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Efficacy and safety of switching to iGlarLixi from premixed insulins in people with type 2 diabetes: The Soli-SWITCH study

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Abstract

Aims: To assess the efficacy and safety of switching from premixed insulin to a once-daily, fixed-ratio combination of insulin glargine 100 U/mL + lixisenatide (iGlarLixi) in people with type 2 diabetes (T2D).

Methods: In this phase 4, 24-week, single-arm study, participants switched from once-daily or twice-daily premixed insulin to iGlarLixi (EudraCT number 2021–003711-25). Key inclusion criteria: ≥18 years; premixed insulin therapy for ≥3 months and < 10 years; ± 1–2 oral antidiabetic drugs (OADs); HbA1c ≥7.5% to ≤10.0%. The primary endpoint was the change in HbA1c from baseline to Week 24. Secondary endpoints included: participants achieving HbA1c <7% and change in body weight at Week 24, and safety.

Results: Overall, 162 participants switched to iGlarLixi (89.5% from twice-daily premixed insulin); mean duration of diabetes was 15.7 (standard deviation [SD]: 8.3) years. Mean baseline HbA1c (8.5%) reduced by least squares (LS) mean of 1.2% (95% confidence interval [CI]: −1.4, −1.1) at Week 24, and 37.6% of participants had achieved an HbA1c target of <7% (95% CI: 30.0, 45.7). LS mean body weight change from baseline to Week 24 was −1.0 kg (95% CI: −1.6, −0.5). Fasting and post-prandial plasma glucose decreased from baseline to Week 24 by 45.6 mg/dL (SD ± 52.4) and 67.6 mg/dL (SD ± 65.1), respectively. Confirmed symptomatic hypoglycaemia occurred in 38.3% of participants (ADA level 1: 35.8%; level 2: 15.4%; level 3: 0.0%).

Conclusions: iGlarLixi initiation was associated with improved glycaemic control, without body weight gain or increased hypoglycaemia over 24 weeks.

KEYWORDS
clinical trial, iGlarLixi, insulin glargine, lixisenatide, phase IV study, type 2 diabetes

1 | INTRODUCTION

Due to the progressive loss of β-cell function in type 2 diabetes (T2D), advancement to injectable therapy may be required to control hyperglycaemia.[1] The American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) state that the fixed-ratio combination therapy (FRC) of glucagon-like peptide-1 receptor agonists (GLP-1 RAs) and basal insulin has potent glucose-

lowering action and recommends FRCs when treatment targets are not met with either basal insulin or GLP-1 RA monotherapy.[2,3]

iGlarLixi is a once-daily (OD) FRC of insulin glargine 100 units/mL plus lixisenatide, a GLP-1 RA, which targets both fasting and post-prandial glucose (PPG) in a single injection, due to their complementary mechanisms of action.[4–6] iGlarLixi has demonstrated its clinical benefits in terms of meaningful HbA1c reductions in pivotal randomized controlled trials (LixiLan-O, LixiLan-L and LixiLan-G), over comparator groups (insulin glargine, lixisenatide and other GLP-1 RAs, respectively).[7–9] Compared with insulin glargine, iGlarLixi demonstrated better glycaemic control without body weight gain and without increasing the risk of hypoglycaemia.[7]

In addition, iGlarLixi has been compared with the premixed insulins BIAsp 30 and insulin degludec/insulin aspart (IDegAsp) in the SoliMix and Soli-D trials, respectively. The SoliMix trial demonstrated that, in participants advancing treatment from basal insulin therapy, iGlarLixi was associated with significantly better glycaemic control versus the twice-daily (BID) premixed insulin analogue BIAsp 30, with body weight benefit and fewer episodes of hypoglycaemia, including nocturnal hypoglycaemia.[10] Furthermore, iGlarLixi was well tolerated, was associated with improvements in patient-reported outcomes and represents a less complex option for people with T2D who need to advance insulin treatment versus BIAsp 30.[10,11]

In the Soli-D trial, the efficacy and safety of iGlarLixi and IDegAsp were compared in Chinese people with T2D sub-optimally controlled with oral antidiabetic drugs (OADs).[12] Participants treated with iGlarLixi experienced statistically significant superiority in HbA1c reduction, alongside body weight benefit and lower hypoglycaemia event rates versus IDegAsp.[12]

Premixed insulins have also been found to be more effective than basal insulin alone in reducing post-prandial glucose (PPG) levels.[13–16] Premixed insulins are also associated with an increased risk of hypoglycaemia and body weight gain compared with basal insulins.[13,15,17,18] They may also require BID injections, which may be more burdensome for people with T2D.

While there have been randomized controlled trials comparing the efficacy and safety of iGlarLixi to premixed insulin in people with T2D previously treated with either basal insulin (SoliMix) or OADs (Soli-D), there are currently no clinical studies that have investigated the clinical outcomes of people who have de-escalated from premixed insulin to iGlarLixi. The Soli-SWITCH study was designed to address this gap in the literature, as it was the first study to assess the efficacy and safety of switching to iGlarLixi in people with T2D currently receiving OD or BID premixed insulin. For people previously receiving BID premixed insulin, reducing the number of injections might reduce the burden of treatment in a chronic disease such as T2D. Thus, an additional, pre-specified analysis was conducted to assess the efficacy and safety of switching to iGlarLixi in the subgroup of participants who were receiving BID premixed insulin at baseline. An additional objective of this study was to evaluate an algorithm for switching to iGlarLixi in people with T2D currently treated with premixed insulins.

2 | METHODS

2.1 | Study design

Soli-SWITCH was a 24-week, single-arm, multinational, interventional, prospective, phase 4 study in people with T2D switching to iGlarLixi from OD or BID premixed insulin (EudraCT number 2021–003711-25; Supplementary Figure S1). The study consisted of a screening period of up to 2 weeks, a 24-week open-label treatment period, including a titration period, and a 7-day safety follow-up period (Supplementary Figure S1).

2.2 | Study population

Eligible participants were adults (≥18 years) diagnosed with T2D for ≥6 months, who had received premixed insulin therapy for ≥3 months and <10 years, ± one or two OADs (metformin alone or in combination with a sodium-glucose co-transporter-2 [SGLT-2] inhibitor, a dipeptidyl peptidase 4 [DPP-4] inhibitor or sulphonylurea [SU]). All participants had to provide written informed consent and agree to comply with protocol requirements. Additional inclusion criteria were a body mass index of ≥20 and <40 kg/m^2, HbA1c of ≥7.5% to ≤10.0% and fasting plasma glucose (FPG) of ≥130 mg/dL. Exclusion criteria are provided in the Supplementary Material.

2.3 | Interventions

At baseline (Week 0), all eligible participants switched from their previous premixed insulin to OD iGlarLixi, which was self-administered by subcutaneous injection via SoloStar prefilled (disposable) pen, OD in the morning and approximately 60 min before breakfast. Participants could continue treatment with metformin and/or an SGLT-2 inhibitor throughout the study period, but daily DPP-4 inhibitors and SU were discontinued before switching to iGlarLixi (with last doses administered on the morning of Day −1).

The starting dose of iGlarLixi was based on a 20% reduction of the previous full premixed insulin dose (if previously receiving BID, the two premixed insulin doses would be added together for the calculation), while also adhering to the maximum allowed starting dose of lixisenatide (10 μg). This meant that for the SoloStar 10–40 (peach colour) pen, the maximum starting dose was 20 dose-steps and for the SoloStar 30–60 (olive colour) pen, the maximum starting dose was 30 dose-steps. To simplify the calculation, the following three rules were used: (1) participants with a previous total premixed insulin dose of <25 units/day initiated iGlarLixi at a 20% reduction of the full premixed dose using a SoloStar 10–40 (peach colour) pen, (2) participants with a previous total premixed insulin dose of ≥25 to <38 units/day initiated iGlarLixi at 20 units/day using a SoloStar 10–40 (peach colour) pen and (3) participants with a previous total premixed insulin dose of ≥38 units/day initiated iGlarLixi at 30 units/day using a SoloStar 30–60 (olive colour) pen. More information on which previous

premixed insulin dose corresponds to the iGlarLixi starting dose can be found in Supplementary Table S1.

During the 12-week titration period, the dose of iGlarLixi was adjusted twice weekly using a recommended titration algorithm at the investigator's discretion, to a glycaemic target of 80–100 mg/dL (Supplementary Table S2). Following this period, the dose was evaluated at least once weekly and adjusted as necessary to maintain the glycaemic target; twice-weekly titration was continued if deemed appropriate by the investigator.

2.4 | Endpoints and assessments

2.4.1 | Primary and secondary efficacy endpoints

The primary endpoint was change in HbA1c from baseline to Week 24. Secondary efficacy endpoints included the proportion of participants at Week 24 achieving: HbA1c <7%; HbA1c <7% without clinically relevant hypoglycaemia (ADA Level 2 or 3)[8]; and HbA1c <7% without clinically relevant hypoglycaemia (ADA level 2 or 3) and without body weight gain.

Additional secondary endpoints were change from baseline to Week 24 in FPG, PPG at 2 h after breakfast (derived from 7-point self-measured plasma glucose [SMPG] profile), average daily blood glucose (derived from 7-point SMPG profile), total daily insulin dose and body weight.

2.4.2 | Safety endpoints

Safety endpoints included the incidence (proportion of participants with ≥1 hypoglycaemia event) and event rate of hypoglycaemia during 24 weeks of treatment. Hypoglycaemia events were reported by type (ADA Levels 1, 2 and 3; defined in Supplementary Material in Data S1), in accordance with the consensus report of a steering committee on levels of hypoglycaemia.[19] These levels are consistent with the ADA Standards of Care 2021 recommendations.[20] Documented symptomatic hypoglycaemia was defined as symptoms of hypoglycaemia accompanied by an SMPG value of ≤70 mg/dL. The numbers of participants with adverse events (AEs), serious AEs (SAEs) and AEs of special interest (AESIs) were also assessed.

2.4.3 | Exploratory endpoints

Key exploratory endpoints included the proportion of participants at Week 24 achieving: HbA1c <7% with body weight benefit (any difference from baseline <0 kg); HbA1c <7% without body weight gain. Further exploratory endpoints included the proportion of participants who switched to iGlarLixi without deterioration of glycaemic control (i.e., without any increase in HbA1c >0% from baseline to Week 24). Derived time-in-range (dTIR) was a *post hoc* analysis calculated using 7-point SMPG data, with a target range of 70–180 mg/dL. Efficacy and safety were also assessed in a (pre-specified) analysis of the subgroup of participants switching to iGlarLixi from BID premixed insulin.

2.4.4 | Assessments

Details of the timings of measurements (e.g., HbA1c and FPG) are available in the Supplementary Material in Data S1.

2.5 | Statistical methods

Sample size calculations, including assumptions used, are in the Supplementary Materials in Data S1.

Efficacy endpoints were assessed using the evaluable analysis set, and safety was assessed using the safety analysis set (definitions are detailed in the Supplementary Material in Data S1).

A mixed-effect linear model with repeated measures (MMRM) was used to estimate the primary endpoint (change in HbA1c from baseline to Week 24), presented as least squares (LS) mean estimates of HbA1c change from baseline, associated standard errors (SEs) and 95% confidence intervals (CIs). Secondary efficacy endpoints were assessed by MMRM in the same way as for the primary endpoint, except for change in total daily insulin dose from baseline to Week 24 and safety endpoints, which were both analysed descriptively.

For the analysis of change in HbA1c from baseline to Week 24 in the BID subgroup, an MMRM was used. Data were analysed using nQuery 7.0.

3 | RESULTS

3.1 | Baseline characteristics

Of the 255 participants who signed the informed consent form and were screened, 162 were enrolled and received iGlarLixi, and 153 (94.4%) participants completed the study (Supplementary Table S3). The mean (standard deviation [SD]) age was 65.1 (8.7) years, 45.1% of the population were female and the mean (SD) BMI of participants was 29.4 (5.2) kg/m^2 (Table 1). Mean (SD) diabetes duration was 15.7 (8.3) years, and 42.0% of participants had diabetes complications (Table 1).

Most participants received OADs prior to switching to iGlarLixi; metformin was the most commonly used (56.2% of participants; Table 1). A total of 145 (89.5%) participants had BID dosing, and the mean (SD) time on premixed insulin treatments was 2.1 (2.3) years (Table 1). The most frequently used premixed insulins prior to study start were insulin aspart and insulin aspart protamine (crystalline; 37.0%) and human insulin and isophane insulin (34.6%) (Table 1).

TABLE 1 Demographic and baseline characteristics in the overall population.

	iGlarLixi (*N* = 162)
Age in years	
Mean (SD)	65.1 (8.7)
<65, *n* (%)	65 (40.1)
≥65 to <75, *n* (%)	80 (49.4)
≥75, *n* (%)	17 (10.5)
Sex, *n* (%)	
Male	89 (54.9)
Female	73 (45.1)
Body weight, kg	
Mean (SD)	80.6 (17.9)
BMI, kg/m^2	
Mean (SD)	29.4 (5.2)
<25	39 (24.1)
≥25 to <30, *n* (%)	53 (32.7)
≥30 to <40, *n* (%)	69 (42.6)
≥40, *n* (%)	1 (0.6)
Country, *n* (%)	
Czech Republic	1 (0.6)
Korea	64 (39.5)
Poland	84 (51.9)
Turkey	13 (8.0)
Baseline HbA1c, %	
Mean (SD)	8.5 (0.7)
<8, *n* (%)	42 (25.9)
≥8 to <9, *n* (%)	71 (43.8)
≥9, *n* (%)	49 (30.2)
Duration of diabetes in years, mean (SD)	15.7 (8.3)
OADs at baseline, *n* (%)	
Metformin	91 (56.2)
Sodium-glucose co-transporter-2 inhibitor	37 (22.8)
Sulphonylurea	12 (7.4)
Dipeptidyl peptidase 4 inhibitor	9 (5.6)
Daily premixed insulin dosing, *n* (%)	
OD	17 (10.5)
BID	145 (89.5)
Time on premixed insulin treatment in years, mean (SD)	2.1 (2.3)
Prior premixed insulin regimen, *n* (%)	
Insulin Aspart; Insulin Aspart Protamine (crystalline)	60 (37.0)
Insulin Human; Insulin Human Injection, Isophane	56 (34.6)
Insulin Aspart; Insulin Aspart Protamine	23 (14.2)
Insulin Lispro; Insulin Lispro Protamine Suspension	20 (12.3)
Insulin Aspart; Insulin Degludec	4 (2.5)
Diabetes complication occurrence, *n* (%)	68 (42.0)

Abbreviations: BID, twice daily; BMI, body mass index; HbA1c, haemoglobin A1c; iGlarLixi, insulin glargine 100 U/mL + lixisenatide; n, number; OAD, oral antidiabetic drug; OD, once daily; SD, standard deviation.

3.2 | Efficacy

3.2.1 | Change in HbA1c

Overall, 157 participants were evaluable for the primary endpoint (HbA1c) at baseline and at least one time point post baseline. Mean baseline HbA1c (8.5%) was reduced to 7.3% (LS mean change ± SE: −1.2 ± 0.1%; 95% CI: −1.4, −1.1) at Week 24 (Figure 1A).

3.2.2 | Proportion of participants achieving HbA1c <7% at Week 24 with composite endpoints

At Week 24, 82.2% of participants switched to iGlarLixi without deterioration of glycaemic control, 37.6% of participants had achieved a HbA1c target of <7% (95% CI: 30.0, 45.7), 29.3% had achieved HbA1c <7% without clinically relevant hypoglycaemia (95% CI: 22.3, 37.1) and 22.3% achieved HbA1c <7% without clinically relevant hypoglycaemia and without body weight gain (95% CI: 16.0, 29.6; Figure 2).

3.2.3 | Change in other efficacy endpoints

Mean FPG was reduced from baseline by 45.6 mg/dL (LS mean change ± SE: −45.9 ± 3.0; 95% CI: −51.8, −40.0) at Week 24 (Figure 1B). Reductions were also observed for mean PPG from baseline by 67.6 mg/dL (LS mean change ± SE: −68.2 ± 3.2; 95% CI: −74.6, −61.9) at Week 24 (Figure 1B). Mean fasting SMPG was reduced from baseline by 51.0 mg/dL (LS mean change ± SE: −51.1 ± 2.0; 95% CI: −55.0, −47.2) at Week 24 (Figure 1B). The 7-point SMPG profile was higher at baseline versus Week 24 at each time point (Figure 1C). After 24 weeks of iGlarLixi treatment, there was a reduction in PPG after breakfast, lunch and dinner, compared with baseline (Figure 1C). Average daily blood glucose concentration decreased from baseline to Week 24 by 43.1 mg/dL (SD ± 41.9; 95% CI: −47.6, −37.2). The mean (SD) dTIR at baseline was 52.8% (29.3), which increased to 83.1% (22.8) at Week 24 (Figure 3). The LS mean ± SE change from baseline to Week 24 in dTIR was 30.4 ± 2.1; derived time below range (<70 mg/dL) was 0.0 ± 0.3, and derived time above range (>180 mg/dL) was −30.4 ± 2.1.

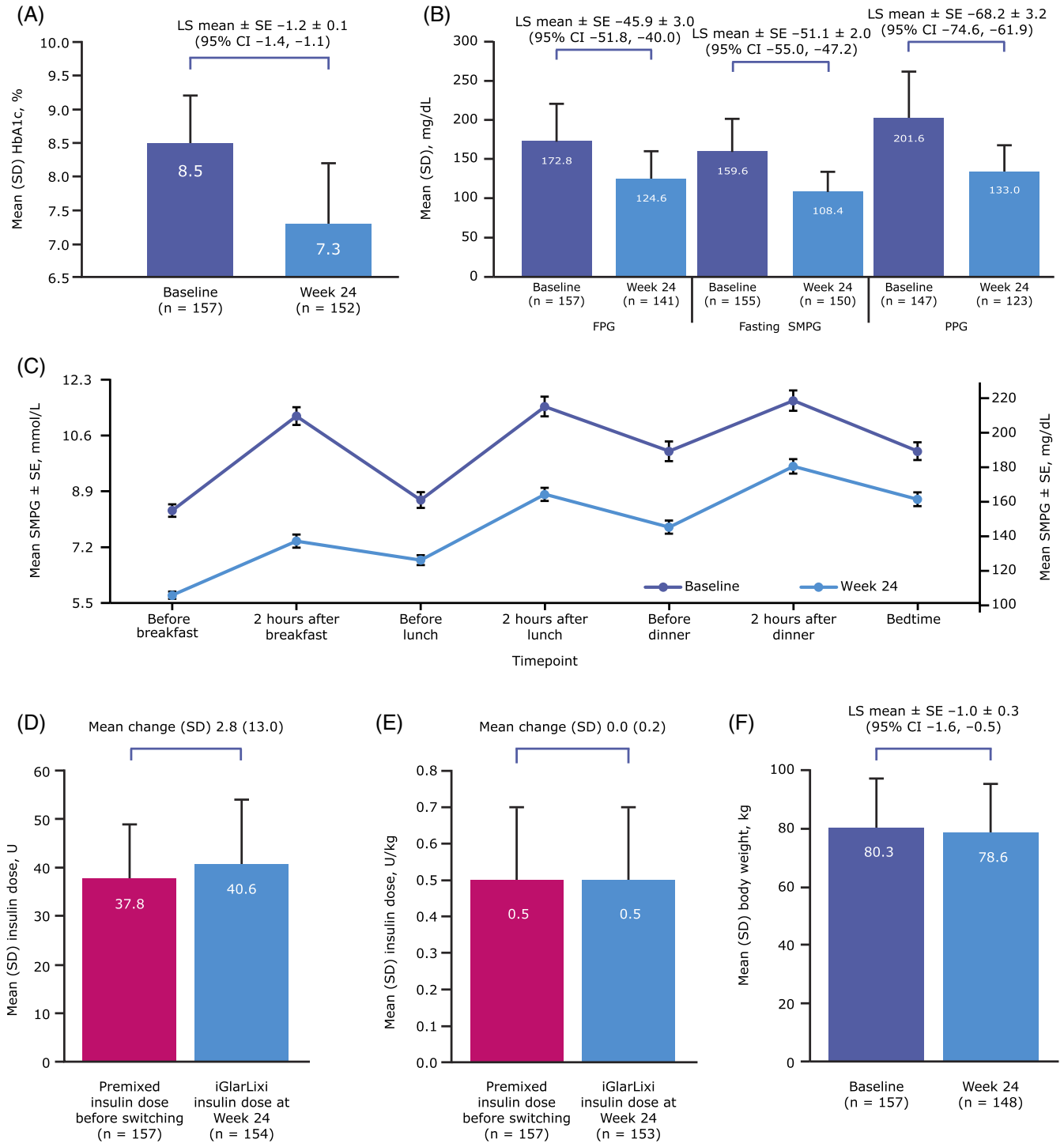

FIGURE 1 Change from baseline to Week 24 in the overall population for (A) HbA1c, (B) FPG, PPG and fasting SMPG and (C) Mean 7-point SMPG profile over a single 24-h period, (D) total daily insulin dose, (E) total daily insulin dose by body weight and (F) body weight. CI, confidence interval; HbA1c, glycated haemoglobin; FPG, fasting plasma glucose; n, number; LS, least squares; PPG, post-prandial glucose; SD, standard deviation; SE, standard error; SMPG, self-measured plasma glucose.

3.2.4 | Change in insulin dose

The mean (SD) previous premixed insulin dose was 37.8 (11.1) units (U) or 0.5 (0.2) U/kg; and the mean (SD) iGlarLixi dose was 40.6 (13.3) dose-steps or 0.5 (0.2) U/kg at Week 24. Mean (SD) change from baseline was 2.8 (13.0) U or 0.0 (0.2) U/kg at Week 24 (Figure 1D,E).

3.2.5 | Change in body weight

Mean (SD) body weight at baseline was 80.3 (17.0) kg in the evaluable analysis set, which decreased to 78.6 (16.9) kg at Week 24; the absolute change in body weight from baseline was mean ± SD of −1.0 ± 3.2 kg (LS mean change ± SE: −1.0 ± 0.3; 95% CI: −1.6, −0.5) at Week 24 (Figure 1F).

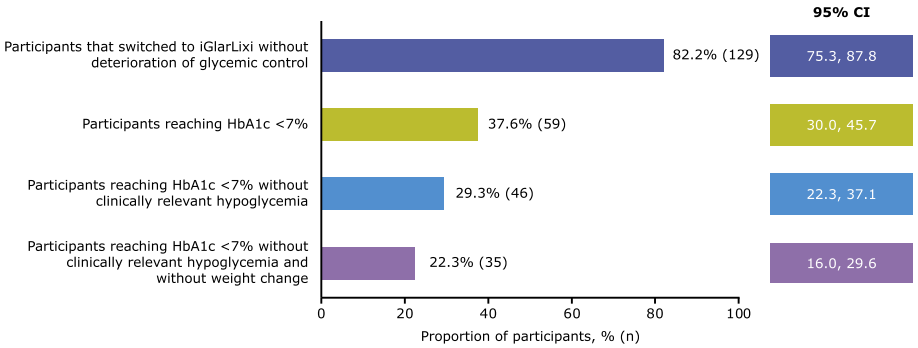

FIGURE 2 Participants in the overall population who switched to iGlarLixi without deterioration of glycaemic control, achieving HbA1c <7% and achieving HbA1c <7% with composite endpoints at Week 24. Clinically relevant hypoglycaemia is defined as any hypoglycaemia (ADA Level 2) or severe hypoglycaemia (ADA Level 3) event. CI, confidence interval; HbA1c, glycated haemoglobin; iGlarLixi, insulin glargine 100 U/mL + lixisenatide.

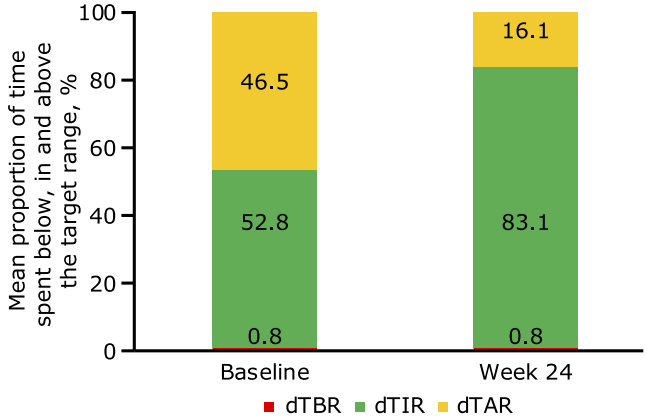

FIGURE 3 Derived time-below-range, derived time-in-range and derived time-above-range at baseline and Week 24 for the overall population. dTAR, derived time above range; dTBR, derived time below range; dTIR, derived time in range; SMPG, self-monitored plasma glucose; SD, standard deviation.

3.3 | Safety

3.3.1 | Hypoglycaemia

The incidence of confirmed symptomatic hypoglycaemia was 38.3% (ADA level 1: 35.8%; ADA level 2: 15.4%; ADA level 3: 0%; Table 2). The event rate was 3.7 events per person-year for all participants (2.9 for ADA Level 1; 0.8 for ADA Level 2). No severe hypoglycaemia (ADA Level 3) was observed during the study period.

3.3.2 | Adverse events

Overall, treatment with iGlarLixi was well tolerated (Supplementary Table S4); no new safety signals were observed. During the study period, 60 (37.0%) participants reported ≥1 treatment-emergent adverse event (TEAE) and 58 of those experienced mild to moderate TEAEs (Supplementary Table S4). The most common TEAEs reported were infections and infestations ($n = 21$; 13.0%) and gastrointestinal disorders ($n = 15$; 9.3%).

A total of four participants (2.5%) had a treatment-emergent SAE (Supplementary Table S4). One participant had a treatment-emergent AESI (an increase in alanine transaminase). No deaths occurred during the study.

3.4 | BID premixed insulin dosing: Efficacy and safety

In total, 145 (89.5%) participants received BID premixed insulin at baseline.

3.4.1 | Change in HbA1c at Week 24 in participants receiving BID premixed insulin at baseline

Similar to the overall population, in evaluable participants with BID premixed insulin dosing at baseline, mean HbA1c decreased from baseline (8.5%) to Week 24 (7.3%) by 1.2% (LS mean change ± SE: −1.2 ± 0.1%; 95% CI: −1.3, −1.0; $n = 128$, Supplementary Figure S2A).

3.4.2 | Proportion of participants receiving BID premixed insulin at baseline achieving HbA1c <7% and composite endpoints at Week 24

The proportions of participants in the BID subgroup achieving HbA1c <7% at Week 24 and other composite endpoints were aligned with the overall study population (Supplementary Figure S3).

3.4.3 | Change in other efficacy endpoints at Week 24 in participants receiving BID premixed insulin at baseline

Within the BID subgroup, changes in FPG, PPG and fasting SMPG were similar to those observed in the overall population (Supplementary Figure S2B). The 7-point SMPG profile was higher at

TABLE 2 Incidence and rates of confirmed symptomatic hypoglycaemic events during the 24-week treatment period.

	iGlarLixi ($N = 162$)		
	n (%)	Events	Event rate (events per person-year)
Confirmed documented symptomatic hypoglycaemia	62 (38.3)	269	3.7
ADA level 1	58 (35.8)	210	2.9
ADA level 2	25 (15.4)	59	0.8
ADA level 3	0	0	0

Note: ADA Level 1: Blood glucose concentration <70 mg/dL (3.9 mmol/L) and ≥54 mg/dL (3.0 mmol/L); ADA Level 2: Blood glucose concentration <54 mg/dL (3.0 mmol/L); ADA Level 3: Severe event characterized by altered mental and/or physical functioning. Event rate is defined as the event rate of hypoglycaemia per person year.
Abbreviations: ADA, American Diabetes Association; iGlarLixi, insulin glargine 100 U/mL + lixisenatide.

baseline versus Week 24 at each time point (Supplementary Figure S2C). The mean ± SD dTIR at baseline was 54.2% (29.4), which increased to 82.6% (23.5) at Week 24 (Supplementary Figure S4).

3.4.4 | Change in insulin dose at Week 24 in participants receiving BID premixed insulin at baseline

The mean previous premixed insulin dose was 38.8 U (SD: 10.9) or 0.5 (0.2) U/kg, and the mean iGlarLixi dose was 41.3 dose-steps (SD: 13.2) or 0.5 (0.2) U/kg at Week 24, with a mean change to Week 24 of 2.5 U (SD: 13.2) or 0.0 (0.2) U/kg (Supplementary Figure S2D,E), similar to the overall population.

3.4.5 | Change in body weight at Week 24 in participants receiving BID premixed insulin at baseline

Similar to the overall population, mean body weight decreased from baseline to Week 24 by 1.2 kg (LS mean change ± SE: −1.2 ± 0.3; 95% CI: −1.8, −0.6; Supplementary Figure S2F).

3.4.6 | Hypoglycaemia

Rates of hypoglycaemia in the BID subgroup were consistent with those in the overall population. Confirmed symptomatic hypoglycaemia occurred in 40.0% of participants (ADA level 1: 37.2%; ADA level 2: 16.6%; ADA level 3: 0%; Supplementary Table S5). The event rate was 3.9 events per person-year for all participants (3.1 for ADA Level 1; 0.8 for ADA Level 2; Supplementary Table S5).

3.4.7 | Adverse events

Adverse events experienced by the BID subgroup were similar to those experienced by the overall population.

4 | DISCUSSION

Soli-SWITCH was the first study to assess the efficacy and safety of switching to iGlarLixi from premixed insulins in people with T2D. The results demonstrated that people with T2D previously treated with premixed insulin can benefit from switching to iGlarLixi, a simple OD injection, with improved glycaemic outcomes and a slight decrease in body weight, with a low hypoglycaemia risk. iGlarLixi was well tolerated; the overall safety profile of iGlarLixi was consistent with what has been previously reported.[7–10] Further, these data support the use of the dose algorithm implemented in this study to safely and effectively de-escalate people with T2D treated with premixed insulin to once-daily iGlarLixi (Supplementary Table S1).

In this study, premixed insulin was previously administered OD or BID, with most of the population (89.5%) receiving BID doses. A pre-specified sub-analysis performed to assess the trial results in participants switching from BID premixed insulin dosing demonstrated similar improvements in glycaemic outcomes to the overall population (HbA1c, FPG, PPG and fasting SMPG), which suggests that iGlarLixi may be a potentially simplified treatment alternative for people with T2D currently receiving BID premixed insulins. Although no insulin-sparing effect was observed with iGlarLixi (premixed insulin prior to study was 0.5 U/kg, and after 24 weeks of iGlarLixi treatment, it was 0.5 U/kg), there was no significant increase in insulin dose, which would have been likely to be required for people treated with premixed insulin to achieve the same level of glycaemic control.

The glycaemic results of the current study (HbA1c reduction of 1.2%) are consistent with those of previous studies reporting data from people with T2D sub-optimally controlled on insulin treatment.[8,10] In the SoliMix study, HbA1c was reduced by 1.3% in participants with T2D inadequately controlled with basal insulin switching to iGlarLixi.[10] In the LixiLan-L study, reductions in baseline HbA1c of 1.1% were observed in participants with T2D inadequately controlled on basal insulin with or without OADs.[8] In the SoliSimplify real-world study, HbA1c reductions of 0.7% over 6 months were observed in patients who had switched from basal insulin to iGlarLixi.[21] These findings complement the data from Soli-SWITCH, although SoliSimplify is a real-world study, which may account for the differences in HbA1c reduction.

In a *post hoc* sub-analysis of DUAL II Japan, in which people with T2D previously treated with either premixed or basal insulin switched to the FRC IDegLira (basal insulin degludec and GLP-1 RA liraglutide), HbA1c decreased by 1.6% over 26 weeks in those previously treated with premixed insulin.[22]

In the Soli-D trial, participants treated with iGlarLixi experienced a statistically significant greater reduction in HbA1c from baseline to Week 24 versus IDegAsp (reductions of 1.9% and 1.7%, respectively; $p < 0.001$ for non-inferiority and $p = 0.003$ for superiority). The greater reductions in HbA1c seen in DUAL II Japan and the Soli-D trial versus Soli-SWITCH may be due to differences within the trial population, as participants in the Soli-D trial had a shorter duration of diabetes and had experienced fewer previous treatments, and in both studies, there were differences in the ethnicity of participants compared with Soli-SWITCH.

In this study, reductions in mean PPG were observed from baseline to Week 24 (LS mean change of −68.2 mg/dL). Similarly, a reduction in PPG was found in the Soli-D trial (mean change of −71.0 mg/dL at Week 24 in participants treated with iGlarLixi).[12,23] PPG was not measured for the SoliMix trial, and so a comparison cannot be made.

An increase in body weight is typically associated with initiating or intensifying treatment with insulin-based therapies in people with T2D, and is a common concern that may result in treatment inertia.[24] In the current study, switching from premixed insulin to iGlarLixi was associated with reductions in body weight of 1.0 kg in addition to a significant improvement in glycaemic control. This is likely due to the impact of combining an insulin therapy with a GLP-1 RA component. GLP-1 RAs have been demonstrated to have a weight benefit, which is partly due to delayed gastric emptying leading to increased satiety and decreased food intake, among other effects.[6,25,26] Similar body weight reductions were observed in participants who switched to iGlarLixi therapy in the SoliMix study, with statistical superiority being demonstrated over switching to the premixed insulin analogue BIAsp 30 (LS mean difference, −1.9 kg; $p < 0.001$).[10] Similarly, in the Soli-D study, people treated with iGlarLixi experienced a statistically significant superior body weight change compared with IDegAsp (LS mean difference, −1.5 kg; $p < 0.001$).[12]

Confirmed symptomatic hypoglycaemia was experienced by 38.3% of participants who switched from premixed insulin to iGlarLixi, with most participants experiencing ADA level 1 (out of 269 events, 210 were ADA level 1). This incidence is broadly in agreement with those of the randomized controlled trials Soli-D (35.2%),[12] SoliMix (31.2%)[10] and LixiLan-L (40.0%),[8] in which participants switched to iGlarLixi from either OADs or basal insulin ± OADs. Furthermore, in the Soli-D and SoliMix trials, most hypoglycaemic events were classified as ADA level 1,[10,12] as observed in the current Soli-SWITCH study. The results of Soli-SWITCH demonstrate that the improvements in glycaemic control observed when switching to iGlarLixi from premixed insulins are achieved without an increase in the risk of hypoglycaemia.

OD FRCs of basal insulin and GLP-1 RA are associated with improved or equivalent glycaemic control, a reduction in body weight,[10,12] and may also have the convenience of a simpler regimen compared with premixed insulin.[10] A reduction from a BID premixed insulin regimen to an OD FRC represents a reduction of 365 injections per year. These benefits may improve treatment satisfaction, potentially improving treatment adherence.

The main limitation of the study was the single-arm trial design. Without a matched comparator, it is not possible to directly compare treatment outcomes seen with switching from premixed insulins to iGlarLixi with those of other treatment options. It is also possible that any observation of clinical improvement could have been impacted by the increased physician support provided by participating in a clinical study, rather than by treatment with iGlarLixi. Further, as there was only one treatment group in the study, participants were not blinded to their treatment, which could introduce bias. Therefore, future real-world studies are important to confirm the results seen in the Soli-SWITCH study. Although this was a single-arm study, assessing key clinical endpoints prior to switching and 24 weeks after switching treatment provides a meaningful insight into the impact of switching between therapies for T2D. An additional limitation is the length of this study, as a longer duration would be required to assess the long-term durability of the clinical effect.

The strengths of the Soli-SWITCH study included its interventional nature, which ensured that enough participants were enrolled to provide adequate statistical power for the analysis. Another strength is that this study included participants from Asia and Europe, rather than focusing on a single country or region. Furthermore, this was the first study on switching to a FRC undertaken where all participants were previously receiving premixed insulin. The study also provided a valuable titration algorithm to facilitate the switch from premixed insulin to iGlarLixi without a loss of glycaemic control or increasing the risk of hypoglycaemia.

In conclusion, participants with T2D who switched from premixed insulin to iGlarLixi achieved improved glycaemic outcomes with a slight decrease in body weight and the expected risk of hypoglycaemia for an insulin-based therapy. Further, this study provides a practical dose algorithm to assist with switching people with T2D previously treated with premixed insulin to iGlarLixi. Data from the Soli-SWITCH study indicate that iGlarLixi might be a simple and effective treatment option for people with T2D not meeting their glycaemic targets with premixed insulin.

AUTHOR CONTRIBUTIONS

FL and SL were involved in the conception, design and conduct of the study, and FL and SL were involved in the analysis and interpretation of the results. All authors edited, reviewed and approved the final version of the manuscript. MH is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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PEER REVIEW

The peer review history for this article is available at https://www.webofscience.com/api/gateway/wos/peer-review/10.1111/dom.16276.

DATA AVAILABILITY STATEMENT

Qualified researchers may request access to patient-level data and related documents. Patient-level data will be anonymized, and study documents will be redacted to protect the privacy of trial participants. Further details on Sanofi's data sharing criteria, eligible studies and the process for requesting access can be found at https://www.vivli.org.

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SUPPORTING INFORMATION

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

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