Received: 21 February 2023 | Revised: 3 May 2023 | Accepted: 5 May 2023

DOI: 10.1111/dom.15125

ORIGINAL ARTICLE

WILEY

Advancing therapy in people with suboptimally controlled basal insulin-treated type 2 diabetes: Subanalysis of the SoliMix trial in participants in Latin American countries

Gustavo Frechtel MD[1] | Leobardo Sauque-Reyna MD[2] | Ricardo Choza-Romero MD[3] | Luis Anguiano MD[4] | Lydie Melas-Melt MSc[5] | María Elena Sañudo-Maury MD[4]

[1]Departamento de Medicina, Orientación Nutrición, Facultad de Medicina, Universidad de Buenos Aires, Buenos Aires, Argentina

[2]Instituto de Diabetes, Obesidad y Nutrición S.C., Cuernavaca, Mexico, Morelos, Mexico

[3]Centro Médico Ono, Aguascalientes, Mexico

[4]Medical Department, Sanofi, Mexico City, Mexico

[5]Ividata Life Sciences, Levallois-Perret, France

Correspondence
María Elena Sañudo-Maury, Medical Department, Sanofi, Avenue Real de Mayorazgo #130 (Torre Mitikah piso 25), Colonia Xoco, Mexico City 03330, Mexico.
Email: mariaelena.sanudo@sanofi.com

Funding information
Sanofi

Abstract

Aims: This subanalysis of the SoliMix trial assessed the efficacy and safety of advancing basal insulin (BI) therapy with iGlarLixi versus BIAsp 30 in people with type 2 diabetes (T2D) living in Latin American (LATAM) countries, i.e. Argentina and Mexico ($N = 160$).

Materials and Methods: SoliMix (EudraCT: 2017-003370-13) was a 26-week, open-label, multicentre study, where adults with T2D suboptimally controlled with BI plus one or two oral glucose-lowering drugs and glycated haemoglobin (HbA1c) ≥7.5% to ≤10% were randomized to once-daily iGlarLixi or twice-daily BIAsp 30. Primary efficacy endpoints were non-inferiority in HbA1c reduction (margin 0.3%) or superiority in body weight change for iGlarLixi versus BIAsp 30.

Results: Both primary efficacy endpoints were met in the LATAM region. After 26 weeks, HbA1c was reduced by 1.8% with iGlarLixi and 1.4% with BIAsp 30, meeting non-inferiority [least squares mean difference −0.47% (95% confidence interval: −0.82, −0.11); $p < .001$]. iGlarLixi was superior to BIAsp 30 for body weight change [least squares mean difference −1.27% (95% confidence interval: −2.41, −0.14); $p = .028$]. iGlarLixi was also superior to BIAsp 30 for HbA1c reduction ($p = .010$). A greater proportion of participants achieved HbA1c <7% without weight gain and HbA1c <7% without weight gain and without hypoglycaemia with iGlarLixi versus BIAsp 30. Incidence and rates of American Diabetes Association Level 1 and 2 hypoglycaemia were lower with iGlarLixi versus BIAsp 30.

Conclusions: Once-daily iGlarLixi provided better glycaemic control with weight benefit and less hypoglycaemia than twice-daily premix BIAsp 30. iGlarLixi may be a favourable alternative to premix BIAsp 30 in people with suboptimally controlled T2D to advance BI therapy in the LATAM region.

Prior Presentation: Parts of this study were presented in the XXIII Argentine Congress of Diabetes (28 September to 1 October 2022) and the Mexican Society of Nutrition and Endocrinology—LXII International Congress (29 November to 3 December 2022).

KEYWORDS
basal insulin, GLP-1 receptor agonist, suboptimal glycaemic control, type 2 diabetes

1 | INTRODUCTION

Type 2 diabetes (T2D) is one of the most critical public health problems to address in low- and middle-income countries, including Latin American (LATAM) countries. In 2019, about 31.6 million people were living with diabetes in the LATAM region, which is expected to reach 40.2 million by 2030 and 49.1 million by 2045.[1] The prevalence of diabetes among adults has been consistently increasing in the LATAM region[1] and varies across countries: for example, 11.9% in Argentina[2] to 15.8% in Mexico,[3] which is higher than the overall worldwide prevalence (10.5%).[4] The variation in the prevalence of diabetes in the LATAM may be attributed to a highly heterogeneous population living in the region, with diverse genetic ancestry, ethnicity, culture of origin, income, education, access to health care and cultural influences on nutrition.[1]

The high prevalence of diabetes in the LATAM region could be attributed to several factors, including low socioeconomic status, dietary patterns, sedentary lifestyle, demographic transition and urbanization.[1] In addition, obesity plays a critical role in the development of T2D.[5] Obesity is a global epidemic; almost 70% of the adult population in Argentina and Mexico are either overweight or obese.[6] This increasing prevalence of obesity in the LATAM region accompanies an increased incidence of T2D.[5]

The American Diabetes Association (ADA) and Asociación Latinoamericana de Diabetes (ALAD) guidelines recommend glycated haemoglobin (HbA1c) target of <7% (<53 mmol/mol) for most people with T2D to slow down or prevent disease progression and diabetes-related complications.[7,8] However, reports show that only up to 32% and 54% of people with T2D in Mexico and Argentina, respectively, achieve the target HbA1c (<7%), despite receiving antidiabetic therapy.[9,10]

Because of the multifaceted pathophysiology of T2D, people with T2D often require combination therapies.[11] In people with T2D advancing from basal insulin to other insulin regimens (e.g. premix insulins), regimen complexity (including dosing frequency) and fear of weight gain and hypoglycaemia are major barriers to treatment adherence, which is essential to achieve optimal glycaemic control.[12]

Furthermore, the latest 2023 ADA guideline recommendations prefer glucagon-like peptide-1 receptor agonist (GLP-1 RA) to insulin whenever feasible. For those in whom insulin must be used, combination therapy with a GLP-1 RA is recommended for greater efficacy, durability of treatment effect, and weight and hypoglycaemia benefit. The guidelines also emphasize that for individuals who do not achieve treatment goals, treatment intensification should not be delayed.[13] The ALAD 2019 guidelines also recommend the combination of GLP-1 RA with insulin glargine because of their glycaemic efficacy and beneficial effects on body weight without increasing the risk of hypoglycaemia.[8]

iGlarLixi, a fixed-ratio combination (FRC) of basal insulin glargine 100 U/ml (iGlar) and the short-acting GLP-1 RA lixisenatide (Lixi), offers a simplified combination therapy; it is well tolerated and efficacious in people with T2D suboptimally controlled by either oral glucose-lowering drugs (OGLDs) or basal insulin.[14,15] iGlarLixi has been shown to provide better glycaemic control than either glargine 100 U/ml or lixisenatide alone without increasing the risk of hypoglycaemia, with less weight gain versus insulin glargine alone and fewer gastrointestinal adverse events (AEs) versus lixisenatide alone.[12]

The SoliMix was the first randomized, head-to-head study directly comparing the efficacy and safety of an FRC (iGlarLixi) with a premixed insulin (BIAsp 30, 30% insulin aspart + 70% insulin aspart protamine) in adults with T2D advancing from basal insulin plus one or two OGLDs. Results showed that once-daily iGlarLixi provided statistically significant reduction in HbA1c with weight benefit and lower incidence and rates of hypoglycaemia than twice-daily premix BIAsp 30.[16] However, the majority of SoliMix participants were from European countries, hence, the overall results might be more representative of the European region. On the other hand, there is scarcity of studies that evaluate novel alternative therapy in Latin American people who are unable to achieve target HbA1c despite previous therapies. To fill this gap, the current subanalysis was conducted with an objective to assess the efficacy and safety of iGlaLixi versus premix BIAsp 30 in people with T2D living in Argentina and Mexico (hereafter referred to as LATAM) in the SoliMix trial.

2 | MATERIALS AND METHODS

2.1 | Study design and participants

Detailed methods have been previously published.[16,17] In brief, SoliMix (EudraCT: 2017-003370-13) was a 26-week, open-label, multicentre, randomized controlled study comparing once-daily iGlarLixi versus BIAsp 30. Participants included adults (≥18 years) with T2D and HbA1c ≥7.5% (≥58 mmol/mol) and ≤10.0% (≤85.8 mmol/mol), despite receiving stable doses of basal insulin plus metformin with or without sodium-glucose cotransporter 2 inhibitor (SGLT2i) for 3 months. Participants were randomized (1:1) to receive once-daily subcutaneous iGlarLixi or twice-daily subcutaneous BIAsp 30. Primary efficacy endpoints were non-inferiority in HbA1c reduction (margin 0.3%) or superiority in body weight change for iGlarLixi versus BIAsp 30.

This study was conducted in accordance with the ethical principles of the 1964 Declaration of Helsinki and all subsequent amendments, the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use for good clinical practice, and all applicable laws, rules and regulations. Informed consent was obtained from all participants before study initiation.

2.2 | Study endpoints

This subanalysis explored the following endpoints. The primary efficacy endpoints were non-inferiority in HbA1c reduction (margin 0.3%) or superiority in body weight change for iGlarLixi versus BIAsp 30. Key secondary endpoints included HbA1c <7% without weight gain at week 26, HbA1c <7% without weight gain at week 26 and without hypoglycaemia [<70 mg/dl (<3.9 mmol/L)] during the treatment period, and the superiority of iGlarLixi versus BIAsp 30 in terms of HbA1c reduction from baseline to week 26. Other secondary endpoints included participants achieving an HbA1c target of <8%, <7% and <6.5% at week 26 and change in fasting plasma glucose (FPG) from baseline to week 26.

Safety endpoints included incidence and rate of hypoglycaemia, AEs, serious AEs (SAEs), AEs leading to treatment discontinuation and AEs leading to death. Hypoglycaemia was defined as 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 hypoglycaemia, characterized by altered mental and/or physical status requiring assistance for the treatment of hypoglycaemia).[18]

2.3 | Statistical analysis

The primary efficacy endpoints were analysed using a multiple imputation strategy and an ANCOVA model including screening for the HbA1c value (<8.0% vs. ≥8%, for the change in body weight endpoint only), basal insulin dose (<30 U vs. ≥30 U) and SGLT2i use (Yes vs. No), treatment group and country as fixed categorical effects and fixed continuous covariates of baseline values for each primary endpoint. The same approach was used to analyse continuous secondary efficacy endpoints, using the baseline values for the endpoint in question as fixed covariates. Categorical secondary efficacy endpoints were analysed using a logistic regression model adjusting for treatment group, randomization strata (basal insulin dose and SGLT2i use), and HbA1c and weight baseline values as covariates.[16]

A multiple testing procedure was used for the analysis of the primary and key secondary efficacy endpoints.[16] Following the two primary endpoints, the three key secondary endpoints were assessed using a hierarchical order, that is, superiority of iGlarLixi versus BIAsp 30 in achieving HbA1c <7% without weight gain, then in achieving HbA1c <7% without weight gain and without hypoglycaemia, and then in HbA1c reduction.

All efficacy analyses were performed on intention-to-treat population, defined as all randomized participants, while safety analyses were based on data from the safety population, defined as all randomized participants who received at least one dose of study drug.

3 | RESULTS

3.1 | Participant disposition and baseline characteristics

In total, 887 participants were included in the SoliMix trial; of these participants, 160 from the LATAM region (Argentina, n = 71; Mexico, n = 89) were included in the current subanalysis. Overall, demographics and baseline characteristics were similar across both treatment groups (Table 1). Briefly, the participants included in this subanalysis had a mean ± standard deviation (SD) age of 60.0 ± 10.3 years, a body mass index of 30.9 ± 4.8 kg/m^2 and a T2D duration of 14.8 ± 8.4 years.

3.2 | Efficacy endpoints

Both primary efficacy endpoints were met. At week 26, non-inferiority of iGlarLixi over BIAsp 30 was shown for the change in HbA1c from baseline to week 26 {least squares mean difference [LS MD] vs. BIAsp 30: −0.47% [95% confidence interval (CI): −0.82, −0.11]; $p < .001$}. Subsequent testing showed superiority of iGlarLixi over BIAsp 30 in HbA1c reduction from baseline to week 26, as part of the key secondary endpoint analysis ($p = .010$; Figure 1A). Superiority of iGlarLixi over BIAsp 30 was shown for the change in body weight from baseline to week 26 [LS MD vs. BIAsp 30: −1.27 kg (95% CI: −2.41, −0.14); $p = .028$; Figure 1B].

Compared with the BIAsp 30 group, a greater proportion of participants in the iGlarLixi group reached HbA1c <7% (<53 mmol/mol) without weight gain at week 26 [odds ratio (OR; 95% CI): 2.57 (1.11, 5.92); $p = .027$], and HbA1c <7% (<53 mmol/mol) without weight gain at week 26 and without hypoglycaemia [<70 mg/dl (<3.9 mmol/L)] [OR (95% CI): 2.79 (0.98, 7.92); $p = .054$] during the treatment period (Figure 2A). The percentage of participants who achieved the HbA1c target of <8%, <7% and <6.5% at week 26 was higher, although not statistically significant, in the iGlarLixi group than in the BIAsp 30 group (Figure 2B).

The mean ± SD FPG at baseline was 144.73 ± 35.85 mg/dl (8.03 ± 1.99 mmol/L) in the iGlarLixi group and 145.22 ± 44.83 mg/dl (8.06 ± 2.49 mmol/L) in the BIAsp 30 group. At week 26, the mean ± SD FPG in the iGlarLixi group decreased to 117.39 ± 36.72 mg/dl (6.52 ± 2.04 mmol/L), while there was no change in mean ± SD FPG in BIAsp 30 group [145.98 ± 66.18 mg/dl (8.10 ± 3.67 mmol/L)]. The LS MD between groups in FPG change from baseline to week 26 was −1.61 mmol/mol (95% CI: −2.87, −0.34) corresponding to −28.97 mg/dl (95% CI: −51.79, −6.15; $p = 0.013$) (Figure 2C).

After 26 weeks, the increase in LS mean total daily insulin dose was smaller in the iGlarLixi than in the BIAsp 30 group. The LS MD between groups in insulin dose change from baseline to week 26 was −6.52 U (95% CI: −13.25, 0.21; $p = .058$) (Figure 2D).

3.3 | Safety

The proportion of participants with at least one hypoglycaemic event was lower in the iGlarLixi group than that in the BIAsp 30 group [OR (95% CI): 0.71 (0.37, 1.35)] (Figure 3). Lower incidences of hypoglycaemia with iGlarLixi versus BIAsp 30 were also observed in ADA Level 1 [<70 to ≥54 mg/dl (<3.9 to ≥3.0 mmol/L)] and Level 2 [<54 mg/dl (<3.0 mmol/L)] hypoglycaemia categories (Figure 3A). Similarly, there was an overall lower rate of any hypoglycaemia with

TABLE 1 Baseline characteristics of randomized population

Characteristic	iGlarLixi (n = 71)	BIAsp 30 (n = 89)	All participants (N = 160)
Age, years	60.3 ± 9.9	59.9 ± 10.6	60.0 ± 10.3
Age groups, years; n (%)			
<50	10 (14.1)	14 (15.7)	24 (15.0)
≥50 to <65	36 (50.7)	45 (50.6)	81 (50.6)
≥65 to <75	20 (28.2)	21 (23.6)	41 (25.6)
≥75	5 (7.0)	9 (10.1)	14 (8.8)
Female, n (%)	36 (50.7)	55 (61.8)	91 (56.9)
BMI, kg/m^2	30.9 ± 4.9	30.9 ± 4.7	30.9 ± 4.8
BMI categories, kg/m^2; n (%)			
<25	8 (11.3)	6 (6.7)	14 (8.8)
≥25 to <30	26 (36.6)	38 (42.7)	64 (40.0)
≥30 to <35	18 (25.4)	25 (28.1)	43 (26.9)
≥35	19 (26.8)	20 (22.5)	39 (24.4)
Duration of T2D, years	14.2 ± 7.7	15.2 ± 8.9	14.8 ± 8.4
Category of duration of diabetes, n (%)			
<10 years	26 (36.6)	27 (30.3)	53 (33.1)
≥10 years	45 (63.4)	62 (69.7)	107 (66.9)
HbA1c, %	8.7 ± 0.7	8.6 ± 0.7	8.6 ± 0.7
mmol/mol	71.2 ± 8.0	70.6 ± 7.4	70.9 ± 7.7
FPG, mg/dl	144.7 ± 35.9	145.2 ± 44.8	145.0 ± 40.9
mmol/L	8.0 ± 2.0	8.1 ± 2.5	8.0 ± 2.3
Prior basal insulin, n (%)[a]			
Insulin glargine 100 U/ml	38 (53.5)	45 (50.6)	83 (51.9)
Insulin glargine 300 U/ml	8 (11.3)	12 (13.5)	20 (12.5)
NPH	20 (28.2)	23 (25.8)	43 (26.9)
Insulin degludec	4 (5.6)	6 (6.7)	10 (6.3)
Insulin detemir	1 (1.4)	3 (3.4)	4 (2.5)
Basal insulin daily dose, U	35.3 ± 10.0	35.6 ± 10.4	35.5 ± 10.2
U/kg	0.449 ± 0.150	0.444 ± 0.136	0.446 ± 0.142
Oral antidiabetic treatment at baseline, n (%)			
Metformin alone	63 (88.7)	85 (95.5)	148 (92.5)
Metformin + SGLT2i	8 (11.3)	4 (4.5)	12 (7.5)
Diabetes-related complications, n (%)			
Diabetic nephropathy	1 (1.4)	8 (9.0)	9 (5.6)
Diabetic neuropathy	8 (11.3)	21 (23.6)	29 (18.1)
Diabetic retinopathy	2 (2.8)	14 (15.7)	16 (10.0)

Note: Data are presented as mean ± SD unless otherwise noted.

[a]A patient can be counted in more than one category.

Abbreviations: BMI, body mass index; FPG, fasting plasma glucose; HbA1c, glycated haemoglobin; NPH, neutral protamine Hagedorn; SD, standard deviation; SGLT2i, sodium-glucose cotransporter 2 inhibitor; T2D, type 2 diabetes.

iGlarLixi compared with BIAsp 30, across all hypoglycaemia categories (Figure 3B). Only two cases of ADA Level 3 hypoglycaemia were reported: one in the iGlarLixi group and one in the BIAsp 30 group.

During the 26-week randomized treatment period, the percentage of participants who reported at least one treatment-emergent AE (TEAE) was similar in the iGlarLixi group (42.3%) and in the BIAsp 30 group (40.4%). Two participants in the iGlarLixi group and three participants in the BIAsp 30 group reported an SAE, and three participants in the BIAsp 30 group (vs. none in the iGlarLixi group) permanently discontinued the treatment because of a TEAE.

The proportion of participants who had at least one specific gastrointestinal TEAE was numerically higher for iGlarLixi versus BIAsp 30 (11.3% vs. 4.5%). The most frequently reported event of special interest in the iGlarLixi group was nausea (n = 7; 9.9%), followed by vomiting

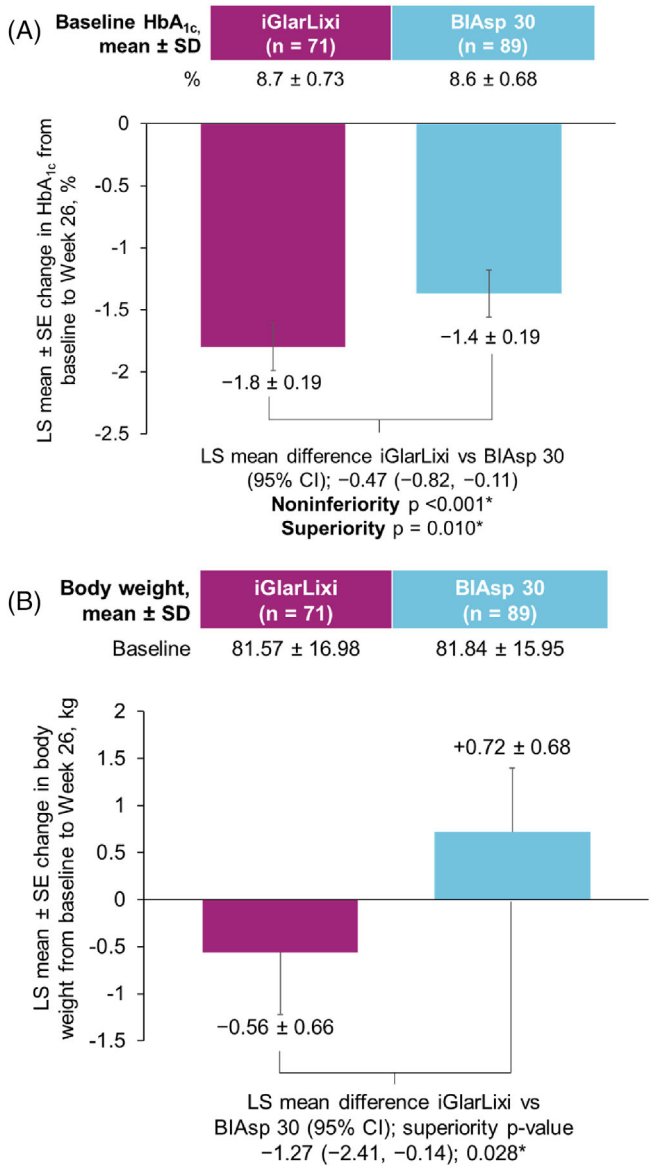

FIGURE 1 Changes in (A) HbA1c and (B) body weight from baseline to week 26 in intention-to-treat population. *p values are for descriptive purpose only. CI, confidence interval; HbA1c, glycated haemoglobin; LS, least squares; SD, standard deviation; SE, standard error.

(n = 2; 2.8%) and diarrhoea (n = 1; 1.4%). In the BIAsp 30 group, diarrhoea was the most reported TEAE of special interest (n = 3; 3.4%), followed by vomiting (n = 1; 1.1%). In both treatment groups, majority of the AEs were considered mild or moderate in severity.

4 | DISCUSSION

SoliMix was the first randomized controlled trial comparing an FRC of basal insulin and a GLP-1 RA with premix insulin. Results from the global study provide evidence supporting better efficacy and safety of iGlarLixi compared with premix BIAsp 30 for advancing treatment in adults with long-standing T2D, suboptimally controlled with basal insulin plus one or two OGLDs.[16] The main findings from the present analysis are aligned with the overall SoliMix cohort. After 26 weeks, iGlarLixi showed both non-inferiority and superiority to premix BIAsp 30 in HbA1c reduction, as well as superiority in body weight change. Compared with BIAsp 30, a higher proportion of participants treated with iGlarLixi reached the HbA1c target <7% without weight gain and HbA1c target <7% without weight gain and without hypoglycaemia. In addition, the mean FPG reduction from baseline to week 26 was higher in the iGlarLixi group compared with the BiAsp 30 group. The mean body weight decreased from baseline to week 26 with iGlarLixi, whereas it increased with premix BIAsp 30.

As a finding, the LS mean reduction in HbA1c with iGlarLixi was higher in LATAM participants as compared with the iGlarLixi group in the overall SoliMix study (−1.8% vs. −1.3%), while the LS mean reduction in body weight with iGlarLixi was slightly lower in LATAM participants compared with the iGlarLixi group in the overall SoliMix study (−0.56 kg vs. −0.7% kg). Furthermore, a greater proportion of participants on iGlarLixi treatment from LATAM achieved HbA1c target <6.5% (25.4% vs. 20.3%) and <7% (50.7% vs. 42.2%) compared with iGlarLixi group in the overall SoliMix study. Similarly, the LS mean reduction in FPG with iGlarLixi treatment in LATAM was higher than the iGlarLixi group in the overall SoliMix study (−27.81 mg/dl vs. −21 mg/dl). On the contrary, the LS mean increase in the total insulin daily dose was higher in iGlarLixi group in LATAM versus iGlarLixi group in the overall SoliMix study (18.63 U vs. 10.6 U). The prevalence of obesity is higher in the LATAM region, which is associated insulin with resistance, and that is probably why participants in the LATAM region required more insulin to achieve target HbA1c.

In the LATAM subanalysis, the incidence of ADA Level 2 [<54 mg/dl (<3.0 mmol/L)] hypoglycaemia reported in the BIAsp 30 group was two-fold higher compared with the iGlarLixi group [20.2% vs. 8.5%; OR, 0.37 (0.14, 0.99)], similar to the pattern seen in overall the SoliMix cohort [12.9% vs. 6.3%; OR, 0.45 (0.28, 0.73)]. The incidence and rates of hypoglycaemia observed in LATAM participants were numerically higher than in the overall SoliMix study (e.g. ADA Level 2: 20.2% vs. 12.9% for BIAsp 30 and 8.5% vs. 6.3% for iGlarLixi). As noted earlier, the mean increase in total daily insulin was higher in LATAM participants versus the overall SoliMix study, which might have led to these higher hypoglycaemia incidences in LATAM participants. However, although there was a small increase in hypoglycaemia incidence in the LATAM participants, a greater proportion of participants achieved target HbA1c <6.5% and <7% than the overall population.

The improvements in glycaemic control seen with iGlarLixi in this analysis are consistent with a multicentric observational study by Bilic-Curcic et al. evaluating the efficacy and safety profile of two FRCs (IDegLira and iGlarLixi) in people with long-standing T2D, suboptimally controlled on different insulin regimens, including premix insulin analogues, basal-bolus regimen, or basal oral therapy. A significant improvement was noted in all glycaemic parameters in insulin-treated participants after switching to FRCs (p < .001 for all).[19] Similarly, in the Mexican population subanalysis of the LixiLan clinical

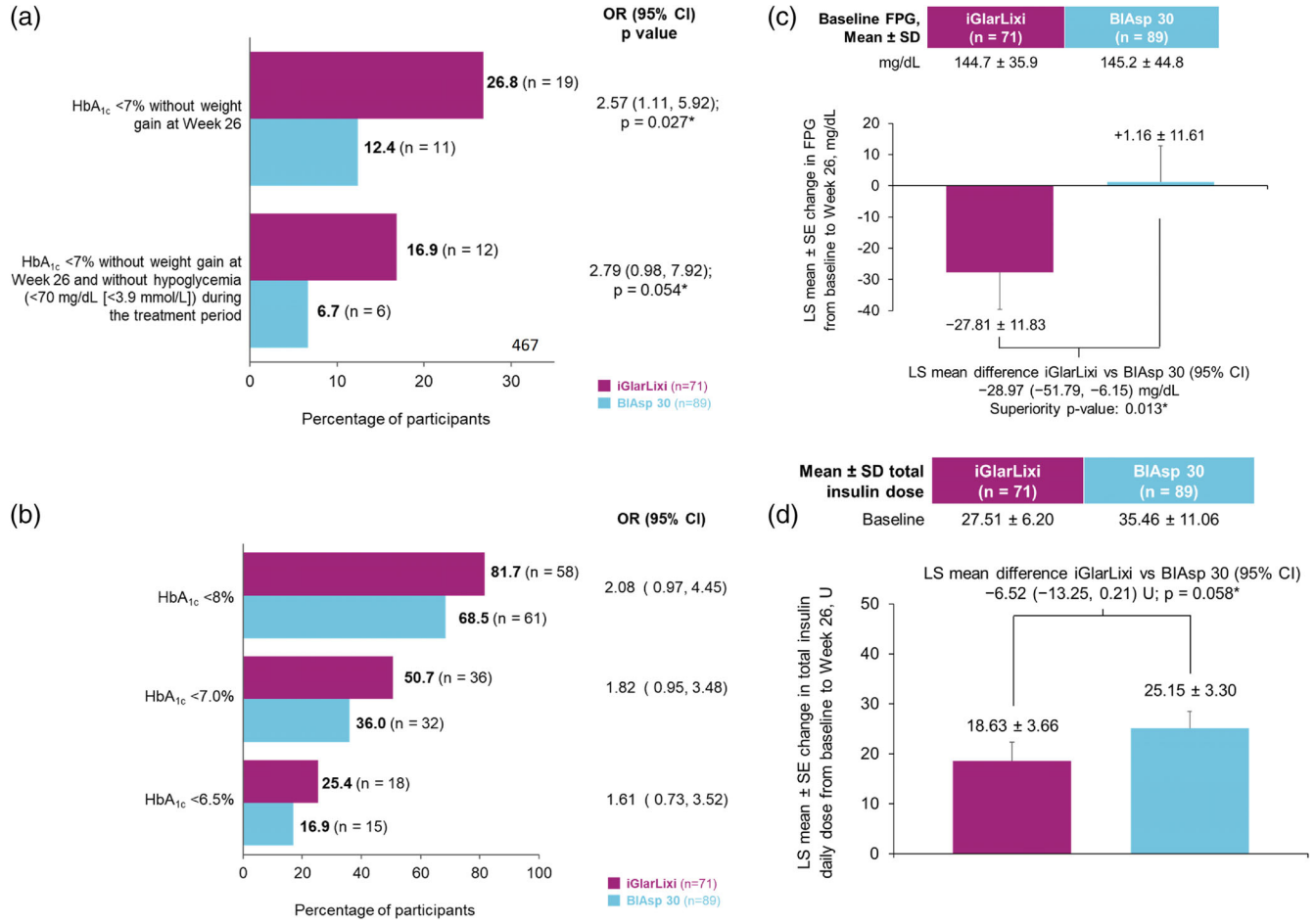

FIGURE 2 (A) Composite endpoints, (B) HbA1c target achievement, (C) FPG reduction and (D) basal insulin dose at week 26 in intention-to-treat population. **p* values are for descriptive purpose only. CI, confidence interval; FPG, fasting plasma glucose; HbA1c, glycated haemoglobin; LS, least squares; OR, odds ratio; SD, standard deviation; SE, standard error.

programme (LixiLan-POC, LixiLan-O and LixiLan-L), an average HbA1c reduction of 1.6% was seen with iGlarLixi, which is similar to the HbA1c reduction observed in the present analysis (LS mean change: −1.84%).[20]

Furthermore, the present analysis results are consistent with the findings of a systematic literature review and indirect treatment comparison, comparing the efficacy and safety of iGlarLixi versus premix IDegAsp.[21] The MD in HbA1c change with iGlarLixi was statistically higher versus IDegAsp {MD = −0.64 [95% credible interval (CrI): −1.01, −0.28] %units}. iGlarLixi was also associated with greater chances of achieving the HbA1c target of <7.0% versus IDegAsp [OR = 2.50; (95% CrI: 1.06, 5.56)]. The change in body weight followed the same pattern as glycaemic parameters, showing a more favourable outcome with iGlarLixi versus IDegAsp [MD = −1.34 (95% CrI: −1.92, −0.74) kg].[21] Similar results were observed in a network meta-analysis by Home et al. that compared iGlarLixi versus basal-bolus or premix insulins. The results of the network meta-analysis showed a greater reduction in HbA1c with iGlarLixi versus premix insulin [MD, −0.50 (95% CrI: −0.93, −0.06) %units], along with favourable body weight changes with iGlarLixi versus premix insulin [−2.2 kg (95% CI: −4.6, −0.1)].[22]

In previous studies, iGlarLixi has been shown to provide improved glycaemic control while attenuating insulin-related body weight gain and having a similar risk of hypoglycaemia versus iGlar alone.[14,15] A meta-analysis of randomized controlled trials comparing basal insulin with twice-daily or thrice-daily premix insulin showed that while premix insulin provided improved glycaemic control, it was also associated with higher risk of hypoglycaemia and increased weight gain.[17,23] Likewise, the present analysis showed a weight benefit with iGlarLixi, where mean body weight decreased from baseline to week 26 with iGlarLixi and increased with BIAsp 30, and a numerically lower incidence and rate of hypoglycaemia in the iGlarLixi group versus BIAsp 30 group. Obesity is associated with increased morbidity and mortality in people with T2D, and increased body weight has been shown to worsen glycaemic control and increase the risk of diabetes progression. As obesity is prevalent in the LATAM region, the weight benefit associated with iGlarLixi could help further alleviate obesity-associated complications in this population.[24] These findings further support that switching to iGlarLixi may reduce the injection burden, help alleviate the fear of hypoglycaemia, and mitigate body weight gain concerns in people requiring insulin-based treatment intensification. These factors may

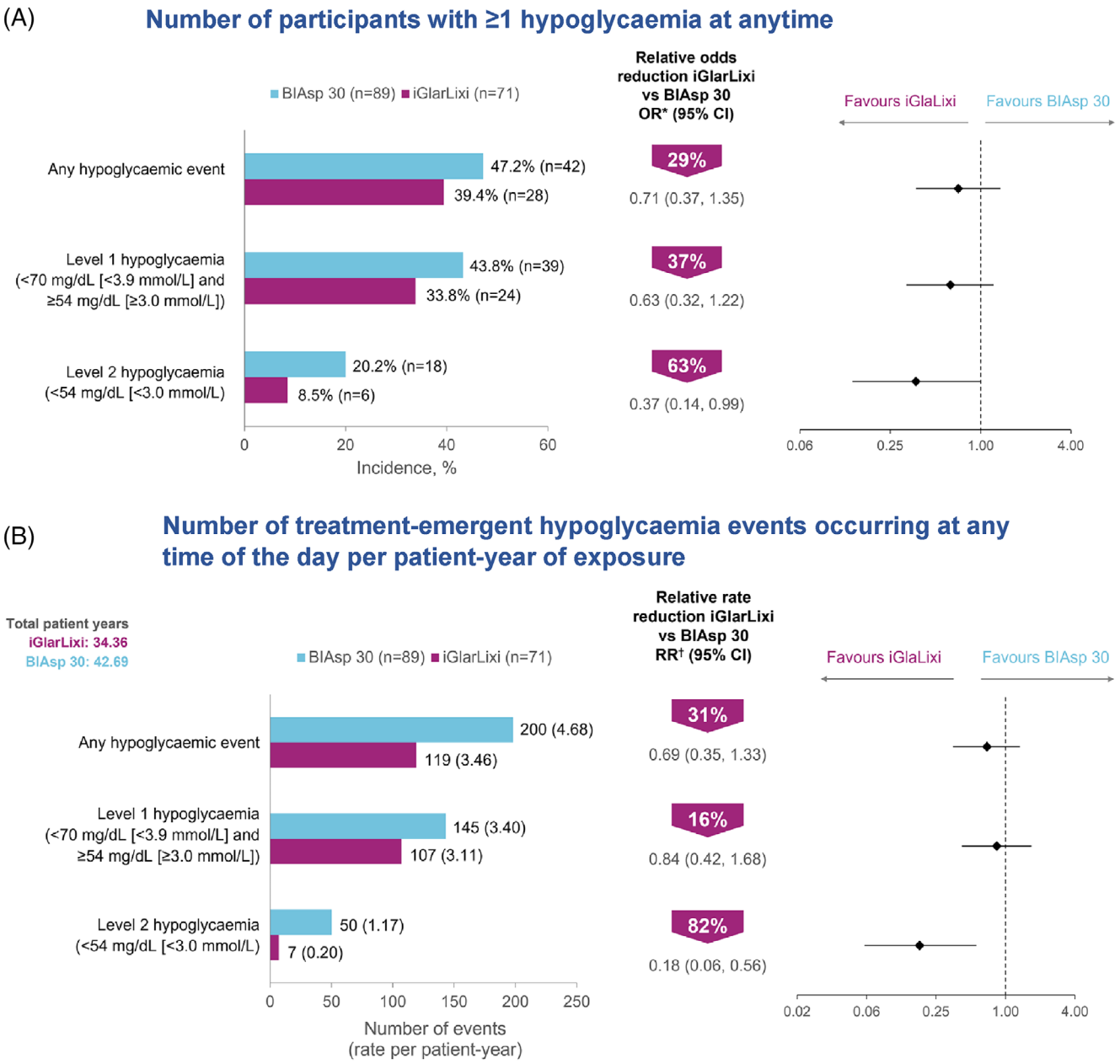

FIGURE 3 (A) Incidence and (B) event rate of hypoglycaemia in safety population. (A) Number of participants with ≥1 hypoglycaemia at any time of the day. (B) Number of treatment-emergent hypoglycaemia events occurring at any time of the day per patient-year of exposure. *OR and its corresponding 95% CI are based on a logistic regression with treatment groups (iGlarLixi and Premix), randomization strata. †Relative risk over Premix and its corresponding 95% CI estimated from a negative binomial regression. The model includes fixed-effect terms for treatment and randomization strata. ADA, American Diabetes Association; CI, confidence interval; OR, odds ratio; RR, risk ratio.

lead to improved treatment adherence, better glycaemic control and a better quality of life.[17]

The overall safety and tolerability profiles of iGlarLixi and premix BIAsp 30 were comparable with those reported in previous studies.[14,15,25–27] Moreover, the safety data of iGlarLixi were consistent with the established safety profiles of its individual components.[14,15] Furthermore, consistent with other GLP-1 RAs, nausea was the most common gastrointestinal TEAE, and its incidence was similar to the overall SoliMix cohort (overall, 7.7% vs. LATAM, 9.9%).

Currently, there is a scarcity of studies directly comparing the efficacy and safety of iGlarLixi versus premix BIAsp 30. Only limited studies have been published, and these studies had performed indirect comparisons. The present analysis complements overall SoliMix results and other previously published indirect findings.

The key strength of this analysis lies in its study design. SoliMix was 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 T2D, suboptimally controlled with basal insulin plus OGLDs.

A potential limitation of this analysis is the small number of participants, which has reduced the statistical power; however, the main findings in terms of efficacy and weight benefit are consistent with the overall SoliMix study cohort. Moreover, participants were from only two LATAM countries and may not represent the entire spectrum of the LATAM population. While it is not a limitation of the present subanalysis, it is worth noting that the SoliMix study was open label; hence, it had inherent disadvantages such as risk of bias.

In conclusion, once-daily iGlarLixi may be a favourable alternative to twice-daily BIAsp 30 in people living with T2D in the LATAM region who are unable to achieve the HbA1c target with basal insulin plus OGLDs while also providing better glycaemic control with weight benefit and less hypoglycaemia.

AUTHOR CONTRIBUTIONS

Maria Elena Sañudo-Maury, Luis Anguiano and Lydie Melas-Melt were involved in the conception and design of the study analysis. Gustavo Frechtel, Ricardo Choza-Romero, Leobardo Sauque-Reyna and Lydie Melas-Melt substantially contributed to data acquisition. All authors substantially contributed to the data analysis/interpretation of the results, critically reviewed the manuscript and approved the final version for submission, and are accountable for the accuracy and integrity of this manuscript.

ACKNOWLEDGEMENTS

This study was funded by Sanofi, Paris, France. The authors thank the study participants, investigators, and staff who participated in the data collection for the study. Scientific writing and editorial support were provided by Preeti Agarwal and Atulya Nagarsenkar, who are employees of Sanofi.

CONFLICT OF INTEREST STATEMENT

Gustavo Frechtel is a consultant and member of the advisory board and Steering Committee or received speaker fees from Astra Zéneca, Boerhinger Ingelheim, Craveri, Eli Lilly, Merck Sharp and Dome, Montpellier, Novartis, Novo Nordisk, Sanofi, Takeda. Leobardo Sauque-Reyna is an advisor and speaker for Novo Nordisk, Sanofi and Boehringer Ingelheim. Ricardo Choza-Romero has no conflict of interests to declare. Lydie Melas-Melt is an employee of IVIDATA Life Sciences, Levallois-Perret, France, contracted by Sanofi. Luis Anguiano and Maria Elena Sañudo-Maury are employees of Sanofi and may hold Sanofi stocks.

PEER REVIEW

The peer review history for this article is available at https://www.webofscience.com/api/gateway/wos/peer-review/10.1111/dom.15125.

DATA AVAILABILITY STATEMENT

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

ORCID

Gustavo Frechtel https://orcid.org/0000-0002-7287-8520
Leobardo Sauque-Reyna https://orcid.org/0000-0003-4353-5753
Ricardo Choza-Romero https://orcid.org/0000-0003-3771-6355
Lydie Melas-Melt https://orcid.org/0000-0001-9698-8196
María Elena Sañudo-Maury https://orcid.org/0000-0002-8463-462X

REFERENCES

1. Aviles-Santa ML, Monroig-Rivera A, Soto-Soto A, Lindberg NM. Current state of diabetes mellitus prevalence, awareness, treatment, and control in Latin America: challenges and innovative solutions to improve health outcomes across the continent. *Curr Diab Rep*. 2020; 20(11):62.
2. Corna R, Fox A, Ranalli C, et al. Prevalencia de diabetes, obesidad y otros factores de riesgo cardiovascular. Estudio Venado Tuerto 3 (VT3). *Rev ALAD*. 2021;11:101-109.
3. Informe de Resultados de la Encuesta Nacional de Salud y Nutrición—Continua 2021. 2021 https://ensanut.insp.mx/encuestas/ensanutcontinua2021/informes.php
4. International Diabetes Federation. IDF Diabetes Atlas, 10th edn. Brussels, Belgium: 2021. Vol 10. https://www.diabetesatlas.org Accessed Accessed 2 July 2023.
5. Gallardo-Rincon H, Cantoral A, Arrieta A, et al. Review: type 2 diabetes in Latin America and the Caribbean: regional and country comparison on prevalence, trends, costs and expanded prevention. *Prim Care Diabetes*. 2021;15(2):352-359.
6. World Obesity Federation Global Obesity Observatory. 2022 https://data.worldobesity.org/. Accessed 2 July 2023
7. American Diabetes Association. 6. Glycemic targets: standards of medical Care in Diabetes-2021. *Diabetes Care*. 2021;44(Suppl 1):S73-S84.
8. Association of Latin America Diabetes. ALAD Guidelines on the Diagnosis, Control and Treatment of Type 2 Diabetes Mellitus with Medicine Based on Evidence. *Revista de la Asociacion Latinoamericana de Diabetes*. 2019; https://www.revistaalad.com/guias/5600AX191_guias_alad_2019.pdf. Accessed 2 July 2023.
9. Basto-Abreu A, Barrientos-Gutierrez T, Rojas-Martinez R, et al. Prevalence of diabetes and poor glycemic control in Mexico: results from Ensanut 2016. *Salud Publica Mex*. 2020;62(1):50-59.
10. Commendatore V, Dieuzeide G, Faingold C, et al. Registry of people with diabetes in three Latin American countries: a suitable approach to evaluate the quality of health care provided to people with type 2 diabetes. *Int J Clin Pract*. 2013;67(12):1261-1266.
11. Skolnik N, Del Prato S, Blonde L, Galstyan G, Rosenstock J. Translating iGlarLixi evidence for the management of frequent clinical scenarios in type 2 diabetes. *Adv Ther*. 2021;38(4):1715-1731.
12. Giorgino F, Caruso I, Napoli R. Titratable fixed-ratio combination of insulin glargine plus lixisenatide: a simplified approach to glycemic control in type 2 diabetes mellitus. *Diabetes Res Clin Pract*. 2020;170: 108478.
13. ElSayed NA, Aleppo G, Aroda VR, et al. 9. Pharmacologic approaches to glycemic treatment: standards of care in diabetes-2023. *Diabetes Care*. 2023;46:S140-S157.
14. Rosenstock J, Aronson R, Grunberger G, et al. Benefits of LixiLan, a titratable fixed-ratio combination of insulin glargine plus Lixisenatide, versus insulin glargine and lixisenatide monocomponents in type 2 diabetes inadequately controlled on oral agents: the LixiLan-O randomized trial. *Diabetes Care*. 2016;39(11):2026-2035.
15. Aroda VR, Rosenstock J, Wysham C, et al. Efficacy and safety of LixiLan, a titratable fixed-ratio combination of insulin glargine plus lixisenatide in type 2 diabetes inadequately controlled on basal insulin and metformin: the LixiLan-L randomized trial. *Diabetes Care*. 2016; 39(11):1972-1980.

16. Rosenstock J, Emral R, Sauque-Reyna L, et al. 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. *Diabetes Care*. 2021;44:2361-2370.
17. McCrimmon RJ, Al Sifri S, Emral R, et al. 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. *Diabetes Obes Metab*. 2021;23(6):1221-1231.
18. ElSayed NA, Aleppo G, Aroda VR, et al. 6. Glycemic targets: standards of care in diabetes-2023. *Diabetes Care*. 2023;46(Suppl 1):S97-S110.
19. Bilic-Curcic I, Cigrovski Berkovic M, Bozek T, Simel A, Klobucar Majanovic S, Canecki-Varzic S. Comparative efficacy and safety of two fixed ratio combinations in type 2 diabetes mellitus patients previously poorly controlled on different insulin regimens: a multi-centric observational study. *Eur Rev Med Pharmacol Sci*. 2022;26(8):2782-2793.
20. Gonzalez-Galvez G, Diaz-Toscano ML, Llamas-Moreno JF, Fernandez-Rodarte K, Sanudo-Maury ME. Mexican population subanalysis of the lixilan clinical program with the fixed ratio combination of insulin glargine and lixisenatide (iGlarLixi). *J Diabetes Complications*. 2020;34(8):107389.
21. Home PD, Mehta R, Hafidh KAS, et al. Efficacy and safety of iGlarLixi versus IDegAsp: results of a systematic literature review and indirect treatment comparison. *Diabetes Obes Metab*. 2021;23(12):2660-2669.
22. Home P, Blonde L, Kalra S, et al. Insulin glargine/lixisenatide fixed-ratio combination (iGlarLixi) compared with premix or addition of meal-time insulin to basal insulin in people with type 2 diabetes: a systematic review and Bayesian network meta-analysis. *Diabetes Obes Metab*. 2020;22(11):2179-2188.
23. Ilag LL, Kerr L, Malone JK, Tan MH. Prandial premixed insulin analogue regimens versus basal insulin analogue regimens in the management of type 2 diabetes: an evidence-based comparison. *Clin Ther*. 2007;29:1254-1270.
24. Ross SA, Dzida G, Vora J, Khunti K, Kaiser M, Ligthelm RJ. Impact of weight gain on outcomes in type 2 diabetes. *Curr Med Res Opin*. 2011;27(7):1431-1438.
25. Liebl A, Prager R, Binz K, et al. Comparison of insulin analogue regimens in people with type 2 diabetes mellitus in the PREFER study: a randomized controlled trial. *Diabetes Obes Metab*. 2009;11(1):45-52.
26. Jin SM, Kim JH, Min KW, et al. Basal-prandial versus premixed insulin in patients with type 2 diabetes requiring insulin intensification after basal insulin optimization: a 24-week randomized non-inferiority trial. *J Diabetes*. 2016;8(3):405-413.
27. Ligthelm RJ, Gylvin T, DeLuzio T, Raskin P. A comparison of twice-daily biphasic insulin aspart 70/30 and once-daily insulin glargine in persons with type 2 diabetes mellitus inadequately controlled on basal insulin and oral therapy: a randomized, open-label study. *Endocr Pract*. 2011;17(1):41-50.

How to cite this article: Frechtel G, Sauque-Reyna L, Choza-Romero R, Anguiano L, Melas-Melt L, Sañudo-Maury ME. Advancing therapy in people with suboptimally controlled basal insulin-treated type 2 diabetes: Subanalysis of the SoliMix trial in participants in Latin American countries. *Diabetes Obes Metab*. 2023;25(9):2526-2534. doi:10.1111/dom.15125