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ORIGINAL ARTICLE

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Improved patient-reported outcomes with iGlarLixi versus premix BIAsp 30 in people with type 2 diabetes in the SoliMix trial

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Abstract

Aim: To assess patient-reported outcomes (PROs) in the SoliMix trial, which compared the efficacy and safety of iGlarLixi versus BIAsp 30 in people with type 2 diabetes (T2D).

Materials and Methods: SoliMix (EudraCT: 2017-003370-13), a 26-week, open-label study, randomized (1:1) 887 adults with T2D and HbA1c ≥7.5%-≤10.0% (≥58-≤86 mmol/mol) on basal insulin plus oral antihyperglycaemic drugs (OADs) to once-daily iGlarLixi or twice-daily premix insulin, BIAsp 30. PROs were assessed using the Treatment-Related Impact Measure Diabetes (TRIM-D) and Global Treatment Effectiveness Evaluation (GTEE) questionnaires.

Results: Over 26 weeks, iGlarLixi showed greater improvement from baseline versus BIAsp 30 in total TRIM-D score (least squares mean difference [95% confidence interval]: 5.08 [3.69, 6.47]; effect size: 0.32) and in each TRIM-D domain, with the greatest differences seen in diabetes management (8.47 [6.11, 10.84]) and treatment burden (6.95 [4.83, 9.07]). GTEE scores showed a greater proportion of participants and physicians rated a complete or marked improvement of diabetes control with iGlarLixi (80.5%, 82.8%) versus BIAsp 30 (63.3%, 65.1%) at week 26. Post hoc analyses showed that after adjusting for HbA1c, body weight and hypoglycaemia outcomes, iGlarLixi continued to show greater improvements in TRIM-D total scores versus BIAsp 30.

Conclusions: In addition to better glycaemic control, weight benefit and less hypoglycaemia, once-daily iGlarLixi provided improved diabetes management, treatment burden and perceived effectiveness versus twice-daily premix BIAsp 30, further supporting iGlarLixi as an advanced treatment option in people with suboptimally controlled T2D on basal insulin plus OADs.

This article has an accompanied **Plain Language Summary in the Supporting Information** Data S1.

KEYWORDS
basal insulin, GLP-1 analogue, glycaemic control, iGlarLixi, patient-reported outcomes, type 2 diabetes

1 | INTRODUCTION

Treatment options for people with type 2 diabetes (T2D) have expanded over past decades to include glucagon-like peptide-1 receptor agonists (GLP-1 RAs), dipeptidyl peptidase-4 (DPP-4) inhibitors and sodium-glucose co-transporter-2 (SGLT-2) inhibitors.[1,2] Guidelines recommend that diabetes treatment should be individualized based on factors such as clinical characteristics (e.g. age, general health status and the presence of co-morbidities such as cardiovascular disease), treatment priorities (e.g. the balance between glucose control and the need to minimize hypoglycaemia and/or weight gain) and the individual's own preferences.[1,2] Of the advanced treatment options recommended for people with suboptimally controlled T2D on basal insulin, differences in mechanism of action can impact glucose control, body weight and safety outcomes, which all have the potential to influence perceptions of treatment benefit, as well as attitudes contributing to adherence.[2-5]

Premix insulin analogues and basal-bolus treatments are widely used to advance basal insulin, resulting in a complex regimen that involves a greater number of injections and often leads to increased hypoglycaemia and weight gain.[6] Adding a GLP-1 RA to basal insulin results in improved glucose control without weight gain or excess hypoglycaemia risk, and spares the need for additional insulin injections compared with premix or basal-bolus insulin, although it can be associated with increased gastrointestinal adverse events, which commonly diminish over time.[6,7] In addition to the impact of a particular treatment on clinical outcomes, factors that reduce daily treatment burden, such as fewer injections and a reduced requirement for glucose testing, can have a positive impact on daily life and psychological health, and may help treatment adherence.[5,8,9] In this respect, patient-reported outcomes (PROs) can complement clinical findings by providing a broader view that encompasses both the individual and clinical perspectives in diabetes treatment and management.

iGlarLixi has been shown to be an efficacious and well-tolerated treatment option for people with suboptimally controlled T2D on basal insulin, GLP-1 RAs or oral antihyperglycaemic drugs (OADs).[10-13] In those advancing treatment from a basal insulin, once-daily iGlarLixi can provide a simpler alternative to premix or basal-bolus insulin, which require multiple daily injections.

The SoliMix trial was the first randomized head-to-head study to directly compare the efficacy and safety of iGlarLixi with premix insulin BIAsp 30 in adults with suboptimally controlled T2D on basal insulin plus one or two OADs.[10] SoliMix showed that iGlarLixi versus BIAsp 30 was associated with greater HbA1c reduction, weight benefit and lower incidence and rates of hypoglycaemia.[10] In addition to these findings, the SoliMix trial also aimed to assess PROs and it is these outcomes that form the focus of this paper.

2 | MATERIALS AND METHODS

Detailed methods have been previously published.[10,14] In brief, SoliMix was a 26-week, open-label, multicentre, randomized controlled trial that compared once-daily iGlarLixi with twice-daily BIAsp 30. iGlarLixi (Suliqua [Soliqua], Sanofi, Paris) is a fixed-ratio combination of basal insulin glargine 100 U/ml (iGlar) and the short-acting GLP-1 RA, lixisenatide (Lixi); BIAsp 30 (NovoMix 30, Novo Nordisk A/S, Bagsværd, Denmark) is a premix insulin comprising 30% insulin aspart and 70% insulin aspart protamine. The study included a 2-week screening period, a 26-week randomized treatment period and a 3-day post-treatment follow-up period (Figure S1). Participants were adults with T2D and HbA1c in the range of ≥7.5%-≤10.0% (≥58-≤86 mmol/mol), despite receiving stable doses of basal insulin plus one or two OADs (metformin ± SGLT-2 inhibitor) for 3 months, who had a body mass index of ≥20-<40 kg/m^2. Participants were randomized (1:1) to receive once-daily iGlarLixi or twice-daily BIAsp 30. It was recommended that iGlarLixi and BIAsp 30 were titrated weekly, according to their respective labels,[15-18] based on fasting or premeal self-measured plasma glucose, respectively, to a target of 80-110 mg/dl (4.4-6.1 mmol/L). Details of the recommended dose adjustment algorithms for iGlarLixi and BIAsp 30 have been published previously.[10,14]

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

2.1 | PRO endpoints

Two PRO instruments were employed in the SoliMix trial design: the Treatment-Related Impact Measure Diabetes (TRIM-D) and the Global Treatment Effectiveness Evaluation (GTEE). TRIM-D is a validated questionnaire evaluating the spectrum of diabetes treatment impact across the five domains of treatment burden, impact on daily life, management of diabetes, compliance and psychological health.[19,20] TRIM-D consists of five domains and a total score (28 questions). All questions were scored on a five-point Likert-like scale ranging from 1 to 5, with higher numbers indicating better treatment satisfaction/lower impact. Higher TRIM-D scores indicated greater satisfaction with diabetes treatment. TRIM-D was completed by study participants at baseline (week 0), and at weeks 12 and 26. The TRIM-D questions are provided in full in Table S1.[19]

The GTEE is a five-point scale adapted from the Global Evaluation of Treatment Effectiveness,[21] and was used to evaluate treatment effectiveness from both participant and physician perspectives. GTEE

questionnaires were completed at weeks 12 and 26. The participant-rated GTEE scale is a single-item scale in which participants were asked the following question? "Overall, how effective has the treatment been in controlling your diabetes, since the start of study medication?" Participants responded using the following five-point scale: 5. Complete control of diabetes, 4. Marked improvement of diabetes, 3. Discernible, but limited improvement in diabetes, 2. No appreciable change in diabetes or 1. Worsening of diabetes. For the physician-rated GTEE scale, physicians were asked? "Overall, how effective has the treatment been in controlling the patient's diabetes, since the start of study medication?" Effectiveness was rated on the same five-point scale as for the participant GTEE.

2.2 | Statistical analysis

Sample size calculations were based on the primary efficacy objectives and have been described previously.[10,14] The analyses of TRIM-D, participant- and physician-rated GTEE scales were performed on the intention-to-treat (ITT) population, defined as all randomized participants. TRIM-D raw data were transformed to a score ranging from 0 (worst) to 100 (best) using the following formula: Domain score = [(raw score – lowest possible raw score) / possible raw score range] × 100. TRIM-D scores and changes from baseline are presented as descriptive statistics by treatment group per visit for each score.

TRIM-D scores were analysed using a mixed-model repeated measures approach, which included treatment group, randomization strata (screening HbA1c value [<8.0% vs. ≥8.0%], basal insulin dose [<30 U, ≥30 U] and SGLT-2 inhibitor use [Yes, No] at screening), visit and visit-by-treatment group interaction and country as fixed categorical effects, and baseline TRIM-D total score and baseline TRIM-D total score-by-visit interaction as continuous fixed covariates. The effect sizes (ESs) of change from baseline in TRIM-D scores and between-treatment differences in TRIM-D scores were calculated post hoc as follows: least squares (LS) mean change from baseline divided by standard deviation (SD) of change from baseline in each treatment arm; and LS mean difference between treatment arms divided by the common SD of change from baseline. The ESs were assessed using Cohen's ES conventions: large ≥0.80, medium 0.50-0.79, small 0.20-0.49 or negligible <0.20.[22] GTEE findings are presented as the proportion of participants or physicians who reported each level of response to treatment.

Subgroup post hoc descriptive analyses were conducted for TRIM-D total scores according to change from baseline to week 26 in HbA1c (reduction of: 2.0% or more, 1.3% to <2.0%, 0.6% to <1.3%, or 0% to <0.6%; or any % increase), hypoglycaemia (0 or ≥1 event of any symptomatic hypoglycaemia occurring during the 26-week reporting period regardless of plasma glucose measurements) and by reaching a composite target (HbA1c < 7% with no weight gain and no hypoglycaemia). Similar descriptive analyses were conducted with GTEE scores changes. Multivariate analyses were also conducted post hoc for change in TRIM-D score from baseline to week 26. The analysis of covariance model included fixed categorical effects of randomization strata at screening, treatment groups, at least one documented hypoglycaemia (<3.9 mmol/L, <70 mg/dl) from baseline to week 26, as well as fixed continuous variables of TRIM-D total score at baseline, HbA1c change from baseline and body weight change from baseline at week 26.

3 | RESULTS

Overall, 887 participants from 89 centres in 17 countries were randomized, of whom 443 were allocated to iGlarLixi and 444 to BIAsp 30 (ITT population). In total, 428 (96.6%) and 416 (93.7%) participants completed the 26-week treatment period with iGlarLixi and BIAsp 30, respectively. Demographics and baseline characteristics were similar across both treatment groups; these have been previously reported in full[14] and are available in abbreviated form in Table S2.

3.1 | Treatment-Related Impact Measure Diabetes

Mean total TRIM-D scores increased from 68.30 at baseline to 80.46 at week 26 in the iGlarLixi group and from 67.82 to 74.97 in the BIAsp 30 group (Figure 1). For the five individual TRIM-D domains, mean scores increased from baseline in both the iGlarLixi and BIAsp 30 groups, with numerically higher scores favouring iGlarLixi versus BIAsp 30 at weeks 12 and 26 (Figure 1). The LS mean (95% confidence interval [CI]) change from baseline to week 26 for the total TRIM-D score was 11.10 (9.87, 12.34) for iGlarLixi and 6.02 (4.81, 7.23) for BIAsp 30 (Figure 2). The ES of the change of the total TRIM-D score from baseline to week 26 was large for iGlarLixi (0.85) and small for BIAsp 30 (0.43). For the individual domains, the ESs for change from baseline to week 26 for iGlarLixi were either medium (treatment burden, diabetes management, compliance and psychological health) or small (daily life) but were small across all five domains for BIAsp 30 (Figure 2). Comparison of the differences in change from baseline between iGlarLixi and BIAsp 30 at week 26 showed small ESs favouring iGlarLixi over BIAsp 30 for the total score (LS mean difference [95% CI] 5.08 [3.69, 6.47]; ES 0.32), treatment burden (LS mean difference [95% CI] 6.95 [4.83, 9.07], ES 0.30) and diabetes management (LS mean difference [95% CI] 8.47 [6.11, 10.84], ES 0.34). Between-treatment comparisons showed LS mean differences (95% CIs) of 3.90 (1.72, 6.08), 3.22 (1.38, 5.06) and 3.37 (1.59, 5.15) for the daily life, compliance and psychological health domains; ESs showed these differences to have small but meaningful clinical impact (0.18, 0.16 and 0.17, respectively) (Figure 2).

3.2 | Global Treatment Effectiveness Evaluation

By week 12, 71.8% of participants in the iGlarLixi group and 59.0% of participants in the BIAsp 30 group reported that their treatment resulted in either complete control of diabetes or marked improvement in diabetes (Figure 3A). The proportion reporting complete

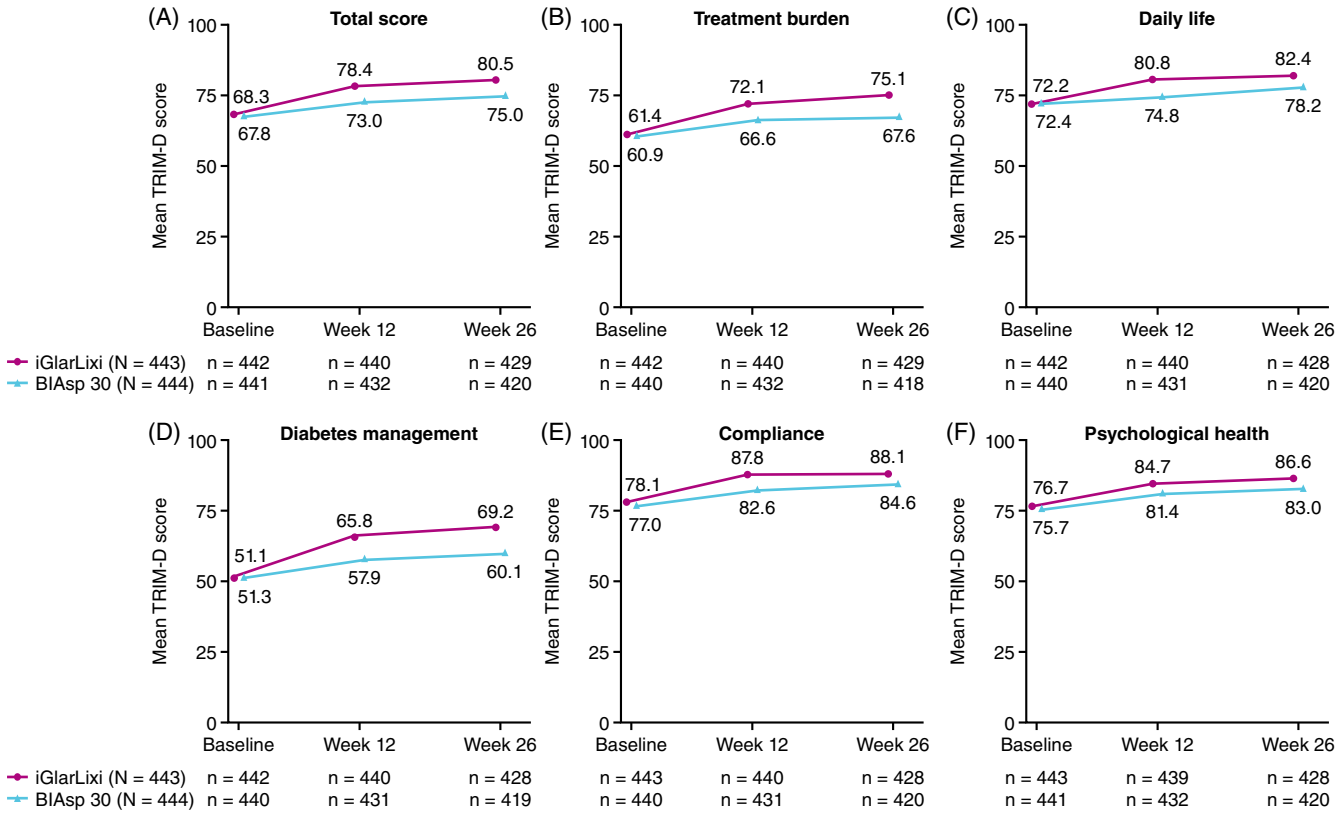

FIGURE 1 Mean TRIM-D scores over the treatment period: (A) Total scores and scores by (B) Treatment burden, (C) Daily life, (D) Diabetes management, (E) Compliance and (F) Psychological health domains (ITT population). ITT, intention-to-treat; TRIM-D, Treatment-Related Impact Measure Diabetes

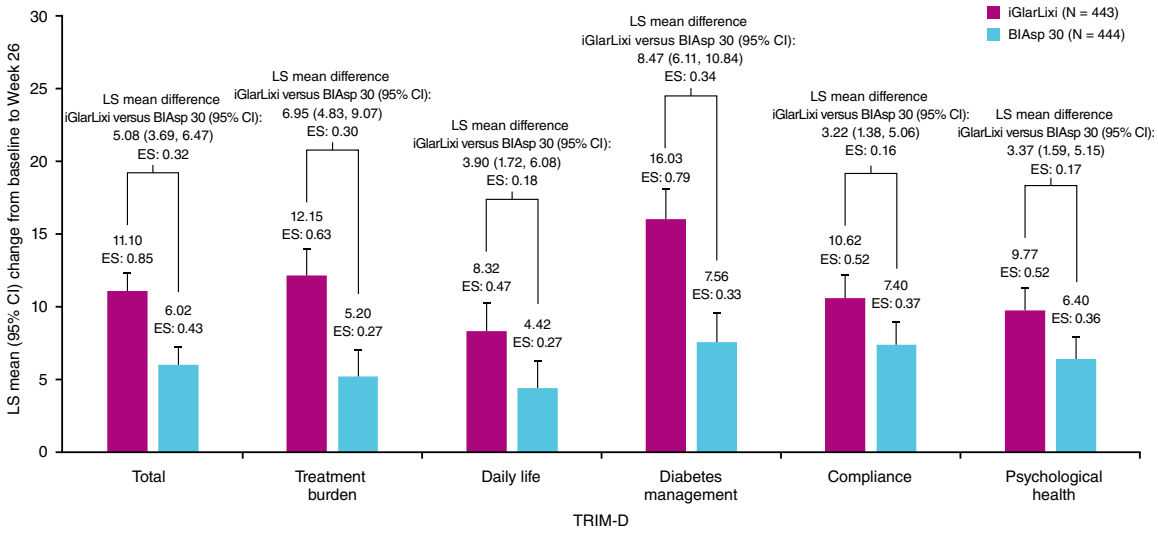

FIGURE 2 TRIM-D score change from baseline to week 26 (ITT population). Magnitude of effect as per Cohen's conventions: negligible, <0.20; small, 0.20-0.49; medium, 0.50-0.79; large, ≥0.80. CI, confidence interval; ES, effect size; ITT, intention-to-treat; LS, least squares; TRIM-D, Treatment-Related Impact Measure Diabetes

control or a marked improvement in their diabetes increased to 80.5% and 63.3%, respectively, at week 26. Likewise, physicians reported complete control or a marked improvement in diabetes in 82.8% of participants in the iGlarLixi group and 65.1% of the BIAsp 30 group, at week 26 (Figure 3B). Only one participant in the iGlarLixi group (0.2%) and five participants in the BIAsp 30 group (1.2%) reported a worsening of diabetes from baseline to week 26 (Table S3).

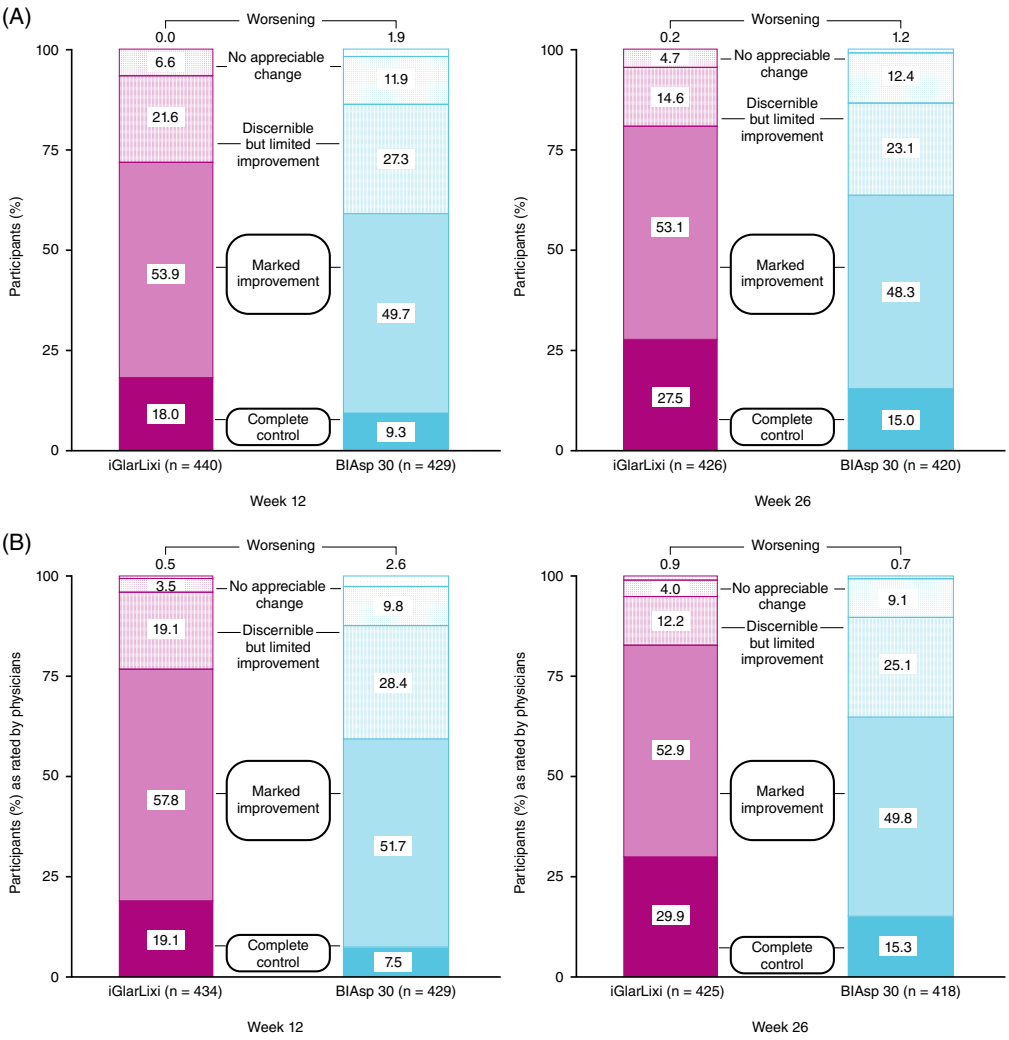

FIGURE 3 (A) Participant-reported and (B) Physician-reported GTEE ratings (ITT population). ITT population: iGlarLixi, N = 443; BIAsp 30, N = 444. GTEE, Global Treatment Effectiveness Evaluation; ITT, intention-to-treat

3.3 | PROs by clinical outcomes

When mean change from baseline to week 26 in TRIM-D total scores was assessed according to change in HbA1c, change in body weight, hypoglycaemia incidence and reaching the composite target (HbA1c < 7% with no weight gain and no hypoglycaemia [<3.9 mmol/L, <70 mg/dl]) (Figure 4), there was an overall trend of a greater difference from baseline in TRIM-D scores in participants receiving iGlarLixi compared with those receiving BIAsp 30 across all subgroups. The improvements in TRIM-D scores in the iGlarLixi group were approximately double those of the respective BIAsp 30 group according to HbA1c subgroups, except for participants with reductions in HbA1c of 2% or more, for whom improvements in TRIM-D scores were similar for iGlarLixi and BIAsp 30 (Figure 4A). Improvements in TRIM-D scores were numerically greater with iGlarLixi versus BIAsp 30 across all categories of body weight change. The greatest treatment difference was seen in participants with a decrease of more than 0 to 2 kg in body weight, and the smallest treatment difference was seen in those with an increase of 0 to less than 2 kg (Figure 4B). Improvements in TRIM-D score were also numerically greater for iGlarLixi versus BIAsp 30 in both those who experienced at least one hypoglycaemia event and those who did not experience any (Figure 4C). With regards to reaching the composite target (HbA1c < 7% with no weight gain and no hypoglycaemia), improvements in TRIM-D were numerically greater for iGlarLixi versus BIAsp 30 in both categories (those who reached the composite target and those who did not) (Figure 4D).

Multivariate analyses of total TRIM-D change from baseline were performed to investigate the PRO benefits of iGlarLixi versus BIAsp 30 after adjusting for baseline factors and clinical outcomes. Model parameters are listed in Table S4. When adjusted for change in HbA1c, change in body weight and hypoglycaemia incidence, iGlarLixi continued to show greater improvements in TRIM-D total score versus BIAsp 30, with an LS mean difference (95% CI) of 4.57 (2.92, 6.21) ($P < .0001$). Additionally, this model indicated that, regardless of treatment, total TRIM-D scores at week 26 were associated with change from baseline in HbA1c ($P < .0001$) and change in body weight ($P = .0304$), but not with hypoglycaemia incidence ($P = .7527$).

The highest proportion of participants who rated their treatment as enabling complete control of their diabetes according to the GTEE scale was in the HbA1c subgroup of those with a decrease of 2% or more (iGlarLixi, 43.9% [58/132] and BIAsp 30, 29.5% [23/78]) (Figure 5A). By contrast, for those participants who did not experience

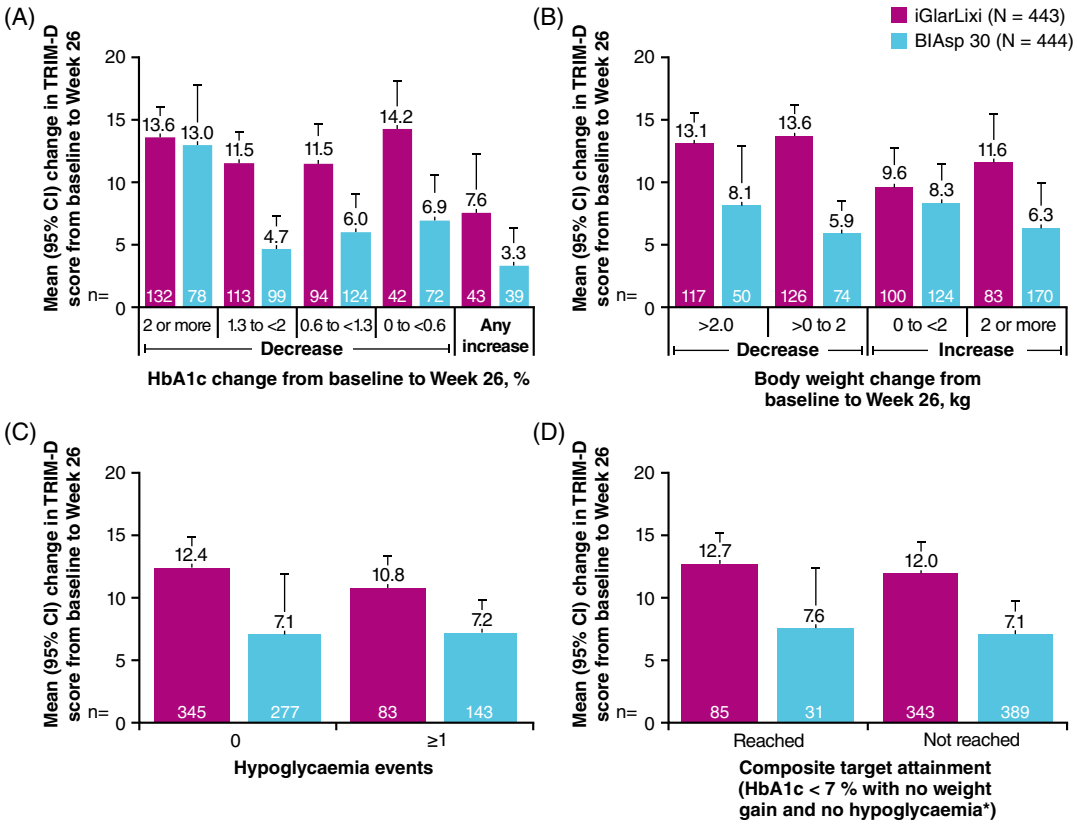

FIGURE 4 Change from baseline to week 26 in TRIM-D total scores by change in (A) HbA1c and (B) Body weight, and by (C) Hypoglycaemia incidence, and (D) Reaching a composite target (HbA1c < 7% with no weight gain and no hypoglycaemia*) (ITT population). *Defined as plasma glucose < 3.9 mmol/L (<70 mg/dl). CI, confidence interval; ITT, intention-to-treat; TRIM-D, Treatment-Related Impact Measure Diabetes

an improvement in HbA1c, 4.7% (2/43) and 5.1% (2/39) indicated that iGlarLixi and BIAsp 30, respectively, provided complete control of their diabetes. Patterns of GTEE responses were generally similar irrespective of body weight change from baseline to week 26 or hypoglycaemia incidence during the treatment period (Figure 5B,C).

4 | DISCUSSION

The SoliMix study showed that in people with suboptimally controlled T2D on basal insulin plus OADs, once-daily iGlarLixi provided better glycaemic control, with weight benefit, and less hypoglycaemia, than twice-daily premix BIAsp 30.[10] The present analysis complements these findings by reporting the perspectives of those who directly experience the impact of diabetes treatment on a daily basis, and is the first time that PROs and treatment satisfaction data for iGlarLixi in comparison with BIAsp 30 have been reported.

In this study, TRIM-D scores showed that initiation of iGlarLixi was associated with greater improvement in overall treatment-related impact, satisfaction, treatment burden and diabetes management compared with premix BIAsp 30. Greater changes in TRIM-D scores were generally seen with iGlarLixi versus premix BIAsp 30 regardless of clinical outcomes, with multivariate analyses showing that these improvements remained after adjustments were made for glycaemic control, weight and hypoglycaemia. The multivariate analysis also revealed that, regardless of which treatment participants received, improvements in total TRIM-D scores were associated with changes in HbA1c and body weight, but not hypoglycaemia incidence. In addition, GTEE scores at week 26 showed that a greater proportion of participants and physicians perceived a complete or marked improvement of diabetes control with iGlarLixi (81% and 83%) compared with premix BIAsp 30 (63% and 65%).

Diabetes treatment adherence can be impacted by burdensome or complicated regimens, multiple daily injections, fear of hypoglycaemia and fear of weight gain.[4,5,9,23] Once-daily treatment with iGlarLixi offers a simpler, more convenient treatment regimen that is less burdensome compared with twice-daily BIAsp 30 and therefore may potentially encourage better real-world treatment adherence and persistence. Indeed, improved adherence and persistence with treatment and a lower risk of treatment discontinuation have been observed when comparing iGlarLixi with a free-dose combination of basal insulin and GLP-1 RA, as well as in comparisons of iGlarLixi with a basal plus prandial insulin, and with premix insulin.[24-26]

One of the strengths of this study is that the PRO measures capture participant perspectives on diabetes treatment that are not provided by clinical trial outcomes. The multinational design is also a strength of the SoliMix study as it allows assessment of PRO data

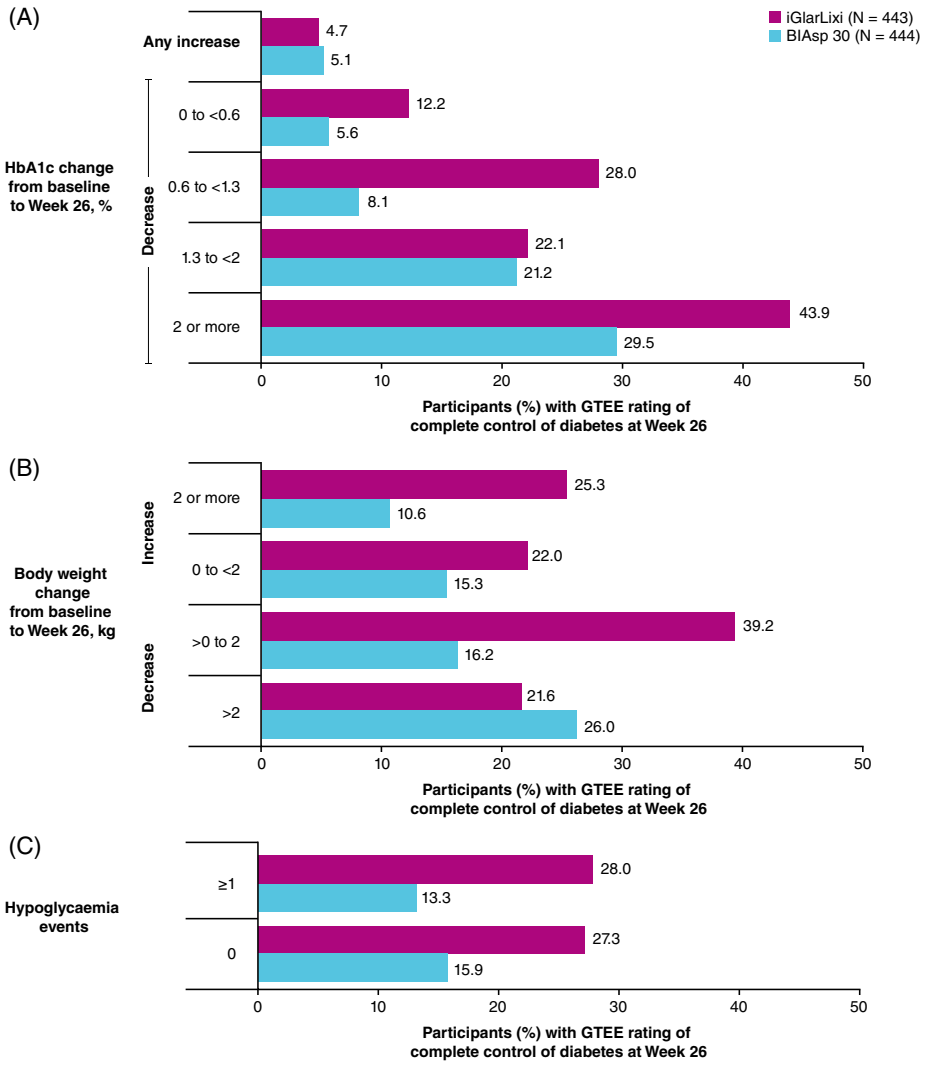

FIGURE 5 Participant GTEE rating of complete control of diabetes by change in (A) HbA1c and (B) Body weight, and by (C) Hypoglycaemia incidence from baseline to week 26 (ITT population). HbA1c change: reductions of 2.0% or more (iGlarLixi, n = 132; BIAsp 30, n = 78), 1.3% to <2.0% (iGlarLixi, n = 113; BIAsp 30, n = 99), 0.6% to <1.3% (iGlarLixi, n = 93; BIAsp 30, n = 124), or 0% to <0.6% (iGlarLixi, n = 41; BIAsp 30, n = 72); or any % increase (iGlarLixi, n = 43; BIAsp 30, n = 39). Body weight change: reductions greater than 2 kg (iGlarLixi, n = 116; BIAsp 30, n = 50) or >0 to 2 kg (iGlarLixi, n = 125; BIAsp 30, n = 74); or increases of 0 to <2 kg (iGlarLixi, n = 100; BIAsp 30, n = 124) or 2 kg or more (iGlarLixi, n = 83; BIAsp 30, n = 170). Hypoglycaemia events shown for symptomatic hypoglycaemia occurring during the 26-week reporting period. No hypoglycaemia events (iGlarLixi, n = 344; BIAsp 30, n = 277); ≥1 hypoglycaemic event (iGlarLixi, n = 82; BIAsp 30, n = 143). GTEE, Global Treatment Effectiveness Evaluation; ITT, intention-to-treat

from a variety of regions, countries and cultures. One limitation of the study is that, because of the difficulty in masking injectable diabetes treatments, the SoliMix trial was open label; it is therefore possible that participant preconceptions about the two therapies may have affected their rating of treatments. It is also recognized that comparing once-daily iGlarLixi with twice-daily BIAsp 30 would probably have had a positive impact on TRIM-D scores for iGlarLixi, in particular on the treatment burden domain, which has questions directly relating to satisfaction with ease and convenience of medication. The dosing frequencies, however, were chosen based on labelling instructions and aimed at maintaining results that would more closely resemble use and outcomes in clinical practice. As an additional potential limitation, it is also recognized that the study does not report minimal important difference (MID) data as the MID has not been fully established for TRIM-D results, and thus the magnitude of effect was calculated using Cohen's ES conventions.

In conclusion, alongside the previously reported better glycaemic control, weight benefit and less hypoglycaemia,[10] once-daily iGlarLixi provided better PROs compared with twice-daily premix BIAsp 30 in people with suboptimally controlled T2D on basal insulin plus OADs. These advantages with iGlarLixi are likely to encourage greater persistence with therapy and thus may lead to better disease management and treatment outcomes.

AUTHOR CONTRIBUTIONS

All the named authors meet the International Committee of Medical Journal Editors criteria for authorship for this article, 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 the authors participated in the study design. WHP, EL, AA, CN and MC contributed to the concept and design of the post hoc analyses. MC was responsible for data collection. All the 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.

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CONFLICT OF INTEREST

WHP has served as a consultant for Eli Lilly, Novo Nordisk and Sanofi. FG has served as an advisor for AstraZeneca; has served as a research investigator for Eli Lilly; has served as a speaker for AstraZeneca and Eli Lilly; has served as a consultant for Abbott, AstraZeneca, Boehringer Ingelheim, Eli Lilly, Merck Sharp & Dohme, Novo Nordisk, Roche Diabetes and Sanofi; and has received grants from Eli Lilly, Lifescan and Takeda. 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. KW has acted as a speaker for Sanofi. EL, MC, AA and CN are employees and stakeholders of Sanofi. RJM has served on advisory panels or as a speaker at educational meetings for Sanofi and Novo Nordisk.

DATA AVAILABILITY STATEMENT

Qualified researchers may request access to participant-level data and related documents. Participant-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 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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