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CLINICAL TRIAL DESIGN

WILEY

Advancing therapy with iGlarLixi versus premix BIAsp 30 in basal insulin-treated type 2 diabetes: Design and baseline characteristics of the SoliMix randomized controlled trial

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Abstract

Aim: Premix insulin is commonly used in some regions of the world, despite the higher risk of hypoglycaemia and weight gain compared with basal insulin, based on the premise that it offers a simplified insulin regimen. iGlarLixi is a once-daily titratable fixed-ratio formulation that combines basal insulin glargine 100 units/mL (iGlar) and the GLP-1 RA, lixisenatide, which offers a single-injection option for treatment intensification, with improved HbA1c reductions, similar hypoglycaemia risk and more favourable bodyweight profiles over iGlar alone. This randomized controlled study directly compares, for the first time, treatment intensification with iGlarLixi versus premix insulin analogue biphasic insulin aspart 30 (BIAsp 30) in adults with T2D inadequately controlled on basal insulin in combination with one or two oral antihyperglycaemic drugs.

Materials and Methods: This was an open-label, active-controlled, comparative, parallel-group, multicentre, phase 3b study. In total, 887 adults with T2D uncontrolled on basal insulin were randomized to switch to either iGlarLixi once daily, or BIAsp 30 twice daily, for 26 weeks.

Results: Overall, 887 participants were enrolled (mean age 59.8 years, 50.2% female) from 89 centres in 17 countries. At baseline, 65.6% had a duration of T2D of 10 years or longer, and the mean HbA1c at baseline was 8.6%.

Conclusions: The study directly compared the efficacy and safety of iGlarLixi versus BIAsp 30 in people with T2D uncontrolled on basal insulin and one or more oral antihyperglycaemic agents. These results provide robust clinical data that may inform clinicians in their therapeutic management of people with T2D uncontrolled on basal insulin requiring additional therapy.

KEYWORDS

basal insulin, GLP-1 analogue, glycaemic control, insulin therapy, randomized trial, type 2 diabetes

1 | INTRODUCTION

Current treatment guidelines recommend an HbA1c value of <7.0% (<53 mmol/mol) for adults with type 2 diabetes (T2D) that can be individualized based on clinical profile.[1,2] Guidelines recommend adding glucose-lowering agents using a stepwise approach with reassessment at 3–6-month intervals, recommending glucagon-like peptide-1 receptor agonists (GLP-1 RAs) as the preferred initial injectable therapy.[1] Basal insulin can also be considered as an initial injectable therapy depending on patient preferences and, for some individuals with T2D who have an HbA1c of <10% or >2% above their individualized target, initial combination therapy with basal insulin plus GLP-1 RA or basal plus prandial insulin can also be considered.[1]

Real-world studies have revealed significant inertia in clinical practice in intensification to basal insulin; this can be delayed by over 6 years in some cases; as a consequence of this delay, individuals may experience poorer glycaemic control.[3] Additionally, once receiving basal insulin, individuals may then experience insulin titration inertia, which may also contribute to poorer glycaemic control.[4] Even following initiation of basal insulin, real-world studies have shown that many adults with T2D fail to achieve their glycaemic target within 6 months of initiation.[4,5] For these individuals, there are four recommendations for advancing basal insulin therapy: (a) progressive addition of rapid-acting insulin to an existing basal insulin regimen,[6,7] (b) multiple doses of premix insulin,[6,7] (c) addition of a daily or weekly GLP-1 RA,[7,8] or (d) switching to a once-daily fixed-ratio combination (FRC) of basal insulin and GLP-1 RA.[7,8]

FRCs are a novel alternative intensification therapy for people with T2D uncontrolled on their current therapy. FRCs have the convenience of a once-daily injection without the need for increased self-monitored plasma glucose (SMPG) measurements. iGlarLixi is a once-daily titratable FRC of the basal insulin, insulin glargine 100 units/mL (iGlar), and the GLP-1 RA, lixisenatide (Lixi).[9,10] iGlarLixi combines the complementary actions of iGlar, which primarily targets fasting plasma glucose (FPG), and the short-acting GLP-1 RA, Lixi, which primarily reduces postprandial plasma glucose levels.[11] The efficacy and safety of iGlarLixi has been previously shown in the LixiLan study programme, which showed that iGlarLixi significantly improved glycaemic control versus iGlar, Lixi, or continuing prior GLP-1 RAs, without increasing the risk of hypoglycaemia, and with a significantly more favourable body weight profile compared with iGlar.[12–14] iGlarLixi was also well tolerated[13,15] and had a better gastrointestinal profile compared with Lixi alone.[15] iGlarLixi is approved in more than 60 countries worldwide for the treatment of T2D.[10] A systematic literature review and network meta-analysis showed that iGlarLixi therapy was associated with greater HbA1c reductions compared with premix and basal plus prandial insulin regimens, in addition to favourable body weight changes compared with premix insulin.[16] Although not confirmed as significant, hypoglycaemia outcomes were also shown to probably favour iGlarLixi versus premix and basal plus prandial insulin.[16] Taken together, these data suggest that in people with T2D uncontrolled on basal insulin, iGlarLixi may present a clinically relevant treatment option compared with basal plus prandial insulin regimens or premix insulin.

This article presents the study design and baseline characteristics of SoliMix, the first study to directly compare an FRC of basal insulin and GLP-1 RA, iGlarLixi, with a premix insulin analogue, biphasic insulin aspart 30 (BIAsp 30) in adults with T2D who have failed to reach their glycaemic target with basal insulin in combination with one or two oral antihyperglycaemic drugs (OADs). In this way, this study will establish whether iGlarLixi provides similar or improved glycaemic efficacy to BIAsp 30, while specifically comparing outcomes that might improve treatment individualization, such as hypoglycaemia, weight gain, therapeutic burden and treatment complexity.

2 | MATERIALS AND METHODS

2.1 | Study objectives

The primary objective of this study was to show that iGlarLixi is non-inferior to premix insulin analogue BIAsp 30 twice daily in terms of HbA1c reduction or superior in body weight change at week 26 in people with T2D inadequately controlled on basal insulin combined with one or two OADs. The key secondary efficacy objectives include evaluation of composite endpoints such as glycaemic control without weight gain, and glycaemic control without weight gain and hypoglycaemia, and the superiority of iGlarLixi versus BIAsp 30 in HbA1c reduction. Other secondary endpoints include the proportion of participants achieving an HbA1c target of <7%; changes in total daily insulin dose and FPG; assessment of the safety and tolerability of each treatment; and patient- and clinician-reported outcomes.

2.2 | Study design

This was an open-label, randomized, active-controlled, 26-week, parallel-group, multicentre, phase 3b study to compare the efficacy and safety of iGlarLixi versus BIAsp 30 in adults with T2D. The active-controlled non-inferiority design was chosen according to US Food and Drug Administration guidance.[17] This study was registered on the European Union Drug Regulating Authorities Clinical Trials Database (2017–003370-13) and conducted in accordance with the ethical principles set out by the Declaration of Helsinki, the International Conference on Harmonization guidelines for good clinical practice, and all applicable laws, rules and regulations. Permission was received from local ethics committees. Institutional review boards or ethics committees at each study site approved the protocol. Each participant provided written informed consent.

2.3 | Study population

In total, 887 participants were recruited from 17 countries (Argentina, Austria, Bulgaria, the Czech Republic, Greece, India, Kingdom of Saudi Arabia, Kuwait, North Macedonia, Mexico, Romania, Serbia, South Korea, Spain, Sweden, Taiwan and Turkey) following provision of signed informed consent. Eligible participants were adults who had a diagnosis of T2D for at least 1 year at the time of screening, and uncontrolled T2D at screening (HbA1c ≥ 7.5% [≥58.5 mmol/mol] and ≤10% [≤85.8 mmol/mol]) despite treatment for at least 3 months prior to screening with any basal insulin (stable dose [maximum ±20%]; ≥20 U and ≤50 U at screening) combined with one or two OADs (metformin alone or metformin combined with a sodium-glucose co-transporter-2 inhibitor [SGLT2i]). Key exclusion criteria included any diabetes other than T2D; body mass index (BMI) values of <20 and ≥40 kg/m^2; use of any glucose-lowering agent other than basal insulin, metformin or an SGLT2i in the 3 months prior to screening; the use of weight-loss drugs in the 12 weeks prior to screening; and an FPG level >200 mg/dL (>11.1 mmol/L) at screening. Women of childbearing potential not protected by effective birth control, and pregnant or breastfeeding women, were also excluded.

2.4 | Randomization and study intervention

Adults with T2D meeting the eligibility criteria at screening were enrolled into the 26-week, open-label treatment period and randomized 1:1 to either iGlarLixi (FRC of iGlar + Lixi: 100 U/mL + 50 μg/mL [10–40 U pen] or 100 U/mL + 33 μg/mL [30–60 U pen]; Suliqua, Sanofi, Paris, France) injected subcutaneously once a day within 1 h prior to a meal (preferably the same meal every day), or BIAsp 30 (rapid-acting soluble insulin aspart/intermediate-acting protamine-crystallized insulin aspart in the ratio 30/70; NovoMix 30, Novo Nordisk A/S, Bagsværd, Denmark) administered subcutaneously twice daily, either half the dose in the morning and half before dinner, or two-thirds in the morning and one-third before dinner. Randomization was stratified by HbA1c value (<8% and ≥8%) at screening, use of an SGLT2i (Yes/No) at screening and dose of basal insulin (<30 U or ≥30 U) at screening.

The choice of iGlarLixi pen and initiation dose according to previous basal insulin dose (<30 or ≥30 U) are described in Figure 1, along with required dose adjustments. It was also recommended that weekly adjustments should be made according to an adjustment algorithm with a self-measured fasting glucose target measurement of 80 to 110 mg/dL (4.4 to 6.1 mmol/L) (Table 1A) and no dose increments if hypoglycaemia occurred within the previous 3 days. While this glycaemic target is more stringent than current clinical recommendations and targets seen in routine clinical practice, particularly for elderly individuals or those with co-morbidities, this was a recommendation for the population overall and the investigators were able to adapt participant targets to suit their individual profiles as necessary.[1] These adjustments were made weekly according to fasting SMPG values measured before breakfast.

The initiation dose of BIAsp 30 reflected the participant's current basal insulin dose on a unit-to-unit basis and started with the same dose twice-daily. The titration of BIAsp 30 was performed weekly with a premeal glucose target measurement of 80 to 110 mg/dL (4.4 to 6.1 mmol/L) (Table 1B). BIAsp 30 titration was based on predinner SMPG values for breakfast dose adjustment and prebreakfast SMPG values for dinner dose adjustment, with dose adjustments made once weekly. The dose of BIAsp 30 was not increased if hypoglycaemia occurred within the previous 3 days, in line with label recommendations.[18]

Participants were switched from their prior basal insulins at randomization and continued with their background OAD treatment throughout the study. Participants were followed for approximately 29 weeks, comprising the 2-week screening period, the 26-week randomized treatment period and a 3-day post-treatment follow-up period (Figure 2).

Participants could withdraw their involvement in the study at any time, irrespective of reason. Those that withdrew their consent for treatment only were encouraged to continue study visits, with key visits being identified to them by the investigators.

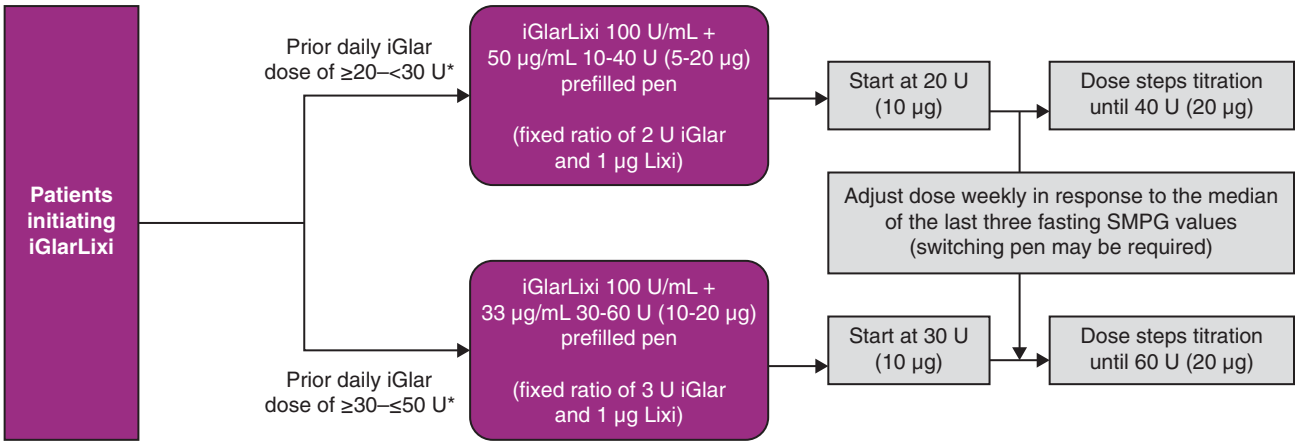

FIGURE 1 iGlarLixi dose and pen usage. *If a twice-daily basal insulin or insulin glargine 300 U/mL was used, the total daily dose previously used should be reduced by 20% to choose the iGlarLixi starting dose. If any other basal insulin was used, the same rule as for iGlar should be applied. iGlar, insulin glargine 100 units/mL; iGlarLixi, once-daily titratable fixed-ratio combination of basal insulin glargine 100 units/mL and the glucagon-like peptide-1 receptor agonist lixisenatide; SMPG, self-monitored plasma glucose

2.5 | Study outcomes

2.5.1 | Endpoints

The two primary efficacy endpoints were the non-inferiority of iGlarLixi to BIAsp 30 in terms of HbA1c reduction (0.3% non-inferiority margin) or superiority in body weight change from baseline to week 26 (Table 2). The key secondary efficacy endpoints in hierarchical analytical order include: superiority of iGlarLixi versus BIAsp 30 in the proportion of participants reaching their HbA1c target (<7% [<53.0 mmol/mol]) without weight gain at week 26; the proportion of participants reaching their HbA1c target without weight gain at week 26 and without hypoglycaemia (plasma glucose <70 mg/dL [<3.9 mmol/L]) during the treatment period; and superiority of iGlarLixi versus BIAsp 30 in HbA1c reduction from baseline to week 26. Other secondary efficacy endpoints, safety endpoints, and patient- and clinician-reported outcomes, can be found in Table 2. Hypoglycaemia was defined according to American Diabetes Association guidelines and included events documented at either 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 hypoglycaemia, defined as severe cognitive impairment requiring external assistance for recovery).[1] Documented hypoglycaemia ≤70 mg/dL (≤3.9 mmol/L), documented symptomatic hypoglycaemia ≤70 mg/dL (≤3.9 mmol/L), asymptomatic hypoglycaemia ≤70 mg/dL (≤3.9 mmol/L), and any symptomatic hypoglycaemia, were also assessed.

2.5.2 | Assessments

The number and type of visits are detailed in Figure 2. SMPG was used to titrate and adjust iGlarLixi and BIAsp 30 doses, monitor glucose control and assist with hypoglycaemia management from week 0 to the end of treatment. The SMPG monitoring schedule for each treatment arm was described earlier in the Randomization and study intervention section (2.4).

HbA1c levels were assessed at week −2 (screening), and weeks 12 and 26. HbA1c was analysed by a certified Level I National Glycohaemoglobin Standardization Program central laboratory.

Body weight was assessed at week −2 (screening), and weeks 0, 12 and 26. When body weight was measured, participants were required to have an empty bladder and to wear undergarments or very light clothing and no shoes.

2.5.3 | Safety evaluation

Adverse events were collected for the whole study period. Participants experiencing any symptoms of hypoglycaemia were asked to immediately perform a fingerstick glucose measurement. Participants were to contact the investigators as soon as possible following severe events of hypoglycaemia for guidance. Both the proportion of participants experiencing one or more hypoglycaemic event and the number of events per participant-year were assessed.

2.5.4 | Patient- and physician-reported outcomes

The Treatment-Related Impact Measure Diabetes (TRIM-D) questionnaire was completed by the study participants at weeks 0, 12 and 26 (or end of treatment) to assess patient-reported outcomes related to treatment burden, daily life, diabetes management, compliance and psychological health. The Global Treatment Effectiveness Evaluation (GTEE) scale was completed by the study participants and their physicians at weeks 12 and 26 (or end of treatment) to assess the proportion of participants with complete control, marked improvement, discernible but limited improvement, no appreciable change or worsening of their diabetes.

TABLE 1 Recommended dose adjustment algorithms for (A) iGlarLixi and (B) BIAsp 30

(A) iGlarLixi Median of fasting SMPG values from the last 3 measurements	iGlarLixi[a] dose adjustments (U/day)
<60 mg/dL (<3.3 mmol/L) or occurrence of 2 (or more) symptomatic hypoglycaemic episodes or 1 severe hypoglycaemic episode (requiring assistance) documented in the preceding week	−2 to −4 or at the discretion of the investigator or medically qualified designee
≥60 mg/dL and <80 mg/dL (≥3.3 mmol/L and <4.4 mmol/L)	−2
Glycaemic target: 80 mg/dL and 110 mg/dL (4.4 mmol/L and 6.1 mmol/L), inclusive	No change
>110 mg/dL and ≤140 mg/dL (>6.1 mmol/L and ≤7.8 mmol/L)	+2
>140 mg/dL (>7.8 mmol/L)	+4
B. BIAsp 30 **The lowest premeal SMPG values of the last 3 days[b]**	**Premix insulin dose adjustment (U)**
<80 mg/dL (<4.4 mmol/L)	−2
Glycaemic target: 80–110 mg/dL (4.4–6.1 mmol/L)	No change
111–140 mg/dL (6.2–7.8 mmol/L)	+2
141–180 mg/dL (7.9–10.0 mmol/L)	+4
>180 mg/dL (>10 mmol/L)	+6

[a]The U/day refers solely to the iGlar component of iGlarLixi.
[b]BIAsp 30 titration utilized predinner SMPG values for breakfast dose adjustment and prebreakfast SMPG values for dinner dose adjustment.
[a]Dose adjustments were made weekly. iGlarLixi dose adjustments were based on once-daily fasting SMPG measurements, BIAsp 30 dose adjustments were twice daily, utilizing predinner SMPG values for breakfast dose adjustment and prebreakfast SMPG values for dinner dose adjustment. BIAsp 30, biphasic insulin aspart 30 (30% insulin aspart and 70% insulin aspart protamine) iGlarLixi, once-daily titratable fixed-ratio combination of basal insulin glargine 100 units/mL and the glucagon-like peptide-1 receptor agonist lixisenatide; SMPG, self-monitored plasma glucose.

2.6 | Statistical analysis

2.6.1 | Sample size

The sample size was based on the two primary efficacy variables of HbA1c and weight changes from baseline to week 26, assuming a standard deviation (SD) of 1.1% for HbA1c changes from baseline, a non-inferiority margin of 0.3% and zero true difference in HbA1c reduction between iGlarLixi and BIAsp 30, an SD of 3.46 kg and detectable difference of 1 kg or more between iGlarLixi and BIAsp 30 for weight change from baseline, and a dropout rate of 10%. A total sample size of 864 randomized participants (432 randomized or 388 evaluable participants per treatment arm) would have >95% power to show the non-inferiority of iGlarLixi versus BIAsp 30 in terms of HbA1c reduction at week 26, or the superiority of iGlarLixi over BIAsp 30 in weight reduction at week 26. A two-sided significance level of 0.025 was assumed for each of the above tests.

2.6.2 | Analysis of primary endpoints

Analyses of the primary efficacy endpoints will be performed using the intent-to-treat (ITT) population (all randomized participants), using values obtained during the 26-week randomized treatment period, including those obtained after study treatment discontinuation or rescue medication use. The two primary endpoints will be analysed using an Analysis of Covariance (ANCOVA) model that will include fixed categorical effects of randomization strata (screening HbA1c value [<8.0 % versus ≥8.0 %] for weight primary endpoint only, basal insulin dose at screening [<30 U, ≥30 U] and SGLT2i use at screening [Yes, No]), treatment group and country, as well as fixed continuous covariates of baseline values for each of the primary endpoints, HbA1c and weight. Missing data for each primary endpoint will be handled through a multiple imputation (MI) strategy, the first step of which will be based on two models: missing data from participants discontinuing the study treatment will be imputed using data from participants also discontinuing treatment but having their endpoint assessed; missing data from participants completing the 26-week treatment period will be imputed using a model estimated from data observed in other participants completing the treatment. Least squares (LS) mean and LS mean differences between groups obtained from imputed datasets in the full ITT population will be combined using Rubin's formula.

2.6.3 | Analyses of secondary endpoints

Analyses of the secondary efficacy endpoints will be performed using the ITT population. Continuous secondary endpoints, such as change from baseline in bodyweight and FPG, and changes in total daily insulin dose, will be analysed using the same approach as the primary endpoint to compare iGlarLixi with BIAsp 30. The model will include the corresponding baseline value for that endpoint instead of baseline HbA1c. All categorical efficacy endpoints for the key secondary endpoints defined for the 26-week randomized treatment period will be analysed using a logistic regression model adjusting for treatment group randomization strata and appropriate baseline covariates.

To control the overall type I error at a 0.05 level (2 sided), a multiple testing procedure with alpha partition and re-allocation will be applied (Figure S1). First, both primary hypotheses will be tested at 0.025 (2 sided) each, i.e. the alpha level will be split into two. If non-inferiority in HbA1c reduction is significant at the 0.025 level, then the alpha will be re-allocated to superiority in weight change that will be tested at the full alpha (0.05); if superiority in weight change is significant at the 0.05 level, then the full alpha (0.05) will be used to test all the key secondary efficacy endpoints in a hierarchical manner

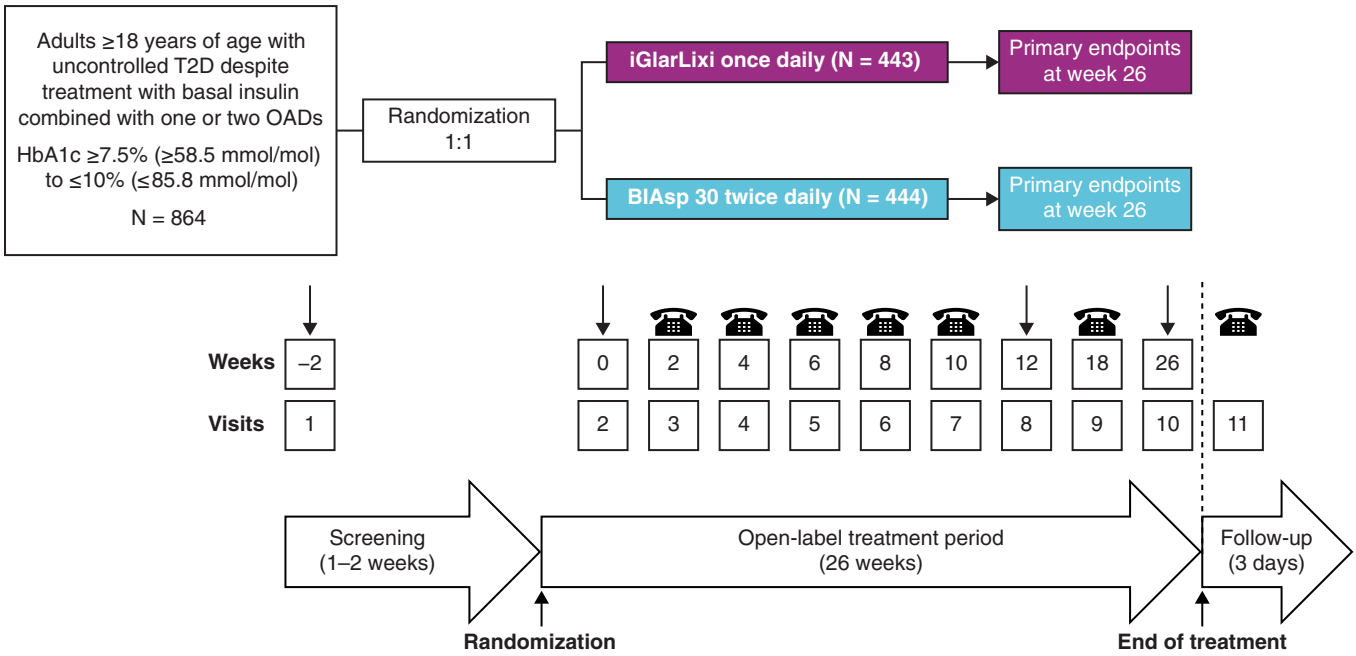

FIGURE 2 Study design and visit schedule. ☎, telephone visit; ↓ on-site visit; BIAsp 30, biphasic insulin aspart 30 (30% insulin aspart and 70% insulin aspart protamine); iGlarLixi, once-daily titratable fixed-ratio combination of basal insulin glargine 100 units/mL and the glucagon-like peptide-1 receptor agonist lixisenatide; IRT, interactive response technology; OADs, oral antihyperglycaemic drugs; T2D, type 2 diabetes

(Table 2). If superiority in weight change is the only primary endpoint significant at the 0.025 level, then the two first key secondary efficacy endpoints (HbA1c target <7% without weight gain and HbA1c <7% without weight gain at week 26 and without hypoglycaemia during the treatment period) will be tested at the same 0.025 alpha following hierarchical order; if both are significant, then the non-inferiority in HbA1c reduction will be re-tested at the 0.05 level. The third key secondary endpoint, superiority of iGlarLixi versus BIAsp 30, will only be tested at the 0.05 level if non-inferiority is first demonstrated. For other exploratory secondary hypotheses, no multiplicity adjustment will be applied.

Safety analyses will be based on the safety population, defined as all randomized participants who receive at least one dose of open-label iGlarLixi or BIAsp 30.

Several sensitivity analyses are planned, including two to correct for any impact of the COVID-19 pandemic (Table S1).

3 | RESULTS

Of the 887 participants who were randomized, 443 were randomized to iGlarLixi and 444 were randomized to BIAsp 30. Of these 887 participants that made up the ITT population, 403 in the iGlarLixi group and 404 in the BIAsp 30 group completed the study visits and assessments without any major protocol deviations related to the COVID-19 pandemic.

3.1 | Baseline characteristics

Overall, baseline characteristics did not differ between the two treatment groups (Table 3). Both treatment groups were predominantly White in ethnicity (iGlarLixi: 58.8%; BIAsp 30: 66.1%). The mean ± SD age of the overall randomized population was 59.8 ± 10.2 years, with 48.9% of that population aged ≥50 to <65 years. Almost two-thirds of the population (65.6%) had a duration of T2D ≥10 years, and the mean ± SD HbA1c at baseline was 8.6% ± 0.7%. The most common prior basal insulin used at baseline was insulin glargine 100 U/mL (44.4%), followed by neutral protamine Hagedorn (NPH) insulin (22.7%), insulin glargine 300 U/mL (21.9%), insulin detemir (6.8%) and insulin degludec (4.3%). Diabetic neuropathy was present in more than a quarter of participants (iGlarLixi: 26.9%; BIAsp 30: 28.6%), whereas diabetic retinopathy was present in 15.1% (iGlarLixi: 15.1%; BIAsp 30: 15.1%) and diabetic nephropathy was present in 9.7% (iGlarLixi: 10.2%; BIAsp 30: 9.2%).

4 | DISCUSSION

People with uncontrolled T2D following initiation of basal insulin treatment need further therapy intensification.[1] Current guidelines recommend intensifying by either adding a second injectable (GLP-1 RA or prandial insulin) or by switching to premix insulin or an FRC of basal insulin and GLP-1 RA.[1] By directly comparing the efficacy and

TABLE 2 Study endpoints

Primary endpoint	Secondary endpoints			
	Key secondary efficacy endpoints[a]	Other efficacy endpoints	Safety endpoints	Patient- and clinician-reported outcomes
• Non-inferiority of iGlarLixi to BIAsp 30 insulin in terms of HbA1c reduction from baseline to week 26 • Superiority of iGlarLixi to BIAsp 30 on body weight change from baseline to week 26	1. The proportion of participants reaching HbA1c target <7% (<53.0 mmol/mol) without weight gain at week 26 2. The proportion of participants reaching HbA1c <7% (<53.0 mmol/mol) without weight gain at week 26 and without hypoglycaemia (plasma glucose <70 mg/dL [<3.9 mmol/L]) during the treatment period 3. The superiority of iGlarLixi versus BIAsp 30 insulin in terms of HbA1c reduction	• The proportion of participants reaching HbA1c target <7% (<53.0 mmol/mol) at week 26 • The proportion of participants reaching HbA1c <6.5% (<47.5 mmol/mol) at week 26 • The proportion of participants reaching HbA1c <7% at week 26 without clinically important hypoglycaemia (plasma glucose <54 mg/dL [<3.0 mmol/L) during the treatment period • The proportion of participants reaching HbA1c <7% without weight gain of >1 kg at week 26 • Change in total insulin dose from baseline to week 26 • Change in FPG from baseline to week 26	• Confirmed hypoglycaemia[b] • Adverse events, adverse events of special interest, serious adverse events	• Change in treatment-related impact scores (TRIM-D total and domain scores) from baseline to week 26 • Proportion of participants with complete control or a marked improvement in their diabetes, as perceived by participants and clinicians at week 26 assessed using the patient- and physician-rated GTEE scales, respectively

Abbreviations: FPG, fasting plasma glucose; GTEE, Global Treatment Effectiveness Evaluation; TRIM-D, Treatment-Related Impact Measure Diabetes.
[a]Key secondary endpoints were tested in the presented hierarchical order;
[b]Defined as symptomatic or asymptomatic hypoglycaemia documented at either Level 1 (<70 mg/dL [<3.9 mmol/L] to ≥54 mg/dL [≥3.0 mmol/L]) or Level 2 (<54 mg/dL [<3.0 mmol/L]) or severe hypoglycaemia (defined as severe cognitive impairment requiring external assistance for recovery).

safety of an FRC of basal insulin and GLP-1 RA versus a premix insulin analogue, this randomized controlled study adds to the knowledge base of intensification options for people with T2D requiring therapy advancement from basal insulin and OAD therapy, helping to inform treatment decisions.

There is a high unmet medical need for people with T2D who require therapy intensification. When considering premix insulin, evidence from a real-world study of the UK THIN database showed that almost 80% of individuals initiating premix insulin still had poor glycaemic control after 6 months.[19] A further limitation of premix insulin compared with basal insulin is the propensity for weight gain and more frequent hypoglycaemia.[20] These data highlight the need for therapies to improve glucose control but involving fewer daily injections, better body weight control, a manageable hypoglycaemia profile and fewer complexities.

Hypoglycaemia risk is an important consideration for most people with T2D and for healthcare professionals. Hypoglycaemia is associated with significant morbidity and mortality,[21,22] and fear of hypoglycaemia may often be a barrier to optimal titration of insulin.[23–25] iGlarLixi has been shown to provide improved glycaemic control, while also mitigating weight gain, and similar risk of hypoglycaemia versus iGlar alone.[15] By contrast, a meta-analysis of randomized controlled trials comparing basal insulin with twice-daily or three-times-daily premix insulin showed that, while premix insulin provided improved glycaemic control, it was also associated with increased weight gain and hypoglycaemia risk.[20] Thus, switching to iGlarLixi may help alleviate fear of hypoglycaemia and mitigate body weight-gain concerns in people intensifying their basal insulin; this may help give these individuals the confidence to optimally titrate their therapy and help them reach their glycaemic targets.

T2D is a chronic disease, and for individuals receiving injectable therapy, multiple daily injections requiring several SMPG measurements and multidose adaptations per day can increase the burden of disease.[26] This has an impact on adherence and persistence with therapy.[26] For people with T2D who are not reaching glycaemic targets on basal insulin, switching to an FRC of basal insulin and GLP-1 RA may enable them to maintain a once-daily injection while intensifying their therapy, in contrast to addition of separate GLP-1 RA, prandial insulin or switching to twice-daily premix insulin. In such people,

TABLE 3 Baseline characteristics of the study population

Demographic/clinical characteristic	iGlarLixi (n = 443)	BIAsp 30 (n = 444)	All participants (N = 887)
Age (years), mean ± SD	59.8 ± 10.3	59.8 ± 10.0	59.8 ± 10.2
Age group (years), n (%)			
<50	73 (16.5)	66 (14.9)	139 (15.7)
≥50 to <65	206 (46.5)	228 (51.4)	434 (48.9)
≥65 to <75	141 (31.8)	120 (27.0)	261 (29.4)
≥75	23 (5.2)	30 (6.8)	53 (6.0)
Sex, n (%)			
Male	224 (50.6)	218 (49.1)	442 (49.8)
Female	219 (49.4)	226 (50.9)	445 (50.2)
Race, n (%)			
White	255 (58.8)	287 (66.1)	542 (62.4)
Asian	168 (38.7)	134 (30.9)	302 (34.8)
American Indian or Alaska native	8 (1.8)	7 (1.6)	15 (1.7)
Black or African American	1 (0.2)	1 (0.2)	2 (0.2)
Unknown	2 (0.5)	4 (0.9)	6 (0.7)
Multiple	0	1 (0.2)	1 (0.1)
World region, n (%)			
European region[a]	189 (42.7)	193 (43.5)	382 (43.1)
Non-European region[b]	254 (57.3)	251 (56.5)	505 (56.9)
Asia region[c]	67 (15.1)	52 (11.7)	119 (13.4)
MENA region[d]	16 (3.6)	28 (6.3)	44 (5.0)
LATAM region[e]	71 (16.0)	89 (20.0)	160 (18.0)
India region	100 (22.6)	82 (18.5)	182 (20.5)
BMI (kg/m^2), mean ± SD	29.7 ± 4.7	30.0 ± 5.1	29.9 ± 4.9
BMI group (kg/m^2), n (%)			
<25	70 (15.8)	78 (17.6)	148 (16.7)
≥25 to <30	180 (40.7)	165 (37.2)	345 (38.9)
≥30 to <35	125 (28.3)	112 (25.2)	237 (26.7)
≥35	67 (15.2)	89 (20.0)	156 (17.6)
Duration of T2D (years), mean ± SD	13.0 ± 7.1	13.0 ± 7.4	13.0 ± 7.2
Duration of T2D group, n (%)			
<10 years	153 (34.5)	152 (34.2)	305 (34.4)
≥10 years	290 (65.5)	292 (65.8)	582 (65.6)
Age of onset of T2D (years), mean ± SD	47.2 ± 9.1	47.3 ± 9.9	47.2 ± 9.5
HbA1c (%), mean ± SD	8.6 ± 0.7	8.6 ± 0.7	8.6 ± 0.7
HbA1c (mmol/mol), mean ± SD	71 ± 7	70 ± 7	70 ± 7
Randomization strata of screening HbA1c, n (%)			
<8%	92 (20.8)	93 (20.9)	185 (20.9)
≥8%	351 (79.2)	351 (79.1)	702 (79.1)
Prior basal insulin at baseline, n (%)			
Insulin glargine 100 U/mL	198 (40.1)	240 (48.7)	438 (44.4)
NPH	128 (25.9)	96 (19.5)	224 (22.7)
Insulin glargine 300 U/mL	112 (22.7)	104 (21.1)	216 (21.9)
Insulin detemir	36 (7.3)	31 (6.3)	67 (6.8)
Insulin degludec	20 (4.0)	22 (4.5)	42 (4.3)
Average basal insulin daily dose (U), mean ± SD[a]	33.8 ± 9.6	33.8 ± 9.9	33.8 ± 9.8

TABLE 3 (Continued)

Demographic/clinical characteristic	iGlarLixi (n = 443)	BIAsp 30 (n = 444)	All participants (N = 887)
Average basal insulin daily dose (U/kg), mean ± SD[a,e,f]	0.43 ± 0.15	0.43 ± 0.14	0.43 ± 0.14
Randomization strata of screening basal insulin dose, n (%)			
<30 U	161 (36.3)	160 (36.0)	321 (36.2)
≥30 U	282 (63.7)	284 (64.0)	566 (63.8)
Average basal insulin daily dose range at baseline (U)	20–50	18–50	18–50
Average basal insulin daily dose range at baseline (U/kg)	0.142–0.933	0.154–0.930	0.142–0.933
Combination of OAD at baseline, n (%)			
Metformin alone	338 (76.3)	340 (76.6)	678 (76.4)
Metformin + SGLT2i	104 (23.5)	100 (22.5)	204 (23.0)
Metformin + other[g]	1 (0.2)	2 (0.5)	3 (0.3)
SGLT2i alone	0	2 (0.5)	2 (0.2)
Daily metformin dose at baseline (mg), mean ± SD	1761 ± 542	1722 ± 549	1741 ± 546
Randomization strata SGLT2i use at screening, n (%)			
Yes	103 (23.3)	104 (23.4)	207 (23.3)
No	340 (76.7)	340 (76.6)	680 (76.7)
Co-morbidities, n (%)			
Diabetic neuropathy	119 (26.9)	127 (28.6)	246 (27.7)
Diabetic retinopathy[h]	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)
Ischaemic stroke	2 (0.5)	0	2 (0.2)
Fasting plasma glucose levels (mg/dL), mean ± SD	151 ± 44	149 ± 41	150 ± 42
Blood pressure (mmHg), mean ± SD			
Systolic	132 ± 14	132 ± 14	132 ± 14
Diastolic	78 ± 9	78 ± 8	78 ± 9
eGFR (mL/min/1.73m^2)			
N	432	431	863
Mean ± SD	85 ± 23	87 ± 24	86 ± 24

Note: BIAsp 30, biphasic insulin aspart 30 (30% insulin aspart and 70% insulin aspart protamine).
Abbreviations: BiAsp 70/30, intermediate-acting protamine-crystallized insulin aspart/rapid-acting soluble insulin aspart in the ratio 70/30; BMI, body mass index; DPP4, dipeptidyl peptidase-4; eGFR, estimated glomerular filtration rate; GLP-1 RA, glucagon-like peptide-1 receptor agonist; iGlarLixi, once-daily titratable fixed-ratio combination of basal insulin glargine 100 units/mL and the GLP-1 RA lixisenatide; NPH, neutral protamine Hagedorn; OAD, oral antihyperglycaemic drug; SD, standard deviation; SGLT2i, sodium-glucose co-transporter-2 inhibitor; T2D, type 2 diabetes.
[a]European region: Austria, Bulgaria, Czech Republic, Greece, Macedonia, Romania, Serbia, Spain, Sweden;
[b]Non-European region: Argentina, India, the Republic of Korea, Kuwait, Mexico, Saudi Arabia, Taiwan, Turkey;
[c]Asia region: the Republic of Korea and Taiwan;
[d]MENA region: Turkey, Kuwait, and Kingdom of Saudi Arabia;
[e]LATAM region: Argentina and Mexico.
[f]Average daily basal insulin dose at baseline within the 3 days immediately before randomization;
[g]Other treatments were homeopathic treatments and therefore not considered to be protocol deviations;
[h]Includes proliferative diabetic retinopathy.

iGlarLixi may provide a more convenient therapy option compared with premix insulin. The ease of use and therapeutic burden of iGlarLixi versus BIAsp 30 will be evaluated in the present study using the TRIM-D and GTEE questionnaires.

The strengths of the study include that it is the first to directly compare an FRC with premix insulin, as well as being a prospective, head-to-head, randomized study, which is the gold standard for comparing two therapies. Furthermore, by measuring patient-reported outcomes, it has the advantage of assessing participant perception of therapeutic burden. The study is clinically relevant in context and design, as it included a typical uncontrolled T2D population who were treated with a stable dose of basal insulin plus one or two OADs

recruited from countries and regions where premix insulin is most often used. The study protocol and degree of follow-up were conducted on a more pragmatic basis than is typically seen in other randomized clinical trials.

Potential limitations include that only the use of metformin with or without an SGLT2i was permitted as concurrent medication, which may limit the generalizability of the results. The open-label design may also be considered a limitation that could have introduced bias, but the injectables could not be masked. On the other hand, the lack of blinded treatment may mean that this study is closer to pragmatic conditions than most randomized controlled trials. Another limitation may be the data being collected during the COVID-19 pandemic; however, two sensitivity analyses are planned to correct for the potential impact of the pandemic on the data.

Data from prospective randomized studies, such as the present study, are important for clinical practitioners as they evaluate new therapies with improved benefit–risk profiles, enabling individualization of therapy. These new therapies should provide people with options involving reduced treatment complexity and therapeutic burden. Results from this head-to-head randomized clinical study comparing iGlarLixi versus a premix insulin analogue provide a robust level of evidence to support clinical decisions when basal therapy needs to be advanced in people with uncontrolled T2D and may inform future treatment guidelines.

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CONFLICT OF INTEREST

RM has acted as an advisor and speaker for Sanofi and Novo Nordisk. SAS has acted as an adviser and speaker for AstraZeneca, Boehringer Ingelheim, Lilly, MSD, Novo Nordisk, Sanofi and Novartis. RE has acted as an advisor and speaker for AstraZeneca, Boehringer Ingelheim, Lilly, MSD, Novo Nordisk and Sanofi. 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 Novo Nordisk, MSD and Sanofi. LS-R has acted as an advisor and speaker for Novo Nordisk, Sanofi and Boehringer Ingelheim. 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. NL has acted as a speaker for Sanofi, AstraZeneca, Boehringer Ingelheim, Eli Lilly, Novo Nordisk and Merck. AA, ND, MC and MB are employees of Sanofi. AS was an employee of Sanofi at the time the study was active and is currently an employee of CSL Behring. 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.

AUTHOR CONTRIBUTIONS

All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article and had full access to all the data in this study and take complete responsibility for the integrity of the data and accuracy of the data analysis. 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.

PEER REVIEW

The peer review history for this article is available at https://publons.com/publon/10.1111/dom.14354.

DATA AVAILABILITY STATEMENT

Proposals relating to the data access should be directed to the corresponding author. To gain access, data requestors will need to sign a data access agreement.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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