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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Running title: Benefits of iGlarLixi added to oral therapies

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ABSTRACT

OBJECTIVE

To evaluate efficacy and safety of LixiLan (iGlarLixi), a novel titratable fixed-ratio combination of insulin glargine (iGlar):lixisenatide (Lixi) compared with both components, iGlar and Lixi, given separately in type 2 diabetes inadequately controlled on metformin ± a second oral glucose-lowering drug.

RESEARCH DESIGN AND METHODS

After a 4-week run-in to optimize metformin and stop other oral antidiabetes drugs, participants (N=1170, mean diabetes duration ~8.8 years, BMI ~31.7kg/m^2) were randomized to open-label once-daily iGlarLixi or iGlar, both titrated to fasting plasma glucose <100mg/dL (<5.6mmol/mol) up to maximum insulin dose 60 U/day, or once-daily Lixi (20µg/day) continuing with metformin. Primary outcome was HbA_{1c} change at 30 weeks.

RESULTS

Greater reductions in HbA_{1c} from baseline (8.1%; 65mmol/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% (48mmol/mol) for iGlarLixi, versus 6.8% (51mmol/mol) and 7.3% (56mmol/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 (−0.3kg) and Lixi (−2.3kg), and increased with iGlar (+1.1kg; difference 1.4kg, p<0.0001). Documented (≤70mg/dL) symptomatic hypoglycemia was similar with

iGlarLixi and iGlar (1.4 and 1.2 events/patient year) and lower with Lixi (0.3). iGlarLixi improved postprandial glycemic control versus iGlar, and demonstrated considerably fewer nausea (9.6%) and vomiting (3.2%) events than Lixi (24%, 6.4%).

CONCLUSIONS

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

The most recent ADA/EASD 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 glucagon-like peptide-1 receptor agonist (GLP-1 RA) (1). However, most clinicians and patients prefer to choose dual or even triple oral therapy before making the decision between injectable basal insulin and a GLP-1 RA to reach each 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 on oral agents, if the basal insulin is properly titrated and especially when it is initiated at early stages of type 2 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 unable to achieve their individualized glycemic targets using basal insulin alone (4–6) can benefit with the addition of PPG-lowering agents.

GLP-1 RAs stimulate postprandial insulin secretion, 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 robust lowering of patients' PPG (7). Similarly to basal insulin, 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.

However, clinical inertia and aversion for 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).

Lixisenatide (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). Lixi and insulin glargine 100 U (iGlar) have similar physicochemical features, allowing both components to be mixed as a defined fixed-ratio iGlar:Lixi formulation (iGlarLixi or LixiLan) and delivered via a single, daily injection. iGlarLixi can deliver iGlar over a range of 10–60 U/day in steps of 1 U, in a 2:1 or a 3:1 ratio with Lixi. For example, 2 U of iGlar will deliver 1 µg Lixi for Pen A while for Pen B the 3:1 ratio results in 3 U 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 also 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, Lixi's known GI AEs can potentially be mitigated by the gradual Lixi dose increments that follow iGlar titration, which is guided solely by the fasting glucose levels (FPG) response and also by hypoglycemia and GI tolerance (1).

In a proof-of-concept study, iGlarLixi (2 U iGlar:1 µg Lixi) achieved robust HbA_{1c} reductions, with weight loss and no increased hypoglycemia compared with iGlar, as well as very low frequency of GI AEs in patients with type 2 diabetes inadequately controlled on metformin (17).

The main objective of the LixiLan-O study is 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-naïve patients with type 2 diabetes inadequately controlled on metformin ± 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 3 clinical trial (NCT02058147). It was initiated (first patient enrolled) on February 12, 2014 and ended (last patient completed) on June 17, 2015. Supplementary Fig. 1 summarizes the study design. Patients (aged ≥18 years) with type 2 diabetes diagnosed at least 1 year prior to screening were eligible if they showed inadequate glycemic control despite being treated for at least 3 months with metformin ± a second oral glucose-lowering therapy. Inadequate glycemic control was defined as HbA_{1c} ≥7.5% and ≤10.0% (58–86 mmol/mol) for those on metformin alone and ≥7.0% and ≤9.0% (53–75 mmol/mol) for patients previously treated with metformin and a second oral glucose-lowering therapy, namely a sulfonylurea, glinide, sodium-glucose cotransporter 2 (SGLT2), or a dipeptidyl peptidase 4 (DPP-4) inhibitor.

Major exclusion criteria included use of an oral agent other than those stated above during the 3 months before screening, previous treatment with insulin (except short-term treatment due to intercurrent illness, including gestational diabetes), and previous discontinuation of a GLP-1 RA because of safety, tolerability, or lack of efficacy. Additional exclusion criteria included amylase and/or lipase >3 times upper limit of the normal range 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 2000 mg/day or to the maximum tolerated dose, which had to be ≥1500 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 randomized 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, Paris, France) pen injectors: Pen A, with a 2:1 ratio of 2 U iGlar:1 µg Lixi, delivers corresponding insulin doses from 10 to 40 U allowing administration of iGlarLixi

doses from 10 U/5 µg up to 40 U/20 µg, and Pen B, with a 3;1 ratio of 3 U iGlar:1 µg Lixi, delivers corresponding insulin doses from 30 to 60 U allowing administration of iGlarLixi doses from 30 U/10 µg up to 60 U/20 µg.

All patients were started on Pen A at 10 U (10 U/5 µg) and continued on the same Pen A up to a dose of 40 U. When patients required doses above 40 U (40 U/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 to 4 units weekly was similarly guided only by the required dose for iGlar based on the following algorithm: +2 U (if FPG was >100 and ≤140 mg/dL [>5.6 and ≤7.8 mmol/L]) or +4 U (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 U/day, while always limiting Lixi component to a maximum of 20 µg/day regardless of the pen used. iGlarLixi was self-administered once daily, 0–60 minutes before breakfast.

iGlar was supplied in a prefilled disposable Lantus SoloStar (sanofi-aventis U.S. LLC, Bridgewater, USA) pen injector (100 U/mL). The pen can deliver doses from 1 to 80 U in steps of 1 U. In the present study, the maximum iGlar once-daily dose allowed was capped at 60 U. 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 U and the titration regimen was the same as with 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 minutes before breakfast or the evening meal at the discretion of patients and investigators, but remained at about the same time throughout treatment.

Efficacy Endpoints

The primary efficacy endpoint was change in HbA_{1c} from baseline to Week 30. Changes in several continuous secondary efficacy endpoints from baseline to Week 30 were assessed: 2-hour PPG levels during standardized meal test; body weight; 7-point self-measured plasma glucose (SMPG) profiles; and FPG.

Categorical secondary efficacy endpoints at Week 30 included percentages of patients reaching: HbA_{1c} <7% (53 mmol/mol) and ≤6.5% (48 mmol/mol); composite endpoints 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; HbA_{1c} <7% (53 mmol/mol) with no body weight gain and with no documented symptomatic hypoglycemia. For 7-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 Endpoints

The safety endpoints 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 included: hematology, clinical chemistry, lipid parameters, serum amylase, lipase, and calcitonin; and urine albumin/creatinine ratio assessment. Clinical safety was assessed by physical examination, systolic and diastolic blood pressure, heart rate, and ECG 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 more than 95% power to show non-inferiority of the iGlarLixi group to the iGlar group in the HbA_{1c} change from baseline to Week 30 based on a true difference between the two groups of zero and a non-inferiority upper margin of 0.3% (standard deviation 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 more than 95% power to detect a difference of 0.4% in the HbA_{1c} change from baseline to Week 30 between the groups (standard deviation 1.1%; 5% significance level two-sided t-test).

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 post-baseline assessment of any primary or secondary efficacy variables. The primary efficacy endpoint 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 well as the between-group difference and the 95% CI for the adjusted mean. A similar MMRM method or analysis of covariance (ANCOVA) was applied on continuous secondary efficacy endpoints and Cochran-Mantel-Haenszel method stratified by randomization strata was applied on categorical efficacy endpoints.

The co-primary hypotheses of statistical superiority of iGlarLixi to Lixi alone and non-inferiority of iGlarLixi to iGlar alone were tested for the primary efficacy endpoint. Both co-primary hypotheses were required to be established for the primary efficacy endpoint before the step-down testing procedure for the secondary efficacy endpoints and a test of superiority of iGlarLixi over iGlar alone were performed at an alpha level of 0.05 (two-sided).

An estimate of the composite endpoint 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 endpoint was not included in the testing order.

The safety population was defined as all randomized 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 according to the group to which they were randomized.

RESULTS

Patient Disposition and Baseline Characteristics

A total of 1170 patients were randomized 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 1167 and 1169 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 approximately 9 years.

Primary Efficacy Endpoint

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; 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 versus Lixi −0.8% [−8.5 mmol/mol] [95% CI: −0.9, −0.7 (−9.8 mmol/mol, −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, −0.2 (−4.2 mmol/mol, −2.1 mmol/mol); p<0.0001]) met non-inferiority of iGlarLixi compared with iGlar and also demonstrated superiority for this primary efficacy endpoint (p<0.0001) based on the step-down testing procedure.

Secondary Efficacy Endpoints

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 (–0.3kg) 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; Fig. 1*C*).

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

Patients treated with iGlarLixi had a significantly greater decrease in average 7-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 (LS mean difference −25.2 mg/dL [−1.40 mmol/L] [95% 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 7-point SMPG profiles were lower in the iGlarLixi group compared with iGlar and Lixi, with the exception of the pre-breakfast value which was similar for iGlarLixi and iGlar (Fig. 1*F*).

As shown in Table 2, higher proportions of patients in the iGlarLixi group, compared with iGlar or Lixi, reached at Week 30 the pre-defined composite endpoints 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 endpoint of HbA_{1c} <7% (53 mmol/mol) with no documented symptomatic hypoglycemia (54% for iGlarLixi compared with 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 U) and the iGlar group (40.3 ± 14.9 U) 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 U and ≤60 U (71% in the iGlarLixi group and 70% in the iGlar group) with 44% and 45% receiving >40 to ≤60 U; only 16% and 20% received the maximum permissible dose of 60 U of insulin respectively.

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 for iGlarLixi and 1.2 for iGlar. The incidence and event rate were lower in the Lixi group (6%; 0.3 events per 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% and 24.0%) and diarrhea (9.0% both) were the most frequent GI AEs associated with iGlarLixi and Lixi groups, respectively – these

subsided over time (Supplementary Fig. 3). Vomiting was also less common with iGlarLixi than Lixi (3.2% versus 6.4%). Adjudicated allergic reactions and major cardiovascular events occurred in low percentages of patients in all three treatment groups. There were no events 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 AE adjudicated as allergic reactions were low and similar between 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 had events in the iGlarLixi group (one case of cardiovascular death and one of unstable angina), seven patients in the iGlar group (two cardiovascular deaths, two hospitalizations for heart failure and one case each of nonfatal stroke, unstable angina and coronary revascularization procedure), and two patients in the Lixi group (one cardiovascular death and one nonfatal stroke).

No clinically significant safety issues were identified based on a review of clinical laboratory parameters (including lipase, amylase, and calcitonin;

Supplementary Table 1), vital signs, physical examination, ECGs, antibody levels, or in a comparison of AEs in antibody-positive and antibody-negative populations (data not shown).

DISCUSSION

This study clearly demonstrated that LixiLan (iGlarLixi), a novel titratable fixed-ratio combination of iGlar and Lixi was more effective in achieving meaningful improvements in glycemic control than iGlar or Lixi alone, achieving 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-naïve type 2 diabetes initiating basal insulin treatment.

Most treat-to-target trials using basal insulin in insulin-naïve 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 this 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 initiation of insulin therapy, and showed no increased risk of hypoglycemia despite the lower HbA_{1c} levels compared with iGlar, while demonstrating 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 is one of the reasons why insulin-naïve patients and physicians may resist initiating insulin treatment (13) despite poor

glycemic control. 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 endpoints 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%) compared with Lixi (nausea 24.0% and vomiting 6.4%), leading to fewer permanent treatment discontinuations and better tolerance. The rate of nausea in the iGlarLixi group was also lower than those observed in previous studies where Lixi was co-administered with basal insulin as separate injections (25–27% and 8–9%, respectively) (14,21,22). These findings are likely due to the gradual small increases of the Lixi dose parallel to the insulin glargine 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 present 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 later by the addition of

a GLP-1 RA in insulin-naïve 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 because of no capping (free titration) of iGlar dose, the GetGoal-Duo 1 study in a similar patient population, starting basal insulin glargine first and then adding 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% using the sequential regimen (10), while in this study 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 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 present study, a lower proportion of patients receiving the fixed-ratio combination developed GI AEs compared with those receiving liraglutide alone (23). However, the GLP-1 RA component of IDegLira has a different mode of action from that of iGlarLixi – liraglutide potentiates the FPG control of degludec, while Lixi targets postprandial glucose levels.

Limitations of our 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 ADA/EASD position statement (1) suggests 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. 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 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, taking advantage of the complementary action of these two therapies and mitigating AEs, reaching, in a majority of patients, robust HbA_{1c} reductions to levels previously unattainable with any of the individual therapies.

In conclusion, insulin-naïve patients with uncontrolled type 2 diabetes randomized 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 side effects compared with Lixi. These findings support revisiting the treatment paradigm and, potentially, moving away from the sequential addition of injectable therapies, towards the use of a titratable fixed-ratio combination of basal insulin and a GLP-1 RA therapy in the same formulation.

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Duality of Interest

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has served on advisory boards for Janssen, Novo Nordisk, and Sanofi; as a consultant for AstraZeneca, Bristol-Myers Squibb, Medtronic, Sanofi, and Takeda; has received research support from Abbott, Andromeda Biotech, AstraZeneca, BD Medical Diabetes Care, Boehringer Ingelheim, Bristol-Myers Squibb, ConjuChem, Diartis Pharmaceuticals, Eli Lilly, Essem Research, GlaxoSmithKline, ICON, Janssen, Medpace, Medtronic, Merck, Novartis, Novo Nordisk, Piramal, Quintiles, Regeneron, Roche, Sanofi, Takeda, and Tolerx; and has other relationships with AstraZeneca, BD Medical Diabetes Care, Boehringer Ingelheim, Bristol-Myers Squibb, Novo Nordisk, Sanofi, and Takeda. G.G. has received research grants from Sanofi, Lilly, Merck, Novo Nordisk, Lexicon, Astra Zeneca, and Medtronic. He has been included in speaker bureaus for Sanofi, Janssen, Boehringer Ingelheim, Novo Nordisk, Lilly, AstraZeneca, and Merck. M.H. has served on an Advisory Panel and as an author for Bristol-Myers Squibb Company, GlaxoSmithKline, Sanofi, and Takeda Pharmaceuticals USA, Inc.; and has served on a Speakers Bureau and as an author for Bayer Health Care, LLC, Eli Lilly and Company, GlaxoSmithKline, Roche Pharmaceuticals, Novartis, Sanofi, and Takeda Pharmaceuticals USA, Inc. M.D. has acted as consultant, advisory board member, and speaker for Novo Nordisk, Sanofi-Aventis, Lilly, Merck Sharp & Dohme, Boehringer Ingelheim, AstraZeneca; and Janssen and as a speaker for Mitsubishi Tanabe Pharma Corporation. She has received grants in support of investigator and investigator initiated trials from Novo Nordisk, Sanofi-Aventis, and Lilly. P.M.P has no conflicts of interest. P.S. has acted on advisory boards for Novo Nordisk. Research Support: Sanofi, Eli Lilly, and Novo Nordisk. X.C., T.Z., E.N., and E.S. are employees of, and own stock/shareholders in, Sanofi. No payment was received for preparation of this manuscript.

Author Contributions

J.R. contributed to the design of the study, conducted the study as an investigator, revised and edited the manuscript, and is the guarantor of this work and, as such, had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. X.C. was the clinical study director for the study. T.Z. was the statistician for the study. R.A. contributed to the design of the study, conducted the study, and edited the manuscript. P.M.P. researched the data. M.D. conducted the study and edited the manuscript. E.S. contributed to the design of the study, wrote the study protocol, ensured medical supervision of the study, contributed to results analysis and study report writing, and revised the manuscript. E.N contributed to results analysis and study report writing, and revised the manuscript. G.G. researched data and edited the manuscript. M.H. helped develop the study concept, was an investigator, and made amendments to the manuscript. P.S. helped develop the study concept, was an investigator and made amendments to the manuscript. All authors critically reviewed the manuscript and approved the final version for publication.

Prior Presentations

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References

1. Inzucchi SE, Bergenstal RM, Buse JB, et al. Management of hyperglycemia in type 2 diabetes, 2015: a patient-centered approach: update to a position statement of the American Diabetes Association and the European Association for the Study of Diabetes. Diabetes Care 2015;38:140-149

2. Raccah D, Bretzel RG, Owens D, Riddle M. When basal insulin therapy in type 2 diabetes mellitus is not enough--what next? Diabetes Metab Res Rev 2007;23:257-264

3. Charbonnel B, Bertolini M, Tinahones FJ, Puig Domingo M, Davies M. Lixisenatide plus basal insulin in patients with type 2 diabetes mellitus: a meta-analysis. J Diabetes Complications 2014;28:880-886

4. Bonora E, Corrao G, Bagnardi V, et al. Prevalence and correlates of post-prandial hyperglycaemia in a large sample of patients with type 2 diabetes mellitus. Diabetologia 2006;49:846-854

5. Erlinger TP, Brancati FL. Postchallenge hyperglycemia in a national sample of U.S. adults with type 2 diabetes. Diabetes Care 2001;24:1734-1738

6. Monnier L, Colette C, Dunseath GJ, Owens DR. The loss of postprandial glycemic control precedes stepwise deterioration of fasting with worsening diabetes. Diabetes Care 2007;30:263-269

7. Uccellatore A, Genovese S, Dicembrini I, Mannucci E, Ceriello A. Comparison review of short-acting and long-acting glucagon-like peptide-1 receptor agonists. Diabetes Ther 2015;6:239-256

8. Korytkowski M. When oral agents fail: practical barriers to starting insulin. Int J Obes Relat Metab Disord 2002;26 Suppl 3:S18-24

9. Meece J. Dispelling myths and removing barriers about insulin in type 2 diabetes. Diabetes Educ 2006;32:9S-18S

10. Sikirica M, Martin AA, Leith A, Wood R, Percy J, Higgins V. Reasons for discontinuation of GLP-1 receptor antagonists: data from a large cross-sectional survey of physicians and type 2 diabetic patients. Diabetes Care 2015;64(Suppl. 1):A297

11. Meier JJ, Rosenstock J, Hincelin-Mery A, et al. Contrasting effects of lixisenatide and liraglutide on postprandial glycemic control, gastric emptying, and safety parameters in patients with type 2 diabetes on optimized insulin glargine with or without metformin: a randomized, open-label trial. Diabetes Care 2015;38:1263-1273

12. Gutniak M, Orskov C, Holst JJ, Ahren B, Efendic S. Antidiabetogenic effect of glucagon-like peptide-1 (7-36)amide in normal subjects and patients with diabetes mellitus. N Engl J Med 1992;326:1316-1322

13. Raccah D, Lin J, Wang E, et al. Once-daily prandial lixisenatide versus once-daily rapid-acting insulin in patients with type 2 diabetes mellitus insufficiently controlled with basal insulin: analysis of data from five randomized, controlled trials. J Diabetes Complications 2014;28:40-44

14. Riddle MC, Aronson R, Home P, et al. Adding once-daily lixisenatide for type 2 diabetes inadequately controlled by established basal insulin: a 24-week,

randomized, placebo-controlled comparison (GetGoal-L). Diabetes Care 2013;36:2489-2496

15. Riddle MC, Forst T, Aronson R, et al. Adding once-daily lixisenatide for type 2 diabetes inadequately controlled with newly initiated and continuously titrated basal insulin glargine: a 24-Week, randomized, placebo-controlled study (GetGoal-Duo 1). Diabetes Care 2013;36:2497-2503

16. Seino Y, Min KW, Niemoeller E, Takami A. Randomized, double-blind, placebo-controlled trial of the once-daily GLP-1 receptor agonist lixisenatide in Asian patients with type 2 diabetes insufficiently controlled on basal insulin with or without a sulfonylurea (GetGoal-L-Asia). Diabetes Obes Metab 2012;14:910-917

17. Rosenstock J, Diamant M, Aroda VR, et al. Efficacy and safety of LixiLan, a titratable fixed-ratio combination of lixisenatide and insulin glargine, versus insulin glargine in type 2 diabetes inadequately controlled on metformin monotherapy: the LixiLan proof-of-concept randomized trial. Diabetes Care 2016;In press:

18. Owens DR, Traylor L, Dain MP, Landgraf W. Efficacy and safety of basal insulin glargine 12 and 24 weeks after initiation in persons with type 2 diabetes: a pooled analysis of data from treatment arms of 15 treat-to-target randomised controlled trials. Diabetes Res Clin Pract 2014;106:264-274

19. Riddle MC, Rosenstock J, Gerich J. The treat-to-target trial: randomized addition of glargine or human NPH insulin to oral therapy of type 2 diabetic patients. Diabetes Care 2003;26:3080-3086

20. Yki-Jarvinen H, Kauppinen-Makelin R, Tiikkainen M, et al. Insulin glargine or NPH combined with metformin in type 2 diabetes: the LANMET study. Diabetologia 2006;49:442-451

21. Riddle MC, Forst T, Aronson R, et al. Adding once-daily lixisenatide for type 2 diabetes inadequately controlled with newly initiated and continuously titrated basal insulin glargine: a 24-Week, randomized, placebo-controlled study (GetGoal-Duo 1). Diabetes Care 2013;36:2497-2503

22. Rosenstock J, Hanefeld H, Gentile S, et al. Advancing basal insulin glargine with prandial lixisenatide QD vs. insulin glulisine QD or TID in T2DM: the GetGoal-Duo2 evidence-based trial (NCT01768559). Diabetes 2015;64:107-LB

23. Gough SC, Bode B, Woo V, et al. Efficacy and safety of a fixed-ratio combination of insulin degludec and liraglutide (IDegLira) compared with its components given alone: results of a phase 3, open-label, randomised, 26-week, treat-to-target trial in insulin-naive patients with type 2 diabetes. Lancet Diabetes Endocrinol 2014;2:885-893

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

	iGlarLixi (n=469)	iGlar (n=467)	Lixi (n=234)	All (N=1170)
Age (years)				
Mean ± SD	58.2 ± 9.5	58.3 ± 9.4	58.7 ± 8.7	58.4 ± 9.3
Sex [n (%)]				
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 [n (%)]				
Caucasian	417 (88.9)	421 (90.1)	216 (92.3)	1054 (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 [n (%)]				
Hispanic/not Hispanic	85 (18.1)/384 (81.9)	87 (18.6)/380 (81.4)	51 (21.8)/183 (78.2)	223 (19.1)/947 (80.9)
Duration of diabetes (years)				
Mean ± SD	8.9 ± 5.5	8.7 ± 5.6	8.9 ± 6.3	8.8 ± 5.7
Baseline BMI (kg/m^2)				
Mean ± SD	31.6 ± 4.4	31.7 ± 4.5	32.0 ± 4.4	31.7 ± 4.4
Proportion of patients ≥30 kg/m^2 (%)	62.9	61.7	67.9	63.4
HbA_{1c} at screening				
Mean ± SD (%)	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				
Mean ± SD (%)	8.1 ± 0.7	8.1 ± 0.7	8.1 ± 0.7	8.1 ± 0.7
mmol/mol	65	65	65	65
Proportion of patients ≥8% (64 mmol/mol)	55.9	55.7	56.0	55.8
Baseline fasting plasma glucose (mmol/mol)				
Mean ± SD	9.9 ± 2.4	9.8 ± 2.3	9.8 ± 2.2	9.8 ± 2.3
Baseline metformin dose (mg)				
Mean ± SD	2246 ± 457	2245 ± 445	2267 ± 427	2250 ± 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

Screening values are at Week −6; baseline values are at Week −1.
BMI, body mass index; DPP-4, dipeptidyl peptidase-4; iGlarLixi, titratable fixed-ratio combination iGlar:Lixi; SD, standard deviation; SGLT-2, sodium-glucose co-transporter-2.

Table 2 – Results (mITT population)

Efficacy endpoint	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, −0.2		
p value	<0.0001		
LS mean (SE) difference vs Lixi*	−0.8 ± 0.06		
95% CI	−0.9, −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, 22.6		
p value	<0.0001		
Difference from Lixi†	36.4%		
95% CI	29.8, 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, 20.3		
p value	<0.0001		
Difference from Lixi†	40.6%		
95% CI	33.6, 47.6		
p value	<0.0001		
2-hour 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, −2.0		
LS mean ± SE difference vs Lixi‡	−1.1 ± 0.3		
95% CI§	−1.6, −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, 0.04		
p value	0.1		
LS mean ± SE difference vs Lixi*	−2.0 ± 0.1		
95% CI	−2.2, −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, −0.9		
p value	<0.0001		
LS mean ± SE difference vs Lixi*	2.0 ± 0.3		
95% CI§	1.4, 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 versus iGlar†	18.1		
95% CI	12.2, 24.0		
p value	<0.0001		
Difference versus Lixi†	15.2		
95% CI§	8.1, 22.4		
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 versus iGlar†	9.3		
95% CI§	3.0, 15.6		
Difference versus Lixi†	23.1		
95% CI§	15.8, 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 versus iGlar†	13.0		
95% CI	7.5, 18.5		

p value	<0.0001
Difference versus Lixi[†]	5.6
95% CI[§]	−1.3, 12.6

Data are mean ± standard deviation unless otherwise specified.
*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-hour plasma glucose excursion value as a covariate.
[§]No p-value as the comparison was not specified in the step-down testing procedure
FPG, fasting plasma glucose; iGlarLixi, titratable fixed-ratio combination iGlar:Lixi; LOCF, last observation carried forward; LS, least squares; mITT, modified intent-to-treat; PPG, postprandial plasma glucose; SE, standard error.

Table 3 – Safety

Patients, n (%) 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, n (%)	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, n (%)	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, n (%)	0	1 (0.2)	0
Number of events per patient-year†	0	<0.01	0

*See Supplemental File 1.

†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 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.

AE, adverse event; iGlarLixi, titratable fixed-ratio combination iGlar:Lixi.

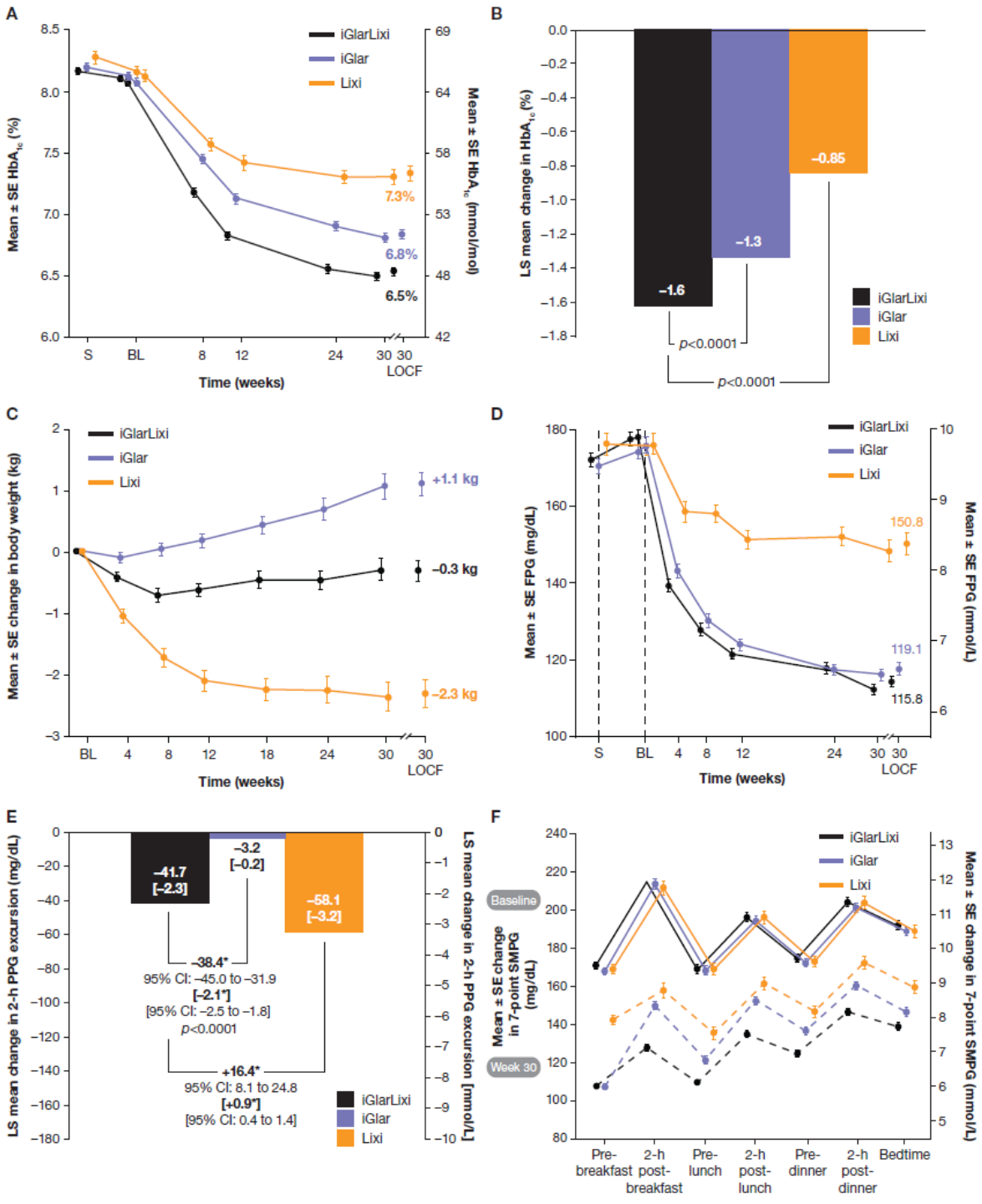
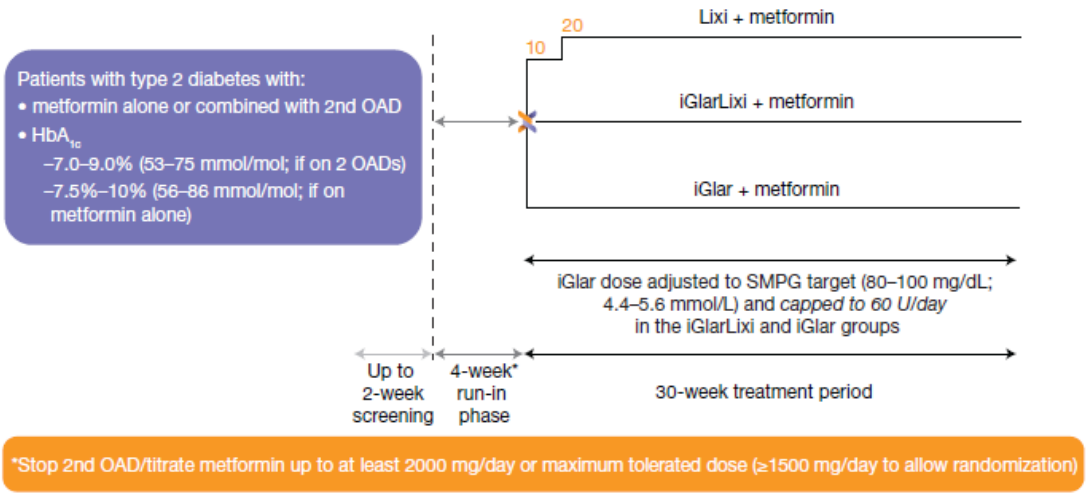


Figure 1 – *A* Mean (± SE) HbA_{1c} (%) by study visit (observed cases); *B* LS mean change in HbA_{1c} (%); *C* Mean (± SE) body weight (kg) by study visit; *D* FPG (mmol/L and mg/dL) by study visit; *E* LS mean change in 2-hour PPG excursion (mmol/L) during a standardized meal test, all from baseline to Week 30; *F* Mean (SE) change in 7-point SMPGs at baseline and at Week 30.

*LS mean difference vs iGlar or Lixi (mITT; ANCOVA)

BL, baseline; FPG, fasting plasma glucose; iGlarLixi, titratable fixed-ratio combination iGlar:Lixi; LOCF, last observation carried forward; LS, least squares; mITT, modified intent-to-treat; PPG, postprandial plasma glucose; SE, standard error; SMPG, Self-Measured Glucose Profile

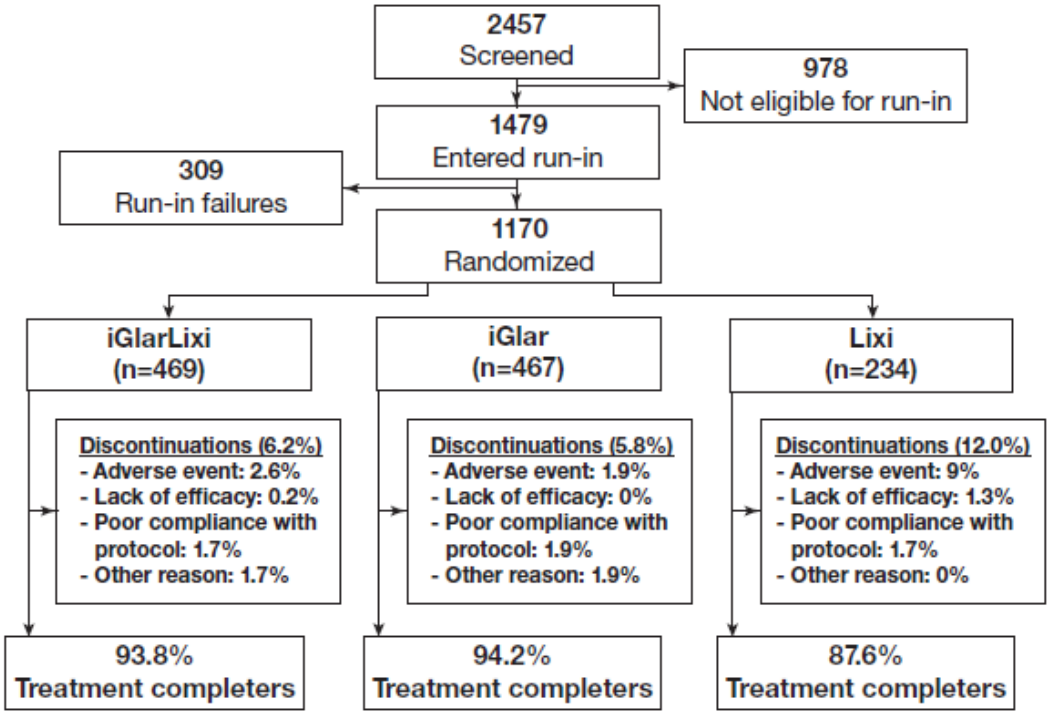
Supplementary figure legends



Supplementary Figure 1 – Schematic of study design

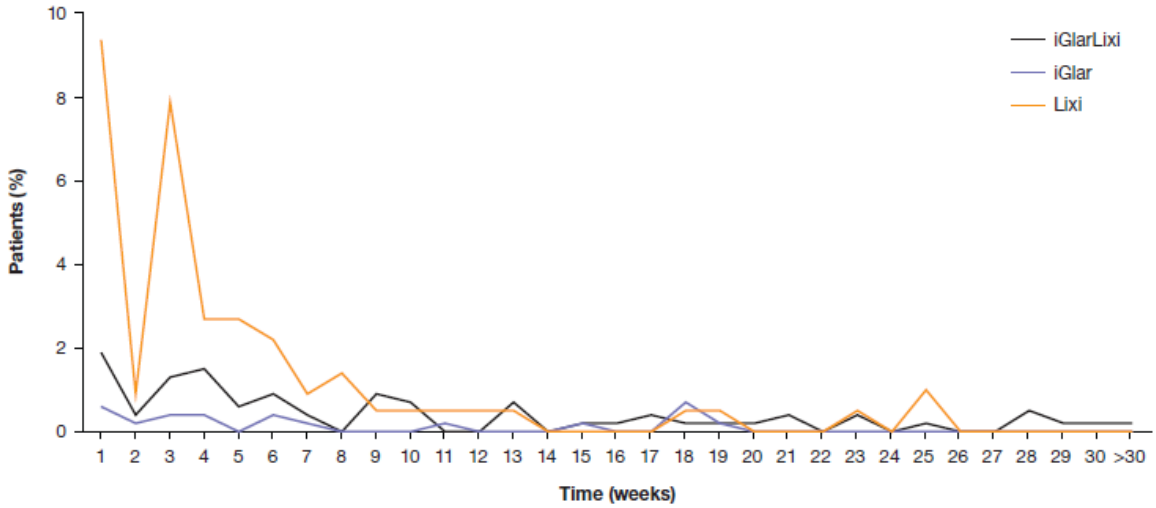
FPG, fasting plasma glucose; iGlarLixi, titratable fixed-ratio combination iGlar:Lixi;

OAD, oral antidiabetic drug



Supplementary Figure 2 – Patient disposition

One patient randomized to the Lixi group requested not to be treated and was excluded from the safety population.



Supplementary Figure 3 – Nausea over time

Supplementary Table 1 – Summary of clinical laboratory parameters

	iGlarLixi (n=468)	iGlar (n=467)	Lixi (n=233)
Lipase ≥3 × ULN	4/468 (0.9%)	6/462 (1.3%)	5/231 (2.2%)
Amylase ≥3 × ULN	1/468 (0.2%)	1/462 (0.2%)	1/231 (0.4%)
Calcitonin			
≤ULN	437/461 (94.8%)	427/456 (93.6%)	203/223 (91.0%)
>ULN – <20 ng/L [pg/mL]	23/461 (5.0%)	27/456 (5.9%)	20/223 (9.0%)
≥20 – <50 ng/L [pg/mL]	1/461 (0.2%)	1/456 (0.2%)	0/223
≥50 ng/L [pg/mL]	0/461	1/456 (0.2%)	0/223
Creatinine ≥150 µmol/L (1.70 mg/dL)	2 (0.4%)	1 (0.2%)	0
Alanine aminotransferase			
>3 × ULN	2/462 (0.4%)	2/456 (0.4%)	1/223 (0.4%)
>5 × ULN	0/462	0/456	1/223 (0.4%)
Aspartate aminotransferase			
>3 × ULN	1/461 (0.2%)	2/455 (0.4%)	2/222 (0.9%)
>5 × ULN	0/461	0/455	1/222 (0.5%)
Alkaline phosphatase >1.5 × ULN	2/462 (0.4%)	3/456 (0.7%)	2/223 (0.9%)
Total bilirubin >1.5 × ULN	1/462 (0.2%)	1/456 (0.2%)	0/223

ULN, upper limit of normal.

Supplementary information

In total, 7 patients died during the study: 2 patients in the iGlarLixi group, 4 patients in the iGlar group, and 1 patient in the Lixi group. None of the fatal events were considered related to the investigational drugs by the investigator.

Six of 7 patients died due to treatment-emergent adverse events (TEAEs): 2 patients (0.4%) in the iGlarLixi group, 3 patients (0.6%) in the iGlar group, and 1 patient (0.4%) in the Lixi group; 1 patient in the iGlarLixi group and 1 patient in the iGlar group died post-treatment due to TEAEs.

In the iGlarLixi group: a 64-year-old male patient died from metastatic lung cancer and a 72-year-old male patient died from congestive cardiac failure. In the iGlar group, a 55-year-old male patient died from acute myocardial infarction and acute pulmonary edema, a 62-year-old male patient died from acute cardiac failure, and a 60-year-old male patient died about 3 months after the treatment period due to the worsening of undifferentiated keratinized squamous cell carcinoma in the mouth which was diagnosed during the on-treatment period. A 70-year-old male patient in the iGlar group died due to the post-treatment AE of gastrointestinal hemorrhage. In the Lixi group, a 63-year-old female patient was reported to be found dead on her bed due to unknown reasons 208 days after the first dose of the study drug. An autopsy was not performed.