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ORIGINAL ARTICLE

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Hypoglycaemia events with iGlarLixi versus premix biphasic insulin aspart 30 (BIAsp 30) in people with type 2 diabetes advancing from basal insulin: An analysis of the SoliMix trial

Rory J. McCrimmon MD[1] | Philip Home DM[2] | Alice Cheng MD[3] | Francesco Giorgino MD[4] | Vivian Fonseca MD[5] | Elisabeth Souhami MD[6] | Agustina Alvarez MD[7] | Pascaline Picard MSc[8] | Julio Rosenstock MD[9]

[1]Division of Systems Medicine, School of Medicine, University of Dundee, Dundee, UK

[2]Translational and Clinical Research Institute, Newcastle University, Newcastle upon Tyne, UK

[3]Department of Medicine, University of Toronto, Toronto, Ontario, Canada

[4]Department of Emergency and Organ Transplantation, Section of Internal Medicine, Endocrinology, Andrology and Metabolic Diseases, University of Bari Aldo Moro, Bari, Italy

[5]School of Medicine, Tulane University, New Orleans, Louisiana

[6]Sanofi, Paris, France

[7]Sanofi, Buenos Aires, Argentina

[8]IVIDATA Life Sciences, Levallois-Perret, France

[9]Dallas Diabetes Research Center at Medical City, Dallas, Texas

Correspondence
Rory J. McCrimmon, MD, Division of Systems Medicine, School of Medicine, University of Dundee, Ninewells Hospital & Medical School Dundee, DD1 9SY, UK.
Email: r.mccrimmon@dundee.ac.uk

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Abstract

Aims: To explore details of the incidence and rates of daytime and nocturnal hypoglycaemia, levels of hypoglycaemia, and relationship to glycated haemoglobin (HbA1c), when comparing iGlarLixi versus premixed biphasic insulin aspart 30 (BIAsp 30) in the SoliMix randomized controlled trial.

Materials and Methods: This exploratory analysis of SoliMix used logistic regression and negative binomial regression analyses to assess between-treatment differences in the incidence and rates of hypoglycaemia by time of day. A negative binomial model was used to derive estimated annualized hypoglycaemia rates as a function of HbA1c.

Results: iGlarLixi was associated with lower incidence and rates of American Diabetes Association Level 2 (<54 mg/dL [<3.0 mmol/L]) hypoglycaemia during both night and day versus BIAsp 30. Incidence and rates of Level 1 (<70 to ≥54 mg/dL [<3.9 to ≥3.0 mmol/L]) hypoglycaemia were also mostly shown to be reduced with iGlarLixi versus BIAsp 30. Severe (Level 3) events were too few for analysis (n = 3). iGlarLixi was associated with lower modelled event rates of Level 2 and Level 1 hypoglycaemia over a wide range of HbA1c levels versus BIAsp 30.

Conclusions: These results show that the lower HbA1c levels and weight benefit seen with iGlarLixi versus premixed BIAsp 30 in people with type 2 diabetes advancing their basal insulin therapy in the SoliMix trial are also accompanied by a lower risk of hypoglycaemia at any time of day and across a broad range of HbA1c levels.

KEYWORDS
BIAsp 30, fixed-ratio combination, hypoglycaemia, iGlarLixi, SoliMix, type 2 diabetes

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

1 | INTRODUCTION

Hypoglycaemia can have a significant impact on the physical and mental health of people with type 2 diabetes (T2D).[1,2] Additionally, the perceived risk of hypoglycaemia is a barrier to timely advancement of insulin therapy from basal insulin alone for healthcare professionals and can hinder proper insulin titration.[3,4] Combined, these obstacles become a major limiting factor in achieving optimal glucose levels. American Diabetes Association (ADA) Level 2 hypoglycaemia (<54 mg/dL [<3.0 mmol/L]) has been recognized as clinically meaningful, because hypoglycaemia of this degree can cause cognitive impairment and repeated exposure can lead to impaired hypoglycaemia awareness and an increased risk of severe (ADA Level 3) hypoglycaemia.[5,6] Furthermore, there is evidence suggesting that severe hypoglycaemia or events <50 mg/dL (<2.8 mmol/L) are associated with an increased risk of mortality.[6-9] Experiencing even "mild" (controlled by the individual with no impact on daily activities) to "moderate" (daily activities interrupted but self-managed) hypoglycaemic events has a major impact on people with T2D, leading to reduced treatment satisfaction scores and significantly worse therapy adherence.[10,11]

People with T2D will often require therapy advancement as their disease progresses to maintain their target glycated haemoglobin (HbA1c) levels.[12,13] When advancing from basal insulin alone, a number of therapeutic options are available, including coformulations of intermediate-acting and short-acting insulin ("premixed insulins"), or fixed-ratio combinations (FRCs) of a basal insulin plus a glucagon-like peptide-1 receptor agonist (GLP-1RA).[12,13] The choice made should reflect individual preferences and consider the benefits and risks of each approach, including hypoglycaemia risk.

iGlarLixi combines the complementary actions of basal insulin glargine 100 U/mL (iGlar) and the GLP-1RA lixisenatide (Lixi)[14-17] and has been shown to provide greater HbA1c reduction than either iGlar or Lixi alone,[14,17] along with fewer gastrointestinal adverse events than Lixi[17] and similar risk of hypoglycaemia versus iGlar. SoliMix (EudraCT: 2017-003370-13) was the first randomized head-to-head study directly comparing the efficacy and safety of iGlarLixi with a premixed insulin, biphasic insulin aspart 30 (BIAsp 30), in adults with T2D advancing from basal insulin + metformin ± sodium-glucose cotransporter-2 (SGLT2) inhibitors.[18] Primary results from SoliMix demonstrated that once-daily iGlarLixi provided significantly greater HbA1c reduction with weight benefit compared with twice-daily BIAsp 30.[18] iGlarLixi was also associated with lower anytime incidence and rates of ADA Level 2 (<54 mg/dL [<3.0 mmol/L]) and Level 1 (<70 to ≥54 mg/dL [<3.9 to ≥3.0 mmol/L]) hypoglycaemia,[18] alongside better patient-reported outcomes.[19]

The primary aim of the present analysis was to further explore the differences in incidence and rates of hypoglycaemia between iGlarLixi and premixed BIAsp 30 in the SoliMix trial.

2 | METHODS AND DESIGN

The present study was a comprehensive exploratory analysis of hypoglycaemia events from the SoliMix study.[18] SoliMix (EudraCT 2017-003370-13) was an open-label, randomized, controlled, 26-week, parallel-group, multicentre, Phase 3b study comparing the efficacy and safety of iGlarLixi with premixed insulin BIAsp 30 (30% insulin aspart and 70% insulin aspart protamine) in adults (≥18 years) with T2D advancing from basal insulin + metformin ± SGLT2 inhibitors (HbA1c ≥7.5% [≥59 mmol/mol] and ≤10.0% [≤86 mmol/mol]). Detailed methods including primary, key secondary, and safety endpoints plus the specifics of the multiple testing approach have been previously reported.[18,20] Briefly, the two primary endpoints (with statistical adjustment for this) were noninferiority of iGlarLixi versus BIAsp 30 in HbA1c reduction or superiority in body weight change from baseline to Week 26. Secondary outcomes assessed superiority of iGlarLixi versus BIAsp 30 for composite outcomes of target HbA1c <7.0% (<53 mmol/mol) achievement without weight gain, or without weight gain and without hypoglycaemia, and superiority of HbA1c reductions using a hierarchical testing procedure. Safety endpoints in the SoliMix trial included incidence and rates of hypoglycaemia assessed according to the following definitions: ADA Level 1 (<70 to ≥54 mg/dL [<3.9 to ≥3.0 mmol/L]), ADA Level 2 (<54 mg/dL [<3.0 mmol/L]), and severe (ADA Level 3) hypoglycaemia.[6,20] The SoliMix study was conducted with written informed consent in accordance with the ethical principles set out by the Declaration of Helsinki, and the International Conference on Harmonization guidelines for good clinical practice, and all applicable laws, rules, and regulations.

Participants were randomized 1:1 to either iGlarLixi (Suliqua® [Soliqua®]; Sanofi, Paris, France) or premixed BIAsp 30 (30% insulin aspart and 70% insulin aspart protamine; NovoMix® 30 [Novo Nordisk A/S, Bagsværd, Denmark]). Starting insulin doses were based on prior insulin doses as per labelling instructions. Background oral glucose-lowering drug (OGLD) therapy was maintained throughout the study.[18,20]

The present analysis explored the following endpoints: incidence and event rates of ADA Level 1–3 hypoglycaemia by time of day (including anytime hypoglycaemia [24 h], nocturnal hypoglycaemia [analysed between bedtime and waking and between 12:00 AM and 6:00 AM], and daytime hypoglycaemia [between 6:01 AM and 11:59 PM]). Estimated event rates of ADA Level 1, ADA Level 2 and severe hypoglycaemia were examined over the study period (Weeks 0–26) as a function of HbA1c at Week 26. Additional analyses of event rates as a function of HbA1c were also performed over Weeks 0 to 12 as a function of HbA1c at Week 12 and over Weeks 13 to 26 as a function of HbA1c at Week 26. These time periods were selected based on the data presented in Figure S1, showing greater insulin dose changes within the first 12 weeks of the study compared with the following 14 weeks, seemingly reflecting more active dose titration over Weeks 0 to 12. While there were no defined titration and maintenance periods in the protocol, more frequent office and telephone consultations occurred during the first 12 weeks of the study.

2.1 | Data analysis and statistics

All hypoglycaemia analyses were based on the safety population (all randomized participants who received ≥1 dose of open-label iGlarLixi or BIAsp 30). Odds ratios (ORs) and the corresponding 95%

TABLE 1 Key participant characteristics at baseline and Week 26 from the SoliMix trial[18]

Demographic/clinical characteristic	iGlarLixi	BIAsp 30
	(n = 443)	(n = 444)
Baseline characteristics (randomized population)		
Age, years	59.8 ± 10.3	59.8 ± 10.0
Sex: female, n (%)	219 (49.4)	226 (50.9)
Body mass index, kg/m^2	29.7 ± 4.7	30.0 ± 5.1
Duration of type 2 diabetes, years	13.0 ± 7.1	13.0 ± 7.4
Study endpoints (ITT population)		
HbA1c, mmol/mol		
Baseline	71 ± 7	70 ± 7
Week 26	56 ± 12	58 ± 11
HbA1c, %		
Baseline	8.6 ± 0.7	8.6 ± 0.7
Week 26	7.3 ± 1.1	7.5 ± 1.0
Body weight, kg		
Baseline	80.7 ± 16.5	82.2 ± 18.5
Week 26	80.2 ± 16.6	83.4 ± 19.0
FPG, mmol/L		
Baseline	8.4 ± 2.4	8.3 ± 2.3
Week 26	7.2 ± 2.4	8.1 ± 2.8
Average basal insulin dose, U/d[a]		
Baseline	26.4 ± 6.2	33.6 ± 11.0
Week 26	39.7 ± 12.0	58.2 ± 23.6

Note: Data are mean ± SD unless stated otherwise.
Abbreviations: BIAsp 30, biphasic aspart insulin 30 (30% insulin aspart and 70% insulin aspart protamine); FPG, fasting plasma glucose; HbA1c, glycated haemoglobin; iGlarLixi, fixed-ratio combination of insulin glargine 100 U/mL and the glucagon-like peptide-1 receptor agonist, lixisenatide; ITT, intention-to-treat; LS, least squares; SD, standard deviation; SE, standard error; U, units.
[a]Baseline value obtained within the 3 days before randomization.

confidence intervals (CIs) for iGlarLixi versus BIAsp 30 for each type of hypoglycaemic event were estimated using a logistic regression model employing the treatment group and randomization strata as factors. Rate ratios (RRs) of hypoglycaemia per participant-year (PPY) and the corresponding 95% CI were estimated using a negative binomial regression model with a log-link function, and the log of the time period in which a hypoglycaemic episode is considered treatment-emergent as offset. The model included fixed-effect terms for treatment and randomization strata. A negative binomial model was used to derive the estimated annualized rates (number of events PPY) as a function of HbA1c at Week 26, with the total number of events that occurred from baseline to Week 26 as the response variable, treatment and HbA1c at Week 26 as covariates, and log-transformed period duration (from baseline to Week 26) as an offset variable. A model including a treatment-by-HbA1c interaction term was implemented to assess hypoglycaemia during Weeks 0 to 26, Weeks 0 to 12, and Weeks 13 to 26 as a function of HbA1c levels achieved at Weeks 12, 26 and 26, respectively.

3 | RESULTS

3.1 | Key results from the SoliMix trial

As noted above, the protocol-defined results from SoliMix have been previously reported.[18] Key participant demographics alongside baseline and end-of-study findings for the two primary endpoints, fasting plasma glucose (FPG) and daily insulin dose, are listed in Table 1. Briefly, iGlarLixi resulted in lower HbA1c levels with weight benefit compared with BIAsp 30 in people with T2D advancing from basal insulin plus OGLDs.

3.2 | Hypoglycaemia events by time of day

3.2.1 | Overall and daytime hypoglycaemia

For both anytime (24 h) and daytime (06:01 AM to 11:59 PM) periods, the incidence (OR 0.45 [95% CI 0.28, 0.73] and OR 0.49 [95% CI 0.29, 0.81], respectively) and event rates (RR 0.40 [95% CI 0.23, 0.71] and RR 0.45 [95% CI 0.25, 0.83], respectively) of ADA Level 2 hypoglycaemia were lower with iGlarLixi versus BIAsp 30 (Figure 1). ADA Level 1 hypoglycaemia was also improved (Figure 1).

Only three severe hypoglycaemic episodes were reported: one in the iGlarLixi group and two in the BIAsp 30 group, all occurring in the daytime period.

3.2.2 | Nocturnal hypoglycaemia

For nocturnal hypoglycaemia (both 12:00 AM–6:00 AM and between bedtime and waking), the incidence (OR 0.32 [95% CI 0.12, 0.90] and OR 0.37 [95% CI 0.16, 0.84], respectively) and event rates (RR 0.30 [95% CI 0.10, 0.88] and RR 0.28 [95% CI 0.11, 0.71], respectively) of ADA Level 2 hypoglycaemia were lower with iGlarLixi versus BIAsp 30 (Figure 1). ADA Level 1 hypoglycaemia findings were inconsistent (Figure 1).

3.3 | Hypoglycaemia as a function of HbA1c

Very few participants recorded HbA1c values below 5.0% (31 mmol/mol) (iGlarLixi, n = 2; BIAsp 30, n = 0) or greater than 97 mmol/mol 11.0% (97 mmol/mol) (iGlarLixi, n = 1; BIAsp 30, n = 2). Consequently, modelled hypoglycaemia event data below and above these

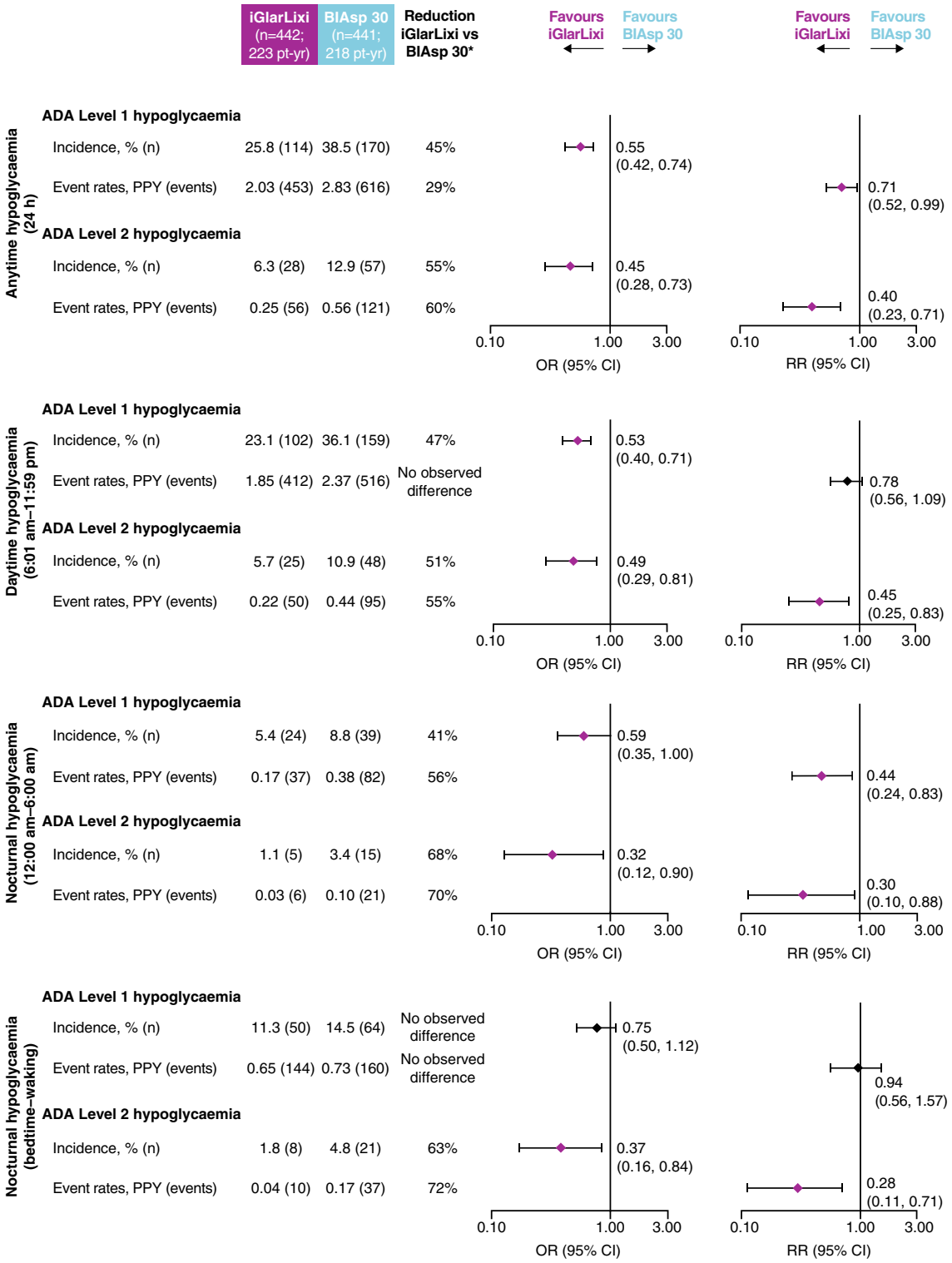

FIGURE 1 Incidence and event rates of hypoglycaemia at any time of day (24 h, first panel; adapted from Rosenstock et al,[18] during the daytime (6:01 AM–11:59 PM, second panel), and nocturnally (12:00 AM–6:00 AM, third panel; bedtime–waking, fourth panel) over the 26-week treatment period (safety population). *Relative odds reduction for incidence; relative rate reduction for rates. Some hypoglycaemia events could not be classified as either daytime or nocturnal due to their time of occurrence not being recorded. American Diabetes Association (ADA) Level 1 hypoglycaemia: <70 to ≥54 mg/dL (<3.9 to ≥3.0 mmol/L); ADA level 2 hypoglycaemia: <54 mg/dL (<3.0 mmol/L). BIAsp 30, biphasic insulin aspart 30 (30% insulin aspart and 70% insulin aspart protamine); CI, confidence interval; iGlarLixi, fixed-ratio combination of insulin glargine 100 U/mL and the glucagon-like peptide-1 receptor agonist, lixisenatide; n, number of participants; OR, odds ratio; PPY, per participant-year; Pt-yr, participant-years; RR, rate ratio

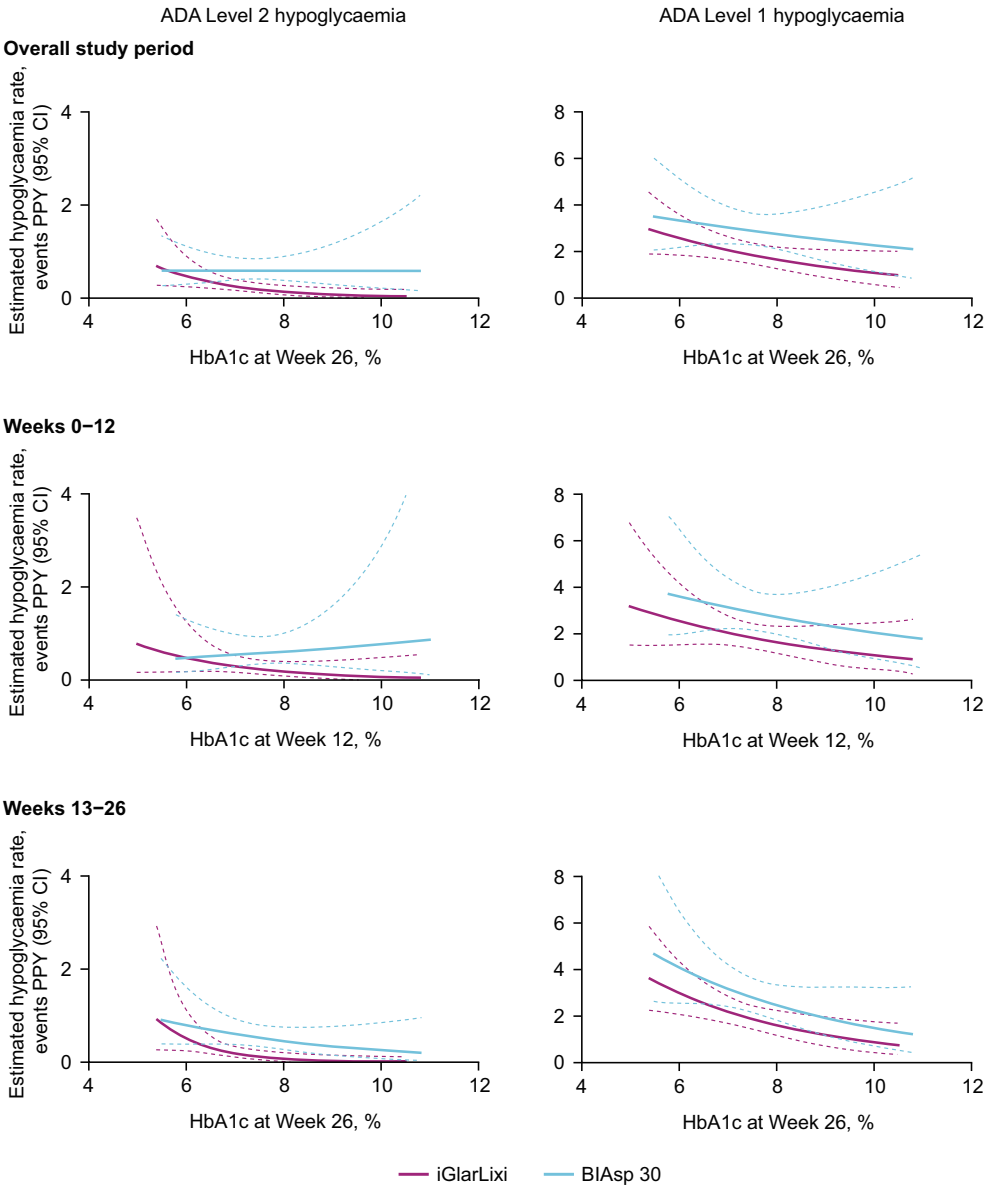

FIGURE 2 Estimated hypoglycaemia event rate during Weeks 0 to 26 (overall study period; first panel), Weeks 0 to 12 (second panel), and Weeks 13 to 26 (third panel) as a function of HbA1c (safety population). Vertical scales differ. Dashed lines represent the 95% CIs. ADA, American Diabetes Association; BIAsp 30, biphasic insulin aspart 30 (30% insulin aspart and 70% insulin aspart protamine); CI, confidence interval; iGlarLixi, fixed-ratio combination of insulin glargine 100 U/mL and the glucagon-like peptide-1 receptor agonist, lixisenatide; PPY, per participant-year

ranges are not shown as data were too few to allow for meaningful interpretation. Estimated event profiles for ADA Level 2 and Level 1 hypoglycaemia during Weeks 0 to 26 (the overall treatment period) were lower in participants receiving iGlarLixi compared with BIAsp 30 as a function of HbA1c at Week 26, with uncertainty below HbA1c ≈6.5% (≈48 mmol/mol) and above HbA1c ≈9.0% (≈75 mmol/mol) Figure 2). Similar patterns were seen for estimated event profiles for ADA Level 2 and Level 1 hypoglycaemia as a function of HbA1c at Week 12 for Weeks 0 to 12 and Week 26 for Weeks 13 to 26 compared with Weeks 0 to 26 (Figure 2). Interestingly, estimated ADA Level 2 hypoglycaemia event rate with BIAsp 30 over Weeks 0 to 26 was consistent across the whole range of analysed HbA1c levels (Figure 2). This appears to be due to the juxtaposition of low and high estimated event rates at low HbA1c levels during Weeks 0 to 12 and Weeks 13 to 26, respectively. This pattern was not observed for iGlarLixi or for ADA Level 1 hypoglycaemia with either treatment. Severe hypoglycaemic events (n = 3) were too infrequent to allow for meaningful analysis.

4 | DISCUSSION

The primary results of the SoliMix trial found that the FRC of iGlarLixi resulted in lower HbA1c and body weight benefit with less risk of anytime (24-h) hypoglycaemia compared with the premixed insulin analogue, BIAsp 30, in people with T2D advancing from basal insulin therapy plus one or two OGLDs.[18] The present analysis of hypoglycaemia during SoliMix shows that participants receiving once-daily iGlarLixi had reduced incidence and event rates of nocturnal (12:00 AM–6:00 AM, and between bedtime and waking) and daytime (6:01AM –11:59 PM) ADA Level 2 hypoglycaemia compared with twice-daily premixed BIAsp 30 (Figure 1). Differences were also found between treatments in incidence and event rates of the less clinically relevant ADA Level 1 hypoglycaemia, although not all estimates were statistically significant. During Weeks 0 to 26 (the overall study period) and Weeks 0 to 12 and 13 to 26, corresponding with the periods of more active dose titration and maintenance, respectively, estimated event

rates of ADA Level 2 and Level 1 hypoglycaemia were also lower with iGlarLixi than premixed BIAsp 30 across the broad spread of HbA1c levels at endpoint (Figure 2), from marked hyperglycaemia to recommended target range.

American Diabetes Association Level 2 hypoglycaemia is defined as a serious and clinically important condition resulting in cognitive impairment that requires prompt action to be addressed.[5,6] Aside from the well-characterized health risks posed by acute hypoglycaemia,[21,22] continued exposure to such low glucose levels can lead to a cycle of defective glucose counter-regulation and impaired hypoglycaemia awareness.[23,24] Nocturnal hypoglycaemia is of great concern to people with insulin-treated diabetes and their families, with more than 50% of severe hypoglycaemic episodes in people with insulin-treated diabetes occurring at night.[25] Nocturnal hypoglycaemia is frequently unrecognized due to suppression of counter-regulatory responses during deep sleep[26] and, in people with type 1 diabetes, has been shown to impact recognition of hypoglycaemia,[27] as well as exerting negative effects on mood and wellbeing the following day.[25] Furthermore, in people with T2D, nonsevere hypoglycaemia may also have as big an impact on fear of hypoglycaemia as severe episodes, affecting quality of life and interfering with effective glucose management by stalling further insulin titration.[22,28] It is therefore encouraging that iGlarLixi demonstrated lower hypoglycaemia risk to a clinically useful extent compared with premixed BIAsp 30 in the SoliMix trial,[18] including reduced incidence and rates of Level 2 and Level 1 hypoglycaemia during both the daytime and nocturnal periods.

The Dual Action of Liraglutide and Insulin Degludec in Type 2 Diabetes VII (DUAL VII) study assessed the efficacy and safety of IDegLira versus basal-bolus insulin and showed a 61% lower risk of confirmed (<56 mg/dL [<3.1 mmol/L]) symptomatic hypoglycaemia incidence with IDegLira versus basal-bolus insulin (19.8% versus 52.6%).[29] Similarly, the rate of hypoglycaemia was 89% lower with IDegLira compared with basal-bolus insulin (1.07 vs 8.17 events PPY of exposure, respectively).[29] Additionally, while no randomized clinical trials have directly compared hypoglycaemia incidence and rates for iGlarLixi versus a basal-bolus insulin regimen, a meta-analysis of 13 randomized clinical trials reported a 54% lower risk of hypoglycaemia with a GLP-1RA added to basal insulin therapy versus basal-plus or basal-bolus insulin regimens.[30] Finally, a propensity score-matched analysis comparing 195 participants randomized to iGlarLixi in the LixiLan-L study[14] with 195 participants randomized to a basal-bolus insulin regimen in the GetGoal Duo-2 study[31] reported a significant estimated treatment difference in the ratio of documented symptomatic hypoglycaemia (<54 mg/dL) events PPY for basal-bolus insulin versus iGlarLixi of 2.85.[32]

There are several potential reasons that may explain the lower hypoglycaemia risk seen with iGlarLixi compared with premixed BIAsp 30, the primary of which is the ability of iGlarLixi to achieve greater HbA1c changes with lower daily insulin doses.[18] In the SoliMix trial, iGlarLixi resulted in a lower insulin dose at Week 26 versus premixed BIAsp 30, while also demonstrating a statistically superior change in HbA1c over the same time period.[18] This is probably attributable to the complementary modes of action of the basal insulin (iGlar) and short-acting GLP-1RA (Lixi) components of iGlarLixi, with iGlar predominantly acting to lower FPG levels and Lixi correspondingly targeting postprandial plasma glucose,[33] thereby providing meal-time coverage. Importantly, the enhanced insulin release and inhibition of glucagon release responses facilitated by Lixi are glucose-regulated, and in combination with reducing the rate of gastric emptying, lower the risk of hypoglycaemia.[34,35] This complementary action has been suggested to have a beneficial effect on glycaemic variability in individuals with T2D receiving iGlarLixi compared with iGlar or Lixi alone,[36] the occurrence of which has been associated with increased hypoglycaemia risk.[37-39] In contrast, premixed BIAsp 30 provides a mixture of prandial and protaminated intermediate-acting insulin.[40,41] Protaminated insulins may not be fully solubilized by proper shaking of the insulin pen[42] and in addition, protaminated insulins can interact with any remaining meal-time insulin in the subcutaneous injection depot, thereby delaying return to basal insulin levels postprandially, a phenomenon known as the "shoulder effect".[43] This can contribute to increased glycaemic variability and the known hypoglycaemia risk with premixed insulins. Given the known limitations of premixed insulins, it could be argued that the lower risk of hypoglycaemia observed with iGlarLixi compared with premixed BIAsp 30 could be anticipated. Nevertheless, despite newer alternative advancement options from basal insulin being available, premixed insulins are still widely used globally as an initial injectable or when advancing from basal insulin in people with T2D,[44-47] regardless of associations with increased hypoglycaemia risk and weight gain compared with optimized basal insulin.[48-50] As such, the present analysis adds to the findings of the SoliMix primary study in highlighting that iGlarLixi can provide a suitable alternative to premixed insulin. Further studies of interest would be to compare iGlarLixi with other options for advancing therapy from a basal insulin, such as basal plus prandial insulin regimens.

The strengths of this analysis include that it is based on participant-level data from the first trial that directly compared an FRC with premixed insulin using a randomized controlled design. The study is clinically relevant in context and design, as it included a T2D population advancing from a stable dose of basal insulin plus one or two OGLDs recruited from countries and regions where premixed insulin is most often used. In order to be more reflective of typical clinical practice, there was no surveillance committee to enforce titration in either treatment arm and the degree of follow-up was conducted on a more pragmatic basis than is typically seen in other randomized controlled trials. In SoliMix, unlike indirect treatment comparisons and network meta-analyses,[30,32,51] hypoglycaemia definitions were standardized, and comparisons are therefore reliable.

A possible limitation of this analysis is the differences in dose and titration protocols. While based on the regulatory prescribing information and following how these formulations are used in clinical practice, weekly dose adjustments based on mean fasting self-measured plasma glucose (SMPG) from the last 3 days for iGlarLixi and on the lowest pre-meal SMPG value of the last 3 days for premixed BIAsp 30 may have resulted in more cautious titration with premixed BIAsp 30.[18] Conversely, as premixed BIAsp 30 was administered twice daily versus once daily with iGlarLixi, this could have led to more frequent

SMPG measurements in the BIAsp 30 arm, potentially leading to more recorded hypoglycaemic events with premixed BIAsp 30. It should also be noted that, while once- or twice-daily SMPG measurements provided a more pragmatic study design, there are consequently no seven-point SMPG profiles to facilitate the comparison of pre- and postmeal glucose levels between therapies. While these differences in SMPG measurement and subsequent dose titration may impact comparisons of hypoglycaemia, it is likely to have only been relevant for comparisons of asymptomatic hypoglycaemia. Indeed, data from the SoliMix trial show that hypoglycaemia incidence and rates were consistently lower with iGlarLixi versus BIAsp 30, except for asymptomatic hypoglycaemia (data not shown) and Level 3 hypoglycaemia (for which numbers were very low). Other limitations include that the higher FPG observed with premixed BIAsp 30 versus iGlarLixi in the SoliMix trial may reflect reduced dose titration as a result of increased hypoglycaemia, and it is therefore possible that a more aggressive treat-to-target study may have demonstrated even greater differences between the two treatment arms. While not a limitation of this particular subanalysis, it is also worth noting that the study was open-label in design, as therapies could not be masked. Finally, the hypoglycaemia as a function of HbA1c analyses were performed post hoc and the results should be interpreted with caution.

In conclusion, this exploratory analysis suggests that individuals with T2D advancing from basal insulin plus one or two OGLDs in the SoliMix trial had consistently lower risk of hypoglycaemia with iGlarLixi compared with premixed BIAsp 30 throughout the study period, regardless of time of day or HbA1c level achieved by the end of the study. Combined with the primary findings of SoliMix, which showed greater HbA1c reduction and weight benefit with iGlarLixi versus premixed BIAsp 30,[18] these results suggest that iGlarLixi may be a suitable therapy advancement option from basal insulin.

AUTHOR CONTRIBUTIONS

All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article and had full access to all the data in this study and take complete responsibility for the integrity of the data and accuracy of the data analysis. All authors participated in the interpretation of the data, the writing, reviewing, and editing of the manuscript, and had final responsibility for approving the published version.

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CONFLICT OF INTEREST

Rory McCrimmon has served on advisory panels or as a speaker at educational meetings for Sanofi and Novo Nordisk. Alice Cheng has received honoraria for speaking or consulting from Abbott, AstraZeneca, Bayer, Bausch, Boehringer Ingelheim, Dexcom, Eli Lilly, Janssen, Insulet, Medtronic, Merck, Novo Nordisk, Sanofi, HLS Therapeutics and Takeda, and has participated in clinical trials supported by Boehringer Ingelheim, Eli Lilly, Sanofi and Applied Therapeutics. Philip Home, or institutions with which he is associated, have received funding for his research, advisory and lecturing activities from Sanofi and Novo Nordisk, and also from other GLP-1RA and insulin manufacturers including AstraZeneca, Boehringer Ingelheim, GlaxoSmithKline and Merck (MSD). Francesco Giorgino has served as an advisor for AstraZeneca, Eli Lilly and Novo Nordisk, as a research investigator for Eli Lilly and Roche Diabetes Care, as a speaker for AstraZeneca and Eli Lilly, and as a consultant for AstraZeneca, Boehringer Ingelheim, Eli Lilly, Merck Sharp & Dohme, Novo Nordisk, Roche Diabetes Care and Sanofi, and has received grants from Eli Lilly, Lifescan and Roche Diabetes Care. Vivian Fonseca has received research support (to Tulane) from Bayer and Boehringer Ingelheim, honoraria for consulting and lectures from Takeda, Novo Nordisk, Sanofi-Aventis, Eli, Abbott, AstraZeneca, Intarcia and Asahi, stock options from Microbiome Technologies, Insulin Algorithms and BRAVO4Health, and has stock in Amgen. Elisabeth Souhami and Agustina Alvarez are employees of Sanofi and may hold shares/stock options in the company. Pascaline Picard is an employee of IVIDATA Life Sciences working as an external contractor on behalf of Sanofi. Julio Rosenstock has served on advisory panels for Applied Therapeutics, Boehringer Ingelheim, Eli Lilly, Intarcia, Janssen, Novo Nordisk, Oramed, Sanofi, Hanmi and Zealand, and has received research support from Applied Therapeutics, AstraZeneca, Boehringer Ingelheim, Eli Lilly, Hanmi Genentech, Intarcia, Janssen, Lexicon, Merck, Novartis, Novo Nordisk, Oramed, Pfizer and Sanofi.

PEER REVIEW

The peer review history for this article is available at https://publons.com/publon/10.1111/dom.14825.

DATA AVAILABILITY STATEMENT

Qualified researchers may request access to patient-level data and related study 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 process for requesting access can be found at: https://www.vivli.org/.

ORCID

Rory J. McCrimmon https://orcid.org/0000-0002-3957-1981
Francesco Giorgino https://orcid.org/0000-0001-7372-2678
Vivian Fonseca https://orcid.org/0000-0002-3381-7151
Julio Rosenstock https://orcid.org/0000-0001-8324-3275

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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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