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Published in:
Diabetes Care

DOI:
10.2337/dc21-0393

Publication date:
2021

Document Version
Peer reviewed version

Advancing therapy in suboptimally controlled basal insulin-treated type 2 diabetes: Clinical outcomes with iGlarLixi versus premix BIAsp 30 in the SoliMix randomized controlled trial

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Clinical trial registration: 2017-003370-13 (EU clinical trials register)

Running Title: Therapy advancement to iGlarLixi vs Premix

Abstract word count: 247 / 250

Word count: 3993 / 4000

Number of references: 31 / 40

Number of figures/tables: 3/1

Supplementary figures/tables: 3/5

Keywords: Premix insulin; basal insulins; Type 2; glycemic control; GLP-1 agonist; hypoglycemia; bodyweight; therapy intensification, GLP-1 RA, fixed-ratio combination

Abstract

Objective: To directly compare the efficacy and safety of a fixed-ratio combination, iGlarLixi, with a premix insulin analog (BIAsp 30) as treatment advancement in type 2 diabetes suboptimally controlled on basal insulin plus oral antihyperglycemic drugs (OADs).

Research Design and Methods: SoliMix, a 26-week, open-label, multicenter study, randomized adults with suboptimally controlled basal insulin-treated type 2 diabetes (HbA_{1c} ≥7.5 % and ≤10 %) to once-daily iGlarLixi or twice-daily BIAsp 30. Primary efficacy endpoints were non-inferiority in HbA_{1c} reduction (margin 0.3 %) or superiority in bodyweight change for iGlarLixi versus BIAsp 30.

Results: Both primary efficacy endpoints were met: after 26 weeks, baseline HbA_{1c} (8.6 %) was reduced by 1.3 % with iGlarLixi and 1.1 % with BIAsp 30, meeting non-inferiority (least squares [LS] mean difference [97.5% CI]: -0.2 [-0.4, -0.1] %; p<0.001). iGlarLixi was also superior to BIAsp 30 for bodyweight change (LS mean difference [95% CI] -1.9 [-2.3, -1.4] kg) and percentage of participants achieving HbA_{1c} <7 % without weight gain and HbA_{1c} <7 % without weight gain and without hypoglycemia (all p<0.001). iGlarLixi was also superior versus BIAsp 30 for HbA_{1c} reduction (p<0.001). Incidence and rates of ADA Level 1 and 2 hypoglycemia were lower with iGlarLixi versus BIAsp 30.

Conclusions: Once-daily iGlarLixi provided better glycemic control with weight benefit and less hypoglycemia than twice-daily premix BIAsp 30. iGlarLixi is a more efficacious, simpler, and well-tolerated alternative to premix BIAsp 30 in suboptimally controlled type 2 diabetes requiring treatment beyond basal insulin plus OAD therapy.

Clinical guidelines recommend a target HbA_{1c} of <7.0 % (<53 mmol/mol) for most non-pregnant adults with type 2 diabetes (1; 2), while recognizing the need to individualize glycemic targets based on patient preference, and treatment efficacy and safety profiles (1; 2). Most current guidelines advocate a stepwise introduction of pharmacotherapy for people with type 2 diabetes not achieving their individualized glycemic targets. With this approach, advancing basal insulin therapy involves four options: 1) adding rapid-acting insulin progressively to an existing basal insulin regimen; 2) multiple daily premix insulin doses (basal and prandial insulin co-formulation); 3) adding a daily or weekly glucagon-like peptide-1 receptor agonist (GLP-1 RA) to an existing basal insulin regimen; 4) switching to a once-daily fixed-ratio combination (FRC) of basal insulin and GLP-1 RA (2; 3).

Each aforementioned treatment option has been shown to improve glycemic control when used to advance therapy from basal insulin but are also associated with specific adverse effects (4-7). GLP-1 RA therapy can be associated with gastrointestinal (GI) adverse events (AEs) and resultant adherence issues (4). Basal plus rapid-acting insulin regimens and premix insulin regimens can increase the risks of hypoglycemia and weight gain, whilst requiring multiple daily injections and frequent glucose monitoring that increase treatment burden and may reduce adherence (5-7). Despite this, premix insulins are widely used globally, particularly in Asia, Africa, the Middle East, China and some EU countries (8-11).

Titratable FRCs of basal insulin and a GLP-1 RA can provide a novel alternative therapy advancement option to premix insulin, as tested for the first time in this randomized controlled trial. FRCs combine the complementary mechanisms of action of two individual components in one formulation; basal insulin primarily reduces fasting plasma glucose (FPG) while the GLP-1 RA targets post-prandial glucose (PPG). Overall, GLP-1 RAs act through a glucose-dependent mechanism by which they stimulate insulin secretion while preventing

glucagon increase (12). Short-acting GLP-1 RAs, specifically target PPG with a predominant gastric emptying effect, while long-acting GLP-1 RAs, exert their effect predominantly through pancreatic functions, resulting in a lesser impact on PPG but larger overall reductions in FPG (12). Two once-daily titratable FRCs of basal insulin and GLP-1 RA are available which are approved for use in adults with type 2 diabetes. iGlarLixi is an FRC of basal insulin glargine 100 units/mL (iGlar) and the short-acting GLP-1 RA lixisenatide (Lixi) (13; 14), while IDegLira is an FRC of the basal insulin degludec and the long-acting GLP-1 RA, liraglutide (15; 16). Both have been shown to provide improved glycemic control versus their individual components, along with weight-benefits compared with basal insulin and fewer gastrointestinal AEs compared with their GLP-1 RA component (17-22).

Here we report the results of the first randomized, head-to-head study directly comparing the efficacy and safety of an FRC (iGlarLixi) with a premix insulin (biphasic insulin aspart 30, BIAsp 30) in adults with type 2 diabetes advancing from basal insulin plus one or two oral antihyperglycemic drugs (OADs).

Research Design and Methods

Detailed methods have been previously published (23). In brief, SoliMix was an open-label, multicenter, randomized, 26-week study undertaken to compare the efficacy and safety of iGlarLixi with BIAsp 30, in adults with suboptimally controlled type 2 diabetes (HbA_{1c} ≥7.5 % [≥58.5 mmol/mol] and ≤10 % [≤85.8 mmol/mol]) despite receiving stable doses of basal insulin plus OADs (metformin ± sodium-glucose cotransporter-2 [SGLT2] inhibitor) for 3 months. Exclusion criteria included individuals with type 1 diabetes, BMI of <20 and ≥40 kg/m^2, basal insulin dose of <20 U or >50 U at screening, and use of any antihyperglycemic agent other than basal insulin, metformin, or SGLT2 inhibitors in the 3 months prior to screening.

Participants were randomized (1:1) to receive once-daily subcutaneous iGlarLixi (Suliqua®, [Soliqua®], Sanofi, Paris, France) or twice-daily subcutaneous BIAsp 30 (30% insulin aspart + 70% insulin aspart protamine; NovoMix® 30, Novo Nordisk A/S, Bagsværd, Denmark). iGlarLixi was injected before a meal using a prefilled disposable SoloSTAR® pen injector. BIAsp 30 was administered subcutaneously twice daily in the morning and before dinner. Participants were switched from their prior basal insulins at randomization; OADs were continued without adjustment. Starting doses of iGlarLixi were based on prior basal insulin doses, according to labelling instructions. If the previous basal insulin dose at randomization was <30 U, the starting dose was 20 dose steps (20 U iGlar, 10 μg Lixi) administered with the 10–40 U pen (2 U:1 μg ratio); if basal insulin was ≥30 to ≤50 U, the starting dose was 30 dose steps (30 U iGlar, 10 μg Lixi) administered with the 30–60 U pen (3 U:1 μg ratio). Further details are shown in **Supplementary Table 1**. Starting total daily doses of BIAsp 30 were the same as the participants' previous basal insulin dose on a unit-to-unit basis and split into two daily doses. Doses of iGlarLixi and BIAsp 30 were recommended for weekly titration based on fasting or premeal self-measured plasma glucose, respectively, to a target of 80–110 mg/dL (4.4–6.1 mmol/L). The recommended dose adjustment algorithms for iGlarLixi and BIAsp 30 were indicated according to label recommendations and are shown in **Supplementary Tables 2 and 3.**

Rescue therapy use was recommended according to the investigator's clinical judgment for both arms to correct hyperglycemia persisting beyond prespecified thresholds (HbA_{1c} >8 % or FPG >200 mg/dL from Week 12). Rescue therapy was to be considered in the iGlarLixi group when the maximal dose of 60 dose steps was reached. The use of any additional antihyperglycemic treatment (basal insulin, rapid-acting insulin, third daily injection of premix, or OADs) administered to participants in either group with the objective of rescue was included in the analysis of the proportion of participants requiring rescue therapy.

This study is registered on the European Union Drug Regulating Authorities Clinical Trials Database (2017-003370-13), and was conducted in accordance with the ethical principles of the Declaration of Helsinki, and the International Conference on Harmonisation guidelines for good clinical practice, and all applicable laws, rules, and regulations.

Study endpoints

The two primary objectives of this study were to demonstrate that, compared with BIAsp 30, iGlarLixi was non-inferior in terms of HbA_{1c} reduction or superior in terms of bodyweight change from baseline to Week 26. Key secondary efficacy endpoints were assessed at Week 26, including HbA_{1c} <7 % without weight gain at Week 26, HbA_{1c} <7 % without weight gain at Week 26 and without hypoglycemia (plasma glucose <70 mg/dL [<3.9 mmol/L]) during the treatment period, and the superiority of iGlarLixi versus BIAsp 30 in terms of HbA_{1c} reduction from baseline to Week 26. Other secondary exploratory glycemic endpoints included the proportion of patients reaching HbA_{1c} target <7 % at Week 26, HbA_{1c} target <7 % without ADA Level 2 hypoglycemia, HbA_{1c} <7 % without weight gain of >1 kg, and HbA_{1c} <6.5 %. Other secondary endpoints included change in total insulin dose and change in FPG, from baseline to Week 26.

Safety endpoints were hypoglycemia, AEs, serious AEs (SAEs), AEs leading to treatment discontinuation, and AEs leading to death. Hypoglycemia was defined by current ADA Level 1 (<70 mg/dL [<3.9 mmol/L] and ≥54 mg/dL [≥3.0 mmol/L]), Level 2 (<54 mg/dL [<3.0 mmol/L]), or Level 3 (severe hypoglycemia). Nocturnal hypoglycemia was also assessed post hoc using two definitions: between bedtime and waking, and between 00:00–06:00 h.

Statistical analysis

A sample size of 864 randomized participants (432 randomized or 388 evaluable participants per treatment group) was calculated based on the primary efficacy variables of HbA_{1c} and weight change from baseline to Week 26. Assuming a drop-out rate of 10%, this

sample size provides over 95% power to demonstrate non-inferiority (margin 0.3 %) of iGlarLixi versus BIAsp 30 for HbA_{1c} reduction or superiority for weight reduction at Week 26. The assumptions made for non-inferiority of HbA_{1c} were a standard deviation (SD) of 1.1 %, a non-inferiority margin of 0.3 % and a zero true difference in HbA_{1c} between treatment groups. Assumptions for superiority testing of iGlarLixi over BIAsp 30 in terms of weight gain included an expected difference of 1 kg between treatment groups and an SD of 3.46 kg for changes from baseline. The two-sided significance level of 0.025 was assumed for each of the above tests.

The primary efficacy endpoints were analyzed using a multiple imputation strategy and an ANCOVA model including screening HbA_{1c} value (<8.0 % vs ≥8.0 %, for the change in bodyweight primary endpoint only), basal insulin dose (<30 U, ≥30 U) and SGLT2 inhibitor use (Yes, No), treatment group, and country as fixed categorical effects, and fixed continuous covariates of baseline values for each primary endpoint (HbA_{1c} and bodyweight).

Continuous secondary efficacy endpoints (e.g. FPG and total daily insulin dose) were analyzed using the same approach as the primary endpoints including the baseline values for the endpoint in question as fixed covariates. Categorical secondary efficacy endpoints (e.g. the first two key secondary endpoints) were analyzed using a logistic regression model adjusting for treatment group randomization strata, and HbA_{1c} and weight baseline covariates.

A multiple testing procedure was pre-specified for analysis of the primary and key secondary efficacy endpoints (**Supplementary Figure 1**). Following the two primary endpoints, the three key secondary endpoints were assessed using a hierarchical order: superiority of iGlarLixi versus BIAsp 30 in achieving HbA_{1c} <7 % without weight gain; then superiority of HbA_{1c} <7 % without weight gain and without hypoglycemia; then superiority

of HbA_{1c} reduction. More detailed information pertaining to control for type I error has been previously published (22).

All efficacy analyses were performed on data from the intention-to-treat (ITT) population, defined as all randomized participants. The COVID-19 pandemic occurred during the last few weeks of the study in some countries, making it difficult for some participants to comply with the protocol. To assess the potential impact of this on the primary and key secondary efficacy endpoints, sensitivity analyses were performed on a subgroup of the ITT population who had no major or critical deviations related to the COVID-19 pandemic situation that could have affected the primary efficacy analysis. Participants who followed the study visits and assessments without being impacted by the COVID-19 pandemic and its consequences (e.g. lockdown, sites closed, postponed/incomplete end-of-treatment visit) were defined as the non-impacted by COVID-19 population. Further sensitivity analyses were performed for the non-inferiority objective in the per protocol population, defined as all participants in the ITT population who completed 26 weeks of randomized treatment without any major protocol violations.

Safety analyses were based on data from the safety population, defined as all randomized participants who received at least one dose of study drug.

Results

Participant disposition and baseline characteristics

In total, 887 participants from 89 centers in 17 countries were randomized in the study, of whom 443 were allocated to iGlarLixi and 444 to BIAsp 30. Of the 887 participants in the ITT population, 403 in the iGlarLixi group and 404 in the BIAsp 30 group were included in the non-impacted by COVID-19 population. No participants discontinued due to COVID-19. Overall, participants received treatment with iGlarLixi or BIAsp 30 for a mean

duration of 184 or 181 days, respectively. In total, 844 (95.2%) participants completed the 26-week treatment period; 428 (96.6%) in the iGlarLixi group and 416 (93.7%) in the BIAsp 30 arm (**Supplementary Figure 2**).

Demographics and baseline characteristics were similar across both treatment groups (**Table 1**) and have been reported previously (22). Briefly, the randomized population was primarily white (62.4%) with a mean ± SD age of 59.8 ± 10.2 years, BMI of 29.9 ± 4.9 kg/m^2 and duration of type 2 diabetes of 13.0 ± 7.2 years. Metformin was used at baseline in 99.8% of all participants: approximately one quarter were also receiving SGLT2i at baseline in both treatment groups. Basal insulins used at randomization were insulin glargine 100 U/mL (46%), insulin glargine 300 U/mL (22%), NPH insulin (21%), insulin detemir (7%), and insulin degludec (5%).

Efficacy endpoints

The two primary efficacy endpoints and all three key secondary efficacy endpoints were met. Mean ± SD baseline HbA_{1c} was 8.6 ± 0.7 % (71 ± 7 mmol/mol) in the iGlarLixi group and 8.6 ± 0.7 % (70 ± 7 mmol/mol) in the BIAsp 30 group. At Week 26, mean ± SD HbA_{1c} had improved to 7.3 ± 1.1 % (56 ± 12 mmol/mol) in the iGlarLixi group and to 7.5 ± 1.0 % (58 ± 11 mmol/mol) in the BIAsp 30 group (**Figure 1A** and **1B**). Statistical non-inferiority (margin 0.3 %) of iGlarLixi over BIAsp 30 was demonstrated for the change in HbA_{1c} from baseline to Week 26 (LS mean difference [97.5% CI] vs BIAsp 30: -0.2 [-0.4, -0.1] %; -2.6 [-4.5, -0.9] mmol/mol; p<0.001). Additionally, statistical superiority in HbA_{1c} reduction from baseline to Week 26 of iGlarLixi over BIAsp 30 was demonstrated as part of the key secondary endpoint analysis, on the basis of the hierarchical testing procedure (**Figure 1B**).

At baseline, mean ± SD bodyweight was 80.7 ± 16.5 kg in the iGlarLixi group and 82.2 ± 18.5 kg in the BIAsp 30 group. From baseline to Week 26, mean ± SD bodyweight decreased to 80.2 ± 16.6 kg for iGlarLixi and increased to 83.4 ± 19.0 kg for BIAsp 30 (**Figure 1C**). Statistical superiority of iGlarLixi over BIAsp 30 was demonstrated for the change in bodyweight from baseline to Week 26 (LS mean difference vs BIAsp 30 -1.9 [95% CI -2.3, -1.4] kg; p<0.001).

Key secondary efficacy endpoints showed that, compared with the BIAsp 30 group, a significantly greater proportion of participants in the iGlarLixi group reached HbA_{1c} <7 % (<53 mmol/mol) without weight gain at Week 26, and without weight gain at Week 26 and without hypoglycemia (<70 mg/dL [<3.9 mmol/L]) during the treatment period (**Figure 2**). The percentage of participants who reached HbA_{1c} target <7 % was higher in the iGlarLixi group than in the BIAsp 30 group (**Figure 2**, exploratory endpoint). iGlarLixi also demonstrated higher proportions of HbA_{1c} <7 % target achievement without ADA Level 2 hypoglycemia, HbA_{1c} <7 % without weight gain of >1 kg, and HbA_{1c} <6.5 % than BIAsp 30 (**Figure 2,** exploratory endpoints).

Mean ± SD FPG at baseline was 151 ± 44 mg/dL (8.4 ± 2.4 mmol/L) in the iGlarLixi group and 149 ± 41 mg/dL (8.3 ± 2.3 mmol/L) in the BIAsp 30 group. At Week 26, mean ± SD FPG was 130 ± 44 mg/dL (7.2 ± 2.4 mmol/L) in the iGlarLixi group and 146 ± 51 mg/dL (8.1 ± 2.8 mmol/L) in the BIAsp 30 group. The LS mean difference (95% CI) between groups in change from baseline to Week 26 was -16 (-26, -6) mg/dL (-0.9 [-1.5, -0.3] mmol/L).

After 26 weeks, the increase in LS mean total daily insulin dose was smaller in the iGlarLixi group than in the BIAsp 30 (**Figure 1D**). The percentage of participants who required rescue therapy was low and similar for iGlarLixi (1.8%) and BIAsp 30 (2.3%).

Detailed data for efficacy endpoints can be found in **Supplementary Table 4**. All key sensitivity analyses performed on the two primary and key secondary endpoints demonstrated similar results to those observed in the ITT population (**Supplementary Table 5**).

Safety profile

The proportion of participants with at least one hypoglycemic event was lower in the iGlarLixi group compared with the BIAsp 30 group (OR [95% CI] 0.62 [0.47, 0.81]) (**Figure 3**). Lower incidence of hypoglycemia with iGlarLixi versus BIAsp 30 was also observed across Level 1 and Level 2 hypoglycemia categories (**Figure 3**).

Rates of hypoglycemia followed the same pattern as incidence. There was an overall lower rate of any hypoglycemia with iGlarLixi compared with BIAsp 30, as well as lower rates of Level 1 and Level 2 hypoglycemia (**Figure 3**).

Three severe hypoglycemic episodes (Level 3) were reported: one occurred in the iGlarLixi group and two in the BIAsp 30 group.

In addition, lower incidence (OR [95% CI]: 0.37 [0.16, 0.84]) and event rates (RR [95% CI]: 0.28 [0.11, 0.71]) of Level 2 nocturnal hypoglycemia (defined as occurring between bedtime and waking) were observed in the iGlarLixi group versus the BIAsp 30 group. Similar patterns were seen when using the between 00:00–06:00 h definition: lower incidence (OR [95% CI]: 0.32 [0.12, 0.90]) and event rates (RR [95% CI]: 0.30 [0.10, 0.88]) were seen with iGlarLixi versus BIAsp 30.

During the 26-week randomized treatment period, the percentage of participants who had at least one AE was slightly higher in the iGlarLixi group (32.6%) compared with the BIAsp 30 group (27.7%), the difference being mainly due to the higher incidence of GI events in the iGlarLixi group (10.4% vs 2.3%). A large proportion of these GI events were reported in the first week of treatment (**Supplementary Figure 3**). The most commonly

reported AE in the iGlarLixi group was nausea (7.7% vs 0% for BIAsp 30), while nasopharyngitis was the most commonly reported AE in the BIAsp 30 group (2.7% vs 3.2% for iGlarLixi). In both treatment groups, the majority of participants had AEs considered mild or moderate in severity. SAEs were reported by a similar proportion of participants in both treatment groups (2.7% iGlarLixi and 2.9% BIAsp 30). Overall, the rate of study discontinuation due to an AE was low and similar in both treatment groups (0.9%). There were two fatal AEs (acute coronary syndrome and cardiac failure/pulmonary edema) during the study period, both in the BIAsp 30 group. Neither of these fatal AEs were considered related to study treatment. During the study, no AEs were considered related to COVID-19.

Conclusions

This study is the first RCT comparing an FRC of basal insulin and a GLP-1 RA with premix insulin. Results from this study provide evidence for the better efficacy and safety of iGlarLixi compared with premix BIAsp 30 for advancing treatment in adults with longstanding type 2 diabetes suboptimally controlled by basal insulin plus one or two OADs. After 26 weeks, iGlarLixi demonstrated both non-inferiority (primary endpoint) and statistical superiority (key secondary endpoint) to premix BIAsp 30 in HbA_{1c} reduction and statistical superiority in bodyweight change (primary endpoint). Although the LS mean difference in HbA_{1c} reduction was modest and may not represent a clinically meaningful difference in isolation, a greater proportion of participants achieved HbA_{1c} target <7 % (<53 mmol/mol) overall, as well as without weight gain or without weight gain and hypoglycemia with iGlarLixi versus BIAsp 30, demonstrating the overall clinical benefit of iGlarLixi in individuals with longstanding type 2 diabetes.

In addition, mean bodyweight decreased from baseline to Week 26 with iGlarLixi and increased with premix BIAsp 30, with a significant between-group difference. Notably, better glucose control (HbA_{1c} and FPG) observed with iGlarLixi compared with premix BIAsp 30

was associated with a smaller mean daily insulin dose at Week 26 in the iGlarLixi group compared with the premix BIAsp 30 arm. The between-treatment differences in Week 26 FPG may also have contributed to the greater HbA_{1c} reductions seen with iGlarLixi versus premix BIAsp 30; however, the lack of PPG data does limit our understanding of the cause of the between-treatment HbA_{1c} change difference.

These results align with a previous network meta-analysis (NMA) by Home *et al.* comparing iGlarLixi versus basal-bolus or premix insulins (24). Results of this NMA estimated greater HbA_{1c} reductions with iGlarLixi versus premix insulin (mean difference of -0.50 [95% credible interval -0.93, -0.06] %), in addition to favorable bodyweight changes with iGlarLixi compared with premix insulin (-2.2 [-4.6, -0.1] kg) (24).

The improvements in glycemic control and reductions in bodyweight seen with iGlarLixi in this study are consistent with those observed in the LixiLan-L study, which compared efficacy and safety of iGlarLixi versus basal insulin in people with longstanding type 2 diabetes suboptimally controlled by basal insulin ± OAD therapy over 30 weeks (17). In LixiLan-L, LS mean reduction in HbA_{1c} from baseline was 1.1 %, while weight was reduced by 0.7 kg. Similarly, the glycemic control and bodyweight changes observed for premix BIAsp 30 in the present study are consistent with previous RCTs of premix BIAsp 30 in adults with type 2 diabetes advancing basal insulin therapy (25-27).

The incidence of hypoglycemia reported in previous RCTs of iGlarLixi and premix BIAsp 30 is difficult to compare with the current study due to the different definitions and blood glucose thresholds used (17; 26; 27). However, incidence of hypoglycemia in previous RCTs was generally higher for both treatments (40% for iGlarLixi and ~70% for premix BIAsp 30) than that observed in the present study (17; 26; 27), possibly due to the absence of sulfonylurea use in this study. It is, therefore, very encouraging that lower incidence and rates of hypoglycemia, including ADA Level 2 nocturnal hypoglycemia between bedtime and

waking, were still observed with iGlarLixi versus premix BIAsp 30 in the present study, despite iGlarLixi demonstrating better glycemic control.

Likewise, the overall safety and tolerability profiles of iGlarLixi and premix BIAsp 30 were comparable with those reported in previous studies (17-19; 26; 27), with very low discontinuation rates due to AEs and no unexpected safety signals identified. The slightly higher incidence of AEs observed for iGlarLixi versus premix BIAsp 30 in this study was due to the higher incidence of nausea in the iGlarLixi group. Nausea incidence in this study is in line with previous reports for FRCs (3.1%–10.4%) (17-22; 28), lower than previously observed in participants initiating GLP-1 RAs alone (18; 20), and very rarely led to treatment discontinuation (0.5%). Similarly, for both groups, low rates of SAEs were reported and few participants required rescue therapy (~2%). No AEs were determined to be COVID-19-related.

Following beta-cell decline in basal insulin-treated type 2 diabetes, prandial insulin is often added to control postprandial hyperglycemia (29; 30). An alternative option is adding a GLP-1 RA to basal insulin. Our results demonstrate that a co-formulation of basal insulin and GLP-1 RA (iGlarLixi) is more efficacious than a co-formulation of a basal insulin and a prandial insulin (premix BIAsp 30) when advancing therapy for people with type 2 diabetes suboptimally controlled on basal insulin alone. In addition to improving clinical outcomes, the lower incidence of hypoglycemia and the weight benefits observed with iGlarLixi may improve patient satisfaction, which could improve treatment adherence. Assessment of patient-reported outcomes from the current study is planned for future analyses. iGlarLixi may also prove to be a cost-effective alternative to premix with fewer injections and less glucose monitoring.

A key strength of the present analysis is the evidence base generated by it being the first randomized head-to-head comparison of the efficacy and safety of an FRC of basal

insulin and a GLP-1 RA versus premix insulin in a clinically relevant population of adults with type 2 diabetes who were suboptimally controlled on basal insulin plus OADs. Furthermore, it was a global study, including individuals with different ethnicities and from varying healthcare systems, without a glucose monitoring committee enforcing titrations and therefore provides relevant, clinically translatable information.

A potential limitation of this study is its open-label design. However, as the injectables could not be masked, a double-blind study design was impractical. Furthermore, iGlarLixi was tested against the most frequently used premix insulin ratio (30:70) but not against other premix ratios. However, hypoglycemia rates have been shown to be higher with other premix insulin regimens than with premix insulin 30/70 (31), so the benefits of iGlarLixi over other premix insulins could be even greater. A further potential limitation is that the COVID-19 pandemic occurred during the last few weeks of the study in some countries. Systems were put in place to ensure participant safety, retention and data capture. Sensitivity analyses in a non-impacted by COVID-19 ITT population showed that COVID-19 was unlikely to have influenced the results of any endpoints assessed.

In conclusion, the once-daily FRC, iGlarLixi, is an efficacious and well-tolerated regimen that is simpler for the patient, providing better glycemic control with weight benefit and less hypoglycemia compared with premix BIAsp 30 as an alternative for advancing therapy in people with type 2 diabetes previously suboptimally controlled with basal insulin plus OADs.

Acknowledgments

The authors thank the study participants, trial staff, and investigators for their participation. We thank Elisabeth Souhami, MD (Sanofi) for a courtesy review from a medical and scientific perspective, Mathieu Coudert, MSc (Sanofi) for a courtesy review from a statistical perspective and Ana Merino-Trigo, PhD (Sanofi) for coordinating the development, facilitating author discussions, and review of this manuscript. Editorial assistance was provided by Fishawack Communications Ltd., part of Fishawack Health.

Funding

Sponsorship for this study was funded by Sanofi, Paris, France. Editorial assistance provided by Fishawack Communications Ltd. was funded by Sanofi.

Author contributions

All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article. All authors participated in the interpretation of the data, the writing, reviewing, and editing of the manuscript, and had final responsibility for approving the published version. Julio Rosenstock, MD, and Pascaline Picard, MSc, are the guarantors of this work and, as such, have full access to all the data in this study and take responsibility for the integrity of the data and accuracy of the data analysis.

Disclosures

JR has served on advisory panels for Applied Therapeutics, Boehringer Ingelheim, Eli Lilly, Intarcia, Janssen, Novo Nordisk, Oramed, Sanofi, and Zealand; and has received research support from Applied Therapeutics, AstraZeneca, Boehringer Ingelheim, Eli Lilly, Genentech, GlaxoSmithKline, Intarcia, Janssen, Lexicon, Merck, Novo Nordisk, Oramed, Pfizer and Sanofi.

RE has acted as an advisor and speaker for AstraZeneca, Boehringer Ingelheim, Lilly, MSD, Novo Nordisk and Sanofi.

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VM has served on advisory panels and has acted as a speaker for Abbott, Boehringer Ingelheim, Eli Lilly, Merck (MSD), Novo Nordisk, Sanofi and several Indian pharmaceutical companies. He has also received research grants from some of these companies.

CT has been an investigator in clinical trials for Eli Lilly and Sanofi, and has acted as a speaker for AstraZeneca, Boehringer Ingelheim, Eli Lilly, Novo Nordisk and Sanofi.

SAS has acted as an advisor and speaker for AstraZeneca, Boehringer Ingelheim, Eli Lilly, MSD, Novartis, Novo Nordisk, and Sanofi.

ND, **AA** and **MB** are employees of Sanofi and may hold shares and/or stock options in the company.

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Tables

Table 1. Abbreviated baseline characteristics (Randomized population)

Demographic/clinical characteristic	**iGlarLixi**	**BIAsp 30**	**All participants**
	(n=443)	**(n=444)**	**(N=887)**
Age (years)			
Mean ± SD	59.8 ± 10.3	59.8 ± 10.0	59.8 ± 10.2
Median	61	60	61
(Q1, Q3)	(52, 67)	(54, 67)	(53, 67)
Sex, n (%)			
Male	224 (50.6)	218 (49.1)	442 (49.8)
Female	219 (49.4)	226 (50.9)	445 (50.2)
BMI (kg/m^2)			
Mean ± SD	29.7 ± 4.7	30.0 ± 5.1	29.9 ± 4.9
Median	29.1	29.2	29.1
(Q1, Q3)	(26.2, 32.9)	(26.2, 34.2)	(26.2, 33.6)
Duration of type 2 diabetes (years)			
Mean ± SD	13.0 ± 7.1	13.0 ± 7.4	13.0 ± 7.2
Median	12.0	12.0	12.0
(Q1, Q3)	(7.6, 17.0)	(7.2, 17.0)	(7.5, 17.0)
Prior basal insulin at baseline*, n (%)			
Insulin glargine 100 U/mL	188 (42.4)	219 (49.2)	407 (45.8)
Insulin glargine 300 U/mL	100 (22.6)	92 (20.7)	192 (21.6)
NPH	102 (23.0)	82 (18.4)	184 (20.7)
Insulin detemir	34 (7.7)	31 (7.0)	65 (7.3)

Insulin degludec	19 (4.3)	21 (4.7)	40 (4.5)
Average basal insulin daily dose (U)†			
Mean ± SD	33.8 ± 9.6	33.8 ± 9.9	33.8 ± 9.8
Median	34.0	34.0	34.0
(Q1, Q3)	(25.0, 40.0)	(24.0, 42.0)	(25.0, 40.0)
Average basal insulin daily dose (U/kg)†			
Mean ± SD	0.43 ± 0.15	0.43 ± 0.14	0.43 ± 0.14
Median	0.42	0.42	0.42
(Q1, Q3)	(0.32, 0.52)	(0.32, 0.51)	(0.32, 0.52)
Previous non-insulin antihyperglycemic treatment*, n (%)			
Metformin	443 (100.0)	442 (99.5)	885 (99.8)
SGLT2i	104 (23.5)	102 (23.0)	206 (23.2)
Other	1 (0.2)	2 (0.5)	3 (0.3)
Daily metformin dose at baseline (mg)			
Mean ± SD	1761 ± 542	1722 ± 549	1741 ± 546
Median	2000	1850	2000
(Q1, Q3)	(1500, 2000)	(1500, 2000)	(1500, 2000)
Diabetes-related complications, n (%)			
Diabetic neuropathy	119 (26.9)	127 (28.6)	246 (27.7)
Diabetic retinopathy (incl. proliferative diabetic retinopathy)	67 (15.1)	67 (15.1)	134 (15.1)
Diabetic nephropathy	45 (10.2)	41 (9.2)	86 (9.7)
Heart failure	11 (2.5)	8 (1.8)	19 (2.1)

Peripheral artery disease	2 (0.5)	9 (2.0)	11 (1.2)
Ischemic stroke	2 (0.5)	0	2 (0.2)

Full baseline characteristics have been reported previously (22).
*A participant can be counted in more than 1 category. †Within the 3 days immediately before randomization.
BIAsp 30, biphasic aspart insulin 30 (30% insulin aspart and 70% insulin aspart protamine); BMI, body mass index; iGlarLixi, a fixed-ratio combination of insulin glargine 100 U/mL and the glucagon-like peptide-1 receptor agonist, lixisenatide; NPH, neutral protamine Hagedorn insulin; OAD, oral antihyperglycemic drug; Q, quartile; SD, standard deviation; SGLT2i, sodium-glucose cotransporter 2 inhibitor.

Figure legends

Figure 1. (**A**) HbA_{1c} over 26 weeks and (**B**) change in HbA_{1c}, (**C**) bodyweight and (**D**) total insulin daily dose from baseline to Week 26 (ITT population)

Missing data in the primary HbA_{1c} and weight endpoints were imputed through a multiple imputation (MI) strategy under the missing not at random (MNAR) framework, with separate MI process function of treatment completeness. Missing values were imputed 1000 times.
[†]Non-inferiority p value was calculated using a non-inferiority margin of 0.3 %.
BIAsp 30, biphasic aspart insulin 30 (30% insulin aspart and 70% insulin aspart protamine); BL, baseline; CI, confidence interval; iGlarLixi, a fixed-ratio combination of insulin glargine 100 U/mL and the glucagon-like peptide-1 receptor agonist, lixisenatide; ITT, intention-to-treat; LS, least squares; SE, standard error, SD, standard deviation; W, week.

Figure 2. Glycemic target achievement and composite secondary efficacy endpoints (ITT population).

*Adjusted odds ratio of iGlarLixi versus BIAsp 30 with associated 2-sided CI (at the specified significance level that is passed from family 1 of the primary objectives), calculated by logistic regression model adjusted for fixed categorical effects of randomization strata (basal insulin dose at screening <30 U and ≥30 U; and SGLT2 inhibitor use [Yes, No] at screening) and treatment group as well as fixed continuous covariates of baseline values for each of the primary endpoints (HbA_{1c} and bodyweight).
†Imputed as not having reached HbA_{1c} target (failure, ie. non-responder) in the case of missing HbA_{1c} or weight values at Week 26.
‡Weight gain defined as any increase >0 kg from baseline.
§Hypoglycemia defined as plasma glucose <70 mg/dL (<3.9 mmol/L) occurring at any point within the 26-week open-label randomized treatment period.

BIAsp 30, biphasic aspart insulin 30 (30% insulin aspart and 70% insulin aspart protamine); CI, confidence interval; iGlarLixi, a fixed-ratio combination of insulin glargine 100 U/mL and the glucagon-like peptide-1 receptor agonist, lixisenatide; ITT, intention-to-treat; n, number of participants; OR, odds ratio.
Assessments were done in hierarchical order, starting with the proportion of participants who reached HbA_{1c} <7 % without weight gain.

Figure 3. (**A**) Incidence and (**B**) rates of hypoglycemic events over the 26-week treatment period (Safety population).

[*] A participant can have more than one documented event.
[†] Odds ratio for iGlarLixi versus BIAsp 30 and 95% CI based on logistic regression with treatment group (iGlarLixi and BIAsp 30) and randomization strata (HbA_{1c} <8.0 % and ≥8.0 %; basal insulin dose at screening <30 U and ≥30 U; and SGLT2 inhibitor use [Yes, No] at screening) as fixed effects.
[‡] Rate ratio for iGlarLixi versus BIAsp 30 and 95% CI estimated from a negative binomial regression model with a log-link function, and the log of the time period in which a hypoglycemia episode is considered treatment emergent as offset. The model included fixed effect terms for treatment group (iGlarLixi and BIAsp 30) and randomization strata (HbA_{1c} <8.0 % and ≥8.0 %; basal insulin dose at screening <30 U and ≥30 U; and SGLT2 inhibitor use [Yes, No] at screening).

ADA, American Diabetes Association; BIAsp 30, biphasic aspart insulin 30 (30% insulin aspart and 70% insulin aspart protamine); CI, confidence interval; iGlarLixi, a fixed-ratio combination of insulin glargine 100 U/mL and the glucagon-like peptide-1 receptor agonist, lixisenatide; n, number of participants; OR, odds ratio; PPY, per participant-year; RR, rate ratio.