-1 RA therapy entirely in the previous 6 months, the most frequently cited reasons were nausea (64.4%) and vomiting (45.4%) (11). The low rates of discontinuation because of nausea and vomiting seen in our study with iGlarLixi have been demonstrated before and are likely related to the slow, gradual uptitration of the GLP-1 RA component within the FRC (12). Another potential barrier to adherence and persistence with the addition of insulin therapy in individuals already on a GLP-1 RA may be the requirement for a separate injection. The FRC should be able to address this through by combining both basal insulin and GLP-1 RA into a single injection.

A previous trial in a similar patient population evaluated IDegLira (DUAL III trial) (9). Treatment with IDegLira was associated with a significantly greater reduction in HbA_{1c} (mean ± SD at baseline of 7.8 ± 0.6%, reduction of 1.3 ± 0.8%) compared with continuing existing GLP-1 RA therapy (7.7 ± 0.5% at baseline, reduction of 0.3 ± 0.9%). Body weight also increased by a mean of 2.0 kg with IDegLira and decreased by a mean of 0.8 kg with GLP-1 RA, and rates of hypoglycemia were higher with the FRC, as in the current study. Although these results correspond broadly to those of the current study, there are noteworthy differences between the two trials. DUAL III permitted only liraglutide or exenatide twice daily as prior GLP-1 RA therapy, whereas the current study also included patients on once-weekly GLP-1 RA therapy. In addition, patients in DUAL III were permitted to take sulfonylurea but not an SGLT2 inhibitor. Finally, the FRC was titrated on the basis of prebreakfast self-monitored blood glucose to an FPG target of 72–90 mg/dL (4.0–5.0 mmol/L) vs. the SMPG target of 80–100 mg/dL (4.4–5.6 mmol/L) used in this trial. The most important difference to note is the inclusion in our study of patients on once-weekly GLP-1 RA therapy (40% of patients), which provides evidence that switching to iGlarLixi in patients treated weekly is effective and safe.

This trial is in keeping with current international treatment guidelines, which generally recommend GLP-1 RA therapy as a first injectable medication for patients with type 2 diabetes inadequately controlled with oral treatment and consideration of an FRC for further intensification if needed (1,2). For patients who have inadequate glycemic control despite treatment with multiple OADs and the maximum tolerated dose of a GLP-1 RA, there may be particular usefulness for an FRC that can provide the complementary actions of a GLP-1 RA, such as lixisenatide, in a single formulation with a basal insulin to provide intensification of treatment.

Strengths of this trial include its randomized design and a population characterized by insufficiently controlled glycemia despite treatment with GLP-1 RAs, most commonly liraglutide or dulaglutide. There were also some study limitations, including the lack of blinding, which theoretically might increase the possibility of bias, particularly for reporting AEs. However, to mask different pen delivery systems would have required a

prohibitively complex set of dummy injections for each treatment arm, which could have adversely affected treatment adherence and generalizability to the usual clinical setting. Additionally, the duration of the comparative phase of the trial was relatively short. Although the 6-month extension will provide additional information on durability, longer-term studies may be needed to fully explore efficacy, persistence, and tolerability. Another limitation is that although the continued GLP-1 RA treatment can be considered active treatment, the study lacked an active comparator that included a basal insulin. Nevertheless, this study is relevant because an increasing number of patients using a GLP-1 RA as their first injectable is expected, and the comparison of switching to an FRC versus continuing one of the full range of available GLP-1 RA options provides novel and clinically translatable information. In addition, this study examined patients with limited remaining appropriate treatment options because of a long duration of disease, prior use of multiple OADs, and insufficient glycemic control using a GLP-1 RA. In these patients, a single injection may offer an efficacious alternative to treatment intensification instead of the standard addition of one or more insulin injections. Finally, the generalizability of the results to the larger population of patients with type 2 diabetes might be limited by the lack of patients who had been treated with antidiabetes drugs other than those described above, including sulfonylureas, which are commonly used for diabetes treatment.

In conclusion, these results suggest that switching to iGlarLixi can further improve glucose control for patients with type 2 diabetes receiving the maximum tolerated dose of a GLP-1 RA with OADs. These findings further suggest that iGlarLixi can offer an efficacious and safe option for intensifying treatment.

Acknowledgments. The authors thank Dr. Xiangling Wang for contributions to the study and earlier presentations of the data. Editorial assistance was provided by Rob Coover of Caudex (New York, NY).

Duality of Interest. This study was sponsored by Sanofi. Editorial assistance was also funded by Sanofi. L.B. has been a consultant for AstraZeneca, Gilead Sciences, Janssen, Merck, Novo Nordisk, and Sanofi; has received grant/research support (including to his institution) from Janssen, Lexicon, Merck, Novo Nordisk, and Sanofi; and has been a speaker for Janssen, Novo Nordisk, and Sanofi. J.R. has been a consultant for Boehringer Ingelheim, Eli Lilly, Intarcia, Janssen, Novo Nordisk, and Sanofi; and has received grant/research support from AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb, Eli Lilly, Genentech, GlaxoSmithKline, Intarcia, Janssen, Lexicon, Merck, Novo Nordisk, Pfizer, and Sanofi. S.D.P. has received grant/research support from AstraZeneca, Boehringer Ingelheim, Merck, and Novartis; and honoraria from Abbott, AstraZeneca, Boehringer Ingelheim, Eli Lilly, Merck, Mundipharma, Novartis, Novo Nordisk, Sanofi, Servier, and Takeda. R.H. has been on advisory panels for AstraZeneca, Boehringer Ingelheim, Elcelyx Therapeutics, Intarcia, Johnson & Johnson, Merck, and Sanofi; has been a consultant for Abbott, Alere, AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb, Intarcia, Ionis, Janssen, Ligand Pharmaceuticals, Merck, and Sanofi; and has received research support from AstaReal, Eli Lilly, Hitachi, Lexicon, and Viacyte. N.S. has been a consultant for Boehringer Ingelheim, Eli Lilly, Novo Nordisk, and Sanofi; and has received grant/research support and honoraria from AstraZeneca, Boehringer Ingelheim, Eli Lilly, Merck, Novo Nordisk, and Sanofi. J.F. has been a consultant for Boehringer Ingelheim, Johnson & Johnson, Eli Lilly, Merck, Novo Nordisk, and Sanofi; has received grant/research support from AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb, Eli Lilly, Johnson & Johnson, Merck, Novo Nordisk, Pfizer, Sanofi, and Theracos; and has been a speaker for Merck and Sanofi. E.N., E.S., and C.J. are employees of Sanofi. V.R.A. has received clinical trial/research support from Fractyl, Novo Nordisk, and Sanofi; and has been a consultant for AstraZeneca, BD, Novo Nordisk, Sanofi, and Zafgen. No other potential conflicts of interest relevant to this article were reported.

Author Contributions. L.B., J.R., S.D.P., R.H., N.S., J.F., E.N., E.S., C.J., and V.R.A. read, reviewed, and agreed to the final version of the manuscript. L.B., R.H., N.S., J.F., and V.R.A. contributed to the data analysis/interpretation and critical revision of the manuscript for important intellectual content. J.R. and S.D.P. contributed to study conception and design, data analysis/interpretation, and critical revision of the manuscript for important intellectual content. E.N., E.S., and C.J. contributed to study conception and design, data acquisition, data analysis/interpretation, and critical revision of the manuscript for important intellectual content. L.B. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Prior Presentation. Parts of this study were presented in oral form at the 79th Scientific Sessions of the American Diabetes Association, San Francisco, CA, 7–11 June 2019.

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