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Switching to iGlarLixi versus continuation of a daily or weekly glucagon-like peptide-1 receptor agonist (GLP-1 RA) in insufficiently controlled type 2 diabetes: A LixiLan-G trial subgroup analysis by HbA1c and GLP-1 RA use at screening

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Abstract

Aim: In people with type 2 diabetes (T2D) requiring intensification beyond glucagon-like peptide-1 receptor agonists (GLP-1 RAs) and oral antihyperglycaemic drugs (OADs), switching to iGlarLixi was shown to be efficacious and well-tolerated in the LixiLan-G trial. This exploratory analysis of LixiLan-G assessed the efficacy and safety of switching to iGlarLixi versus continuing GLP-1 RA therapy, stratified by screening HbA1c level (≥7.0 to ≤7.5 %; >7.5 to ≤8.0 %; >8.0 to ≤9.0 % [≥53 to ≤58 mmol/mol; >58 to ≤64 mmol/mol; >64 to ≤75 mmol/mol]) and previous GLP-1 RA regimen at screening (once/twice daily or once weekly).

Materials and Methods: Endpoints for all subgroups included: change in HbA1c, achievement of HbA1c <7 % and hypoglycaemia events. Adverse events and changes in fasting plasma glucose (FPG), 2-hour postprandial plasma glucose (PPG), 2-hour PPG excursion and weight were analysed according to previous GLP-1 RA regimen.

Results: Switching to iGlarLixi in all subgroups resulted in significantly greater reductions in HbA1c and proportions of participants reaching HbA1c <7 % (including with no documented hypoglycaemia) at Week 26 compared with continued GLP-1 RA treatment. Switching to iGlarLixi also led to significantly greater reductions in FPG, 2-hour PPG, and 2-hour PPG excursion, irrespective of previous GLP-1 RA regimen. Rates of hypoglycaemia were low, but slightly higher in those who switched to iGlarLixi for all subgroups. Modest weight gain was seen with iGlarLixi, irrespective of previous GLP-1 RA regimen.

Conclusions: Switching to iGlarLixi improved glycaemic control, regardless of screening HbA1c or previous GLP-1 RA type, offering a simple, efficacious and well-tolerated treatment intensification option for people with T2D inadequately controlled by GLP-1 RAs and OADs.

KEYWORDS
basal insulin, GLP-1 analogue, glycaemic control, incretin therapy, insulin therapy, type 2 diabetes

1 | INTRODUCTION

Updated guidelines and consensus from the American Diabetes Association and the European Association for the Study of Diabetes recommend that, in most people with type 2 diabetes (T2D) uncontrolled by two or more oral antihyperglycaemic drugs (OADs), the preferred initial injectable therapy is a glucagon-like peptide-1 receptor agonist (GLP-1 RA), with the addition of basal insulin therapy as required.[1,2] Combination therapy with a GLP-1 RA plus basal insulin may be considered as an initial injectable therapy in patients with glycated haemoglobin (HbA1c) >10 % (>86 mmol/mol) and/or patients with HbA1c >2 % (>23 mmol/mol) above target.[2] The sequential combination of basal insulin and GLP-1 RA therapy has been extensively studied, demonstrating complementary mechanisms of action and clinical effect.[2] GLP-1 RAs improve postprandial plasma glucose (PPG) excursions by stimulating insulin secretion, reducing glucagon secretion and, in particular for those that are rapid-acting such as lixisenatide, by decelerating gastric emptying.[2] Basal insulins improve fasting glucose mainly through reduction of hepatic glucose production.

Simplification of treatment regimens in people with T2D has been shown to offer medication adherence benefits.[3] Fixed-ratio combinations (FRCs) of a basal insulin and a GLP-1 RA enable administration of both therapies simultaneously, and thereby reduce the number of injections required per day compared with administering these two therapies separately. FRCs have also shown robust HbA1c reductions with mitigation of the weight gain usually observed with insulin therapy, no increased hypoglycaemic risk compared with basal insulin, and a reduction in gastrointestinal adverse events (AEs) compared with GLP-1 RA therapy alone – primarily due to the slow titration of the GLP-1 RA concomitant with basal insulin adjustments.[4,5]

iGlarLixi, a once-daily injectable FRC of basal insulin glargine 100 units/mL (iGlar) and the short-acting GLP-1 RA lixisenatide (Lixi), has been shown to be well tolerated and efficacious in people with T2D inadequately controlled by either OADs (LixiLan-O study) or basal insulin (LixiLan-L study).[4,5]

LixiLan-G was a multinational, open-label, active-controlled, Phase 3, 26-week study, which randomized participants with T2D uncontrolled by GLP-1 RA and OAD therapy to either continue with their current GLP-1 RA treatment or to switch to iGlarLixi.[6] Switching to iGlarLixi was shown to offer a very effective and well-tolerated treatment option in those requiring intervention beyond GLP-1 RAs and OADs. In total, 62% of those participants who switched to iGlarLixi reached target HbA1c <7 % (<53 mmol/mol) within 26 weeks, compared with 26% of those who continued GLP-1 RA therapy, despite monitoring and encouraging adherence to the GLP-1 RA regimen.

The objective of this exploratory analysis was to evaluate the endpoints of the LixiLan-G study by screening HbA1c and by the type of preceding daily or weekly GLP-1 RA regimen to determine whether these baseline factors influenced outcomes seen when switching to iGlarLixi.

To address this objective, a post hoc exploratory analysis of the LixiLan-G study was performed, which assessed the efficacy and safety of switching to iGlarLixi versus continuing GLP-1 RA therapy by screening HbA1c level (≥7.0 to ≤7.5 %; >7.5 to ≤8.0 %; >8.0 to ≤9.0 % [≥53 to ≤58 mmol/mol; >58 to ≤64 mmol/mol; >64 to ≤75 mmol/mol]) and by previous GLP-1 RA treatment regimen at screening (once-daily [QD] or twice-daily [BID] GLP-1 RA versus once-weekly [QW] GLP-1 RA).

2 | MATERIALS AND METHODS

2.1 | Study design and participants

The methodology of the LixiLan-G study (NCT02787551) has been described previously.[6] In brief, this was a randomized, open-label, active-controlled, parallel-group, 26-week, phase 3 trial in adults with T2D with suboptimal glycaemic control despite receiving the maximum tolerated dose of a QD, BID or QW GLP-1 RA in combination with OADs.

Eligibility criteria included: diagnosis of T2D at least 1 year prior to screening visit; HbA1c 7 % to 9 % (53 to 75 mmol/mol); body mass index >20 or ≤40 kg/m^2 at screening; treatment with the maximum tolerated doses of QD liraglutide or BID exenatide for at least 4 months prior to screening, or QW exenatide extended release or albiglutide or dulaglutide for at least 6 months prior to screening; treatment with metformin, with or without pioglitazone, with or without a sodium-glucose co-transporter-2 (SGLT-2) inhibitor, all at a stable dose for at least 3 months prior to screening; no history of hypoglycaemia unawareness; no previous treatment with insulin in the year prior to screening visit; no treatment with other antidiabetic drugs within 3 months, including sulphonylureas; and amylase and/or lipase levels less than three times the upper limit of normal or calcitonin 5.9 pmol/L (≥20 pg/mL).

After a screening period of ≤2 weeks, participants were randomized (1:1) to switch to iGlarLixi or to remain on their current GLP-1 RA regimen, with reinforced adherence closely monitored throughout the study. Randomization was stratified by HbA1c value (HbA1c <8.0 %, ≥8.0 % [<64 mmol/mol, ≥64 mmol/mol) and GLP-1 RA subtype (QD/BID, QW formulations), and existing OAD therapies were not modified. iGlarLixi was self-administered using one of two prefilled SoloSTAR (Sanofi, Paris, France) disposable pen-injector devices that allowed insulin glargine titration from 10 to 60 U while limiting the lixisenatide dose to ≤20 μg/day. Depending on the insulin dose required, two pens were available. Individuals with lower insulin requirements used a pen that allowed daily combination doses between 10 U (10 U iGlar/5 μg Lixi) and 40 U (40 U iGlar/20 μg Lixi), with an iGlar to Lixi ratio of 2:1. This pen was used to start treatment at a 10-U dose (10 U iGlar/5 μg Lixi). For daily combination doses between 30 U (30 U iGlar/10 μg Lixi) and 60 U (60 U iGlar/20 μg Lixi), a second pen with an iGlar to Lixi ratio of 3:1 was used, allowing a higher dose of iGlar. Once initiated, iGlarLixi was titrated to attempt to reach and maintain a fasting self-monitored plasma glucose target of 4.4 to 5.6 mmol/L (80 to 100 mg/dL), with the participants switching to the 3:1 pen if a dose above 40 U was required.

2.2 | Outcomes

This exploratory analysis assessed the efficacy and safety of switching to iGlarLixi versus continuing GLP-1 RA therapy, stratified by screening HbA1c level (≥7.0 % to ≤7.5 % [≥53 to ≤58 mmol/mol]; >7.5 % to ≤8.0 % [>58 to ≤64 mmol/mol]; >8.0 % to ≤9.0 % [>64 to ≤75 mmol/mol]) and by previous GLP-1 RA regimen (QD/BID, or QW GLP-1 RA use at screening). Subgroup stratifications were selected to ensure approximately equal distribution of study completers between subgroups.

The primary endpoint assessed was HbA1c change from screening (by HbA1c subgroup) or baseline (by previous GLP-1 RA regimen) to Week 26. Secondary endpoints in each subgroup analysis included proportion of participants achieving HbA1c <7 % (<53 mmol/mol) at Week 26 and proportion of participants achieving HbA1c <7 % at Week 26 with no documented symptomatic hypoglycaemia (<3.0 mmol/L [<54 mg/dL]). In addition, changes from baseline to Week 26 in fasting plasma glucose (FPG), 2-hour PPG, 2-hour PPG excursion during a standardized liquid meal test and body weight were analysed by previous GLP-1 RA regimen.

Safety endpoints included AEs and incidence and rates of documented symptomatic hypoglycaemia (≤3.9 mmol/L [≤70 mg/dL] and <3.0 mmol/L [<54 mg/dL]). AEs were not assessed by screening HbA1c levels.

2.3 | Data analysis and statistics

Efficacy analyses were evaluated using the modified intention-to-treat (mITT) population, defined as all randomized participants with a baseline assessment and at least one postbaseline assessment of any primary or secondary efficacy variable. The safety population included all randomized participants who received at least one dose of open-label investigational medicinal product, regardless of the amount of treatment administered.

The treatment effects across the subgroups were estimated for the change from baseline to Week 26 in HbA1c in the mITT population, using the mixed-effect model with a repeated measures approach, with treatment group, randomization strata at screening (HbA1c <8.0 %, ≥8.0 %; GLP-1 RA subtype QD/BID, QW formulations), scheduled visit, subgroup factor, treatment-by-visit, treatment-by-subgroup factor, visit-by-subgroup factor, treatment-by-visit-by-subgroup factor, and world region as fixed effects, and using the baseline HbA1c value-by-visit interaction as a covariate. The adjusted estimates of treatment mean differences (iGlarLixi vs GLP-1 RA) with standard errors (SEs) and 95% confidence intervals (CIs) were provided as appropriate across the subgroups. The randomization strata factor of HbA1c category or GLP-1 RA category was omitted from the model when it corresponded to the subgroup factor being analysed.

Differences in FPG and weight were analysed using a similar model to that used for HbA1c. Differences in PPG and PPG excursion were analysed using an analysis of covariance model with treatment groups, randomization strata of HbA1c (<8.0 %, ≥8.0 %) at Visit 1 (Week −2), and world region as fixed effects, and either baseline 2-hour PPG or baseline 2-hour PPG excursion, respectively, as a covariate. Safety analyses were performed using descriptive analysis.

2.4 | Ethics and participant consent

The study was designed and monitored in accordance with Good Clinical Practice guidelines, the International Conference on Harmonization, and the Declaration of Helsinki. Institutional review boards or ethics committees at each study site approved the protocol. Each participant provided written informed consent.

3 | RESULTS

3.1 | Participant disposition and baseline characteristics

Overall, 514 participants were randomized: 257 participants to each treatment group. Baseline characteristics were similar between subgroups; mean age was 59 to 60 years, 43% to 55% of participants were women, mean duration of diabetes was 10.5 to 11.5 years and 7% to 15% of participants were using SGLT-2 inhibitors at screening (Table 1). Greater proportions of participants with screening HbA1c >8.0 % were on QD/BID formulations of GLP-1 RAs (65.4%) prior to screening than participants with screening HbA1c ≤7.5 % (53.0%).

Of the 505 participants in the mITT population, 303 (60.0%) were on QD/BID GLP-1 RAs and 202 (40.0%) were on QW GLP-1 RA at screening. Of the participants on QD/BID GLP-1 RA regimens, 91.4% were administered liraglutide and 8.6% were administered exenatide. For those on QW GLP-1 RAs, 50.0% were prescribed dulaglutide, 45.5% were prescribed extended-release exenatide and 4.5% were prescribed albiglutide. In total, 165 (32.7%) had HbA1c ≥7.0 % to ≤7.5 % at screening, 150 (29.7%) had HbA1c >7.5 % to ≤8.0 % and 190 (37.6%) had HbA1c >8.0 % to ≤9 %.

3.2 | Change in HbA1c and HbA1c target achievement by screening HbA1c

Mean reduction in HbA1c from screening to Week 26 was greater for participants who switched to iGlarLixi than for those who remained on GLP-1 RAs, irrespective of screening HbA1c ($P < 0.0001$ for all subgroups; Figure 1). Mean ± standard deviation (SD) HbA1c at Week 26 was lower in each screening HbA1c subgroup for those who switched to iGlarLixi (≥7.0 % to ≤7.5 %: 6.6 ± 0.7 %; >7.5 % to ≤8.0 %: 6.6 ± 0.7 %; >8.0 % to ≤9.0 %: 7.0 ± 0.8 %) compared with those who remained on GLP-1 RAs (≥7.0 % to ≤7.5 %: 7.2 ± 0.6 %; >7.5 % to ≤8.0 %: 7.3 ± 0.7 %; >8.0 % to ≤9.0 %: 7.7 ± 0.9 %).

Irrespective of screening glycaemic control, HbA1c target achievement at Week 26 was greater in those receiving iGlarLixi than

TABLE 1 Baseline characteristics and disease characteristics by subgroup, randomized population

Baseline characteristic or disease characteristic	Previous GLP-1 RA regimen subgroup		Screening HbA1c subgroups		
	QD/BID regimen (N = 307)	QW regimen (N = 207)	≥7.0 to ≤7.5 %; ≥53 to ≤58 mmol/mol (N = 168)	>7.5 to ≤8.0 %; >58 to ≤64 mmol/mol (N = 155)	>8.0 to ≤9.0 %; >64 to ≤75 mmol/mol (N = 191)
Age, years	59.9 ± 10.0	59.2 ± 10.0	59.6 ± 9.7	60.4 ± 10.3	59.0 ± 10.0
Women, n (%)	150 (48.9)	94 (45.4)	93 (55.4)	69 (44.5)	82 (42.9)
BMI, kg/m^2	32.7 ± 4.38	33.1 ± 4.39	33.5 ± 4.19	32.5 ± 4.40	32.6 ± 4.50
Duration of T2D, years	11.5 ± 6.90	10.5 ± 6.57	11.0 ± 6.57	10.9 ± 6.69	11.4 ± 7.05
Duration of GLP-1 RA treatment, years	2.24 ± 2.07	1.41 ± 1.17	1.88 ± 1.68	2.03 ± 2.03	1.82 ± 1.72
HbA1c at screening					
%	7.92 ± 0.55	7.81 ± 0.53	7.27 ± 0.17	7.79 ± 0.14	8.47 ± 0.27
mmol/mol	63 ± 6	62 ± 6	56 ± 2	62 ± 2	69 ± 3
GLP-1 RA use by type at screening, n (%)					
QD/BID formulation	307 (100.0)	0	89 (53.0)	93 (60.0)	125 (65.4)
Liraglutide QD	280 (91.2)	0	80 (47.6)	84 (54.2)	116 (60.7)
Exenatide BID	27 (8.8)	0	9 (5.4)	9 (5.8)	9 (4.7)
QW formulation	0	207 (100.0)	79 (47.0)	62 (40.0)	66 (34.6)
Dulaglutide	0	105 (50.7)	40 (23.8)	31 (20.0)	34 (17.8)
Exenatide ER	0	93 (44.9)	35 (20.8)	28 (18.1)	30 (15.7)
Albiglutide	0	9 (4.3)	4 (2.4)	3 (1.9)	2 (1.0)
Pioglitazone use at screening, n (%)	14 (4.6)	20 (9.7)	12 (7.1)	11 (7.1)	11 (5.8)
SGLT-2 inhibitor use at screening, n (%)	22 (7.2)	30 (14.5)	17 (10.1)	18 (11.6)	17 (8.9)

Note: Data are mean ± SD unless otherwise stated.
Abbreviations: BMI, body mass index; ER, extended-release; GLP-1 RA, glucagon-like peptide-1 receptor agonist; HbA1c, glycated haemoglobin; SD, standard deviation; SGLT-2, sodium glucose co-transporter; T2D, type 2 diabetes mellitus.

those remaining on GLP-1 RA treatment; 53% to 69% of those switching to iGlarLixi had achieved HbA1c <7 % by Week 26 (Figure 2A). Target achievement with no documented symptomatic hypoglycaemia (<3.0 mmol/L [<54 mg/dL]) was also higher in those switching to iGlarLixi than in those remaining on a GLP-1 RA in each subgroup (Figure 2B). Results in each subgroup were consistent with those observed in the overall mITT population.

3.3 | Change in HbA1c and HbA1c target achievement by previous GLP-1 RA regimen

Irrespective of previous GLP-1 RA regimen, participants who switched to iGlarLixi had a greater reduction in HbA1c from baseline to Week 26, compared with those who remained on GLP-1 RAs ($P < 0.0001$ for all subgroups; Figure 1). Mean ± SD HbA1c at Week 26 was lower in each GLP-1 RA regimen subgroup for those who switched to iGlarLixi (QD/BID: 6.8 ± 0.8 %; QW: 6.7 ± 0.7 %) compared with those who remained on GLP-1 RAs (QD/BID: 7.4 ± 0.9 %; QW: 7.4 ± 0.7 %).

Furthermore, for previous QD/BID and QW GLP-1 RA regimen subgroups, HbA1c <7 % target achievement at Week 26 was greater amongst those switching to iGlarLixi (61% and 63%, respectively) compared with those remaining on GLP-1 RAs (28% and 22%, respectively; Figure 2A). Target achievement with no documented symptomatic hypoglycaemia (<3.0 mmol/L [<54 mg/dL]) was also higher in those switching to iGlarLixi compared with those remaining on GLP-1 RA in both subgroups (Figure 2B). Results in each subgroup were consistent with those observed in the overall mITT population.

3.4 | Changes in FPG, PPG and PPG excursion by previous GLP-1 RA regimen

Participants switching to iGlarLixi showed greater mean reductions in FPG from baseline to Week 26 than participants who remained on GLP-1 RAs, both for those receiving QD/BID GLP-1 RA regimens (LS mean difference ± SE: −1.6 ± 0.2 mmol/L; $P < 0.0001$) and those on QW GLP-1 RA regimens (LS mean difference ± SE: −1.8 ± 0.3 mmol/L; $P < 0.0001$) at screening (Figure 3A). The same pattern was also seen for 2-hour PPG and 2-hour PPG excursion. The LS mean difference ± SE between switching to iGlarLixi versus

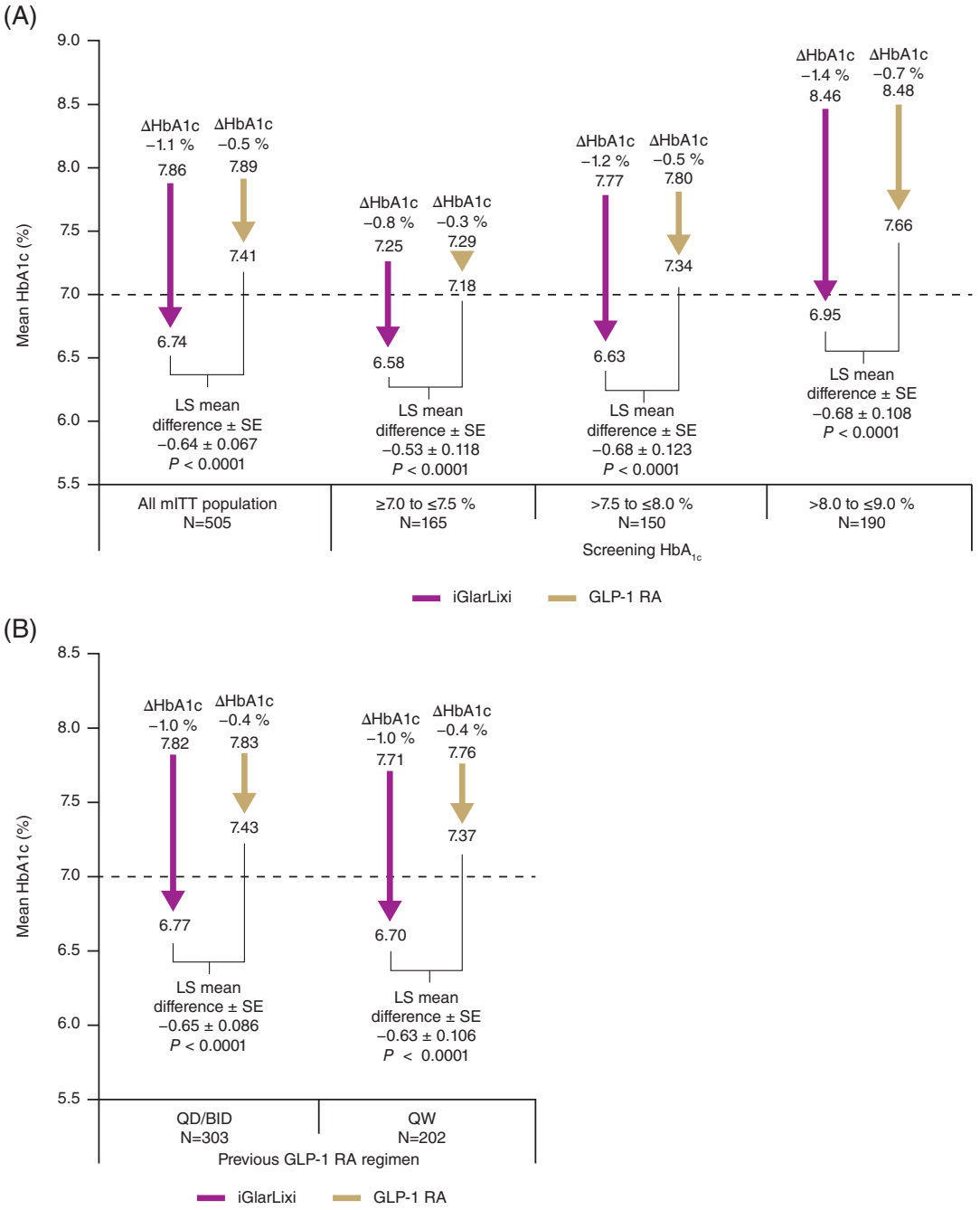

FIGURE 1 Change in mean glycated haemoglobin (HbA1c) (A) from screening to week 26 by HbA1c subgroup and (B) from baseline to Week 26 by previous glucagon-like peptide-1 receptor agonist (GLP-1 RA) regimen subgroups in the modified intention-to-treat (mITT) population (mixed model repeated measures). ΔHbA1c indicates least squares (LS) mean change from (A) screening to Week 26 or (B) baseline to Week 26. *Abbreviations:* BID, twice daily; QD, once daily; QW, once weekly; SE, standard error

remaining on GLP-1 RAs for change in 2-hour PPG from baseline to Week 26 was −2.6 ± 0.4 mmol/L for those on QD/BID GLP-1 RA regimens ($P < 0.0001$) and −3.2 ± 0.4 mmol/L for those on QW regimens ($P < 0.0001$) at screening (Figure 3B). The LS mean difference ± SE for change in 2-hour PPG excursion from baseline to Week 26 was −0.7 ± 0.3 mmol/L for those on QD/BID GLP-1 RA regimens ($P = 0.0251$) and −1.4 ± 0.4 mmol/L for those on QW regimens ($P = 0.0002$) at screening (Figure 3C).

3.5 | Change in weight by previous GLP-1 RA regimen

Mean ± SD baseline weight was comparable between participants who switched to iGlarLixi and those continuing GLP-1 RAs, irrespective of previous GLP-1 RA regimen. In participants receiving QD/BID GLP-1 RA regimens at screening, LS mean ± SE change in weight from baseline to Week 26 was +2.1 ± 0.3 kg in those who

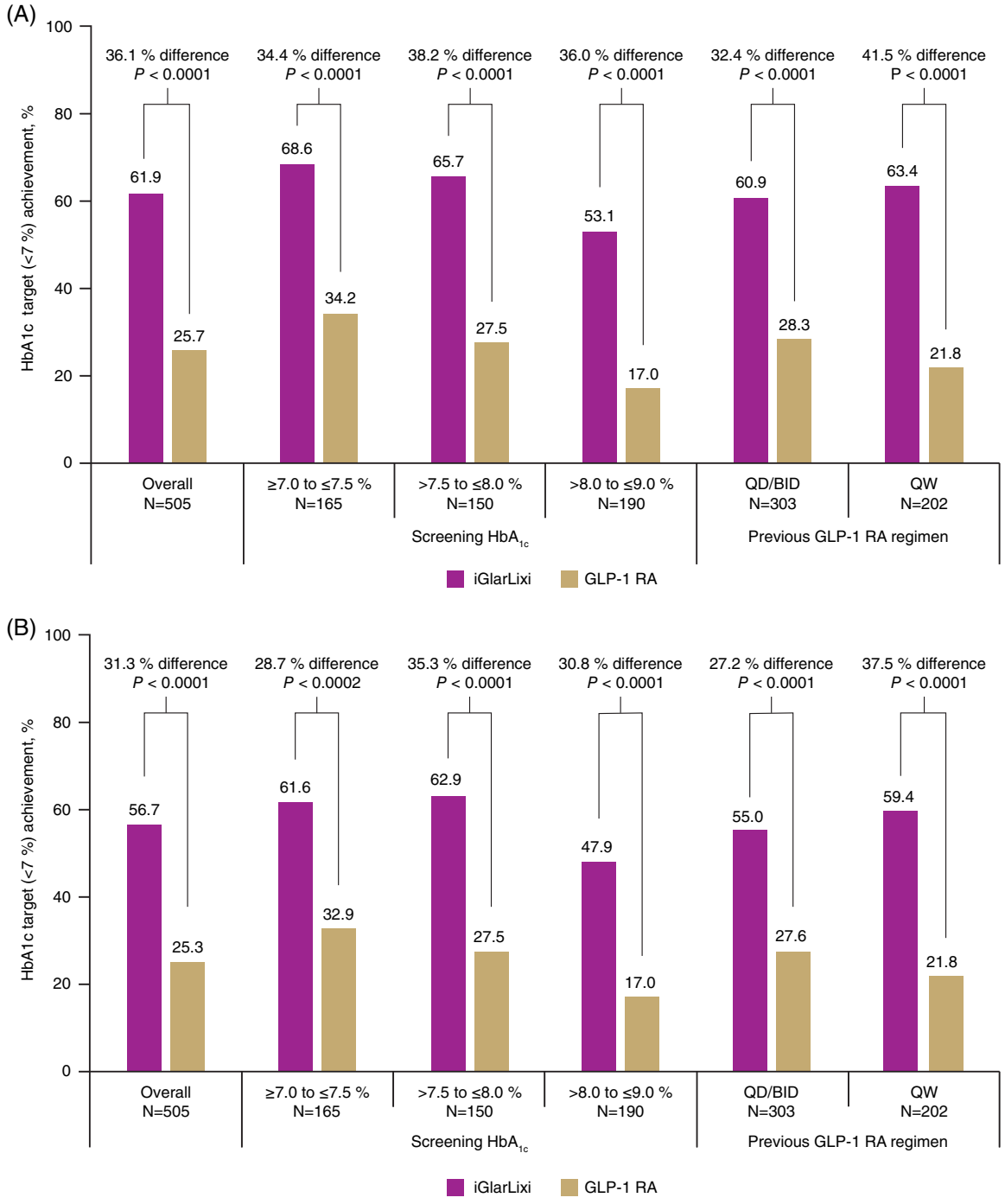

FIGURE 2 (A) Glycated haemoglobin (HbA1c) target (<7 %) achievement, and (B) HbA1c target (<7 %) achievement with no documented symptomatic hypoglycaemia (<3.0 mmol/L [<54 mg/dL]) over the 26-week treatment period by screening HbA1c and previous glucagon-like peptide 1 receptor agonist (GLP-1 RA) regimen subgroup, modified intention-to-treat population. *Abbreviations:* BID, twice daily; QD, once daily; QW, once weekly

switched to iGlarLixi and −1.4 ± 0.3 kg in those who continued on GLP-1 RAs: LS mean difference ± SE = 3.5 ± 0.4 kg, $P < 0.0001$ (Figure 3D). In participants receiving QW GLP-1 RA regimens at screening, LS mean ± SE change from baseline to Week 26 was +1.6 ± 0.3 kg in those switching to iGlarLixi and −0.8 ± 0.3 kg in those remaining on GLP-1 RA: LS mean difference ± SE = 2.4 ± 0.5 kg ($P < 0.0001$).

3.6 | Hypoglycaemia by screening HbA1c and previous GLP-1 RA regimen

Overall, the incidence and rates of documented symptomatic hypoglycaemia (≤3.9 and <3.0 mmol/L [≤70 and <54 mg/dL]) were relatively low. Nevertheless, incidence and rates were higher in those who switched to the iGlarLixi therapy than in those who

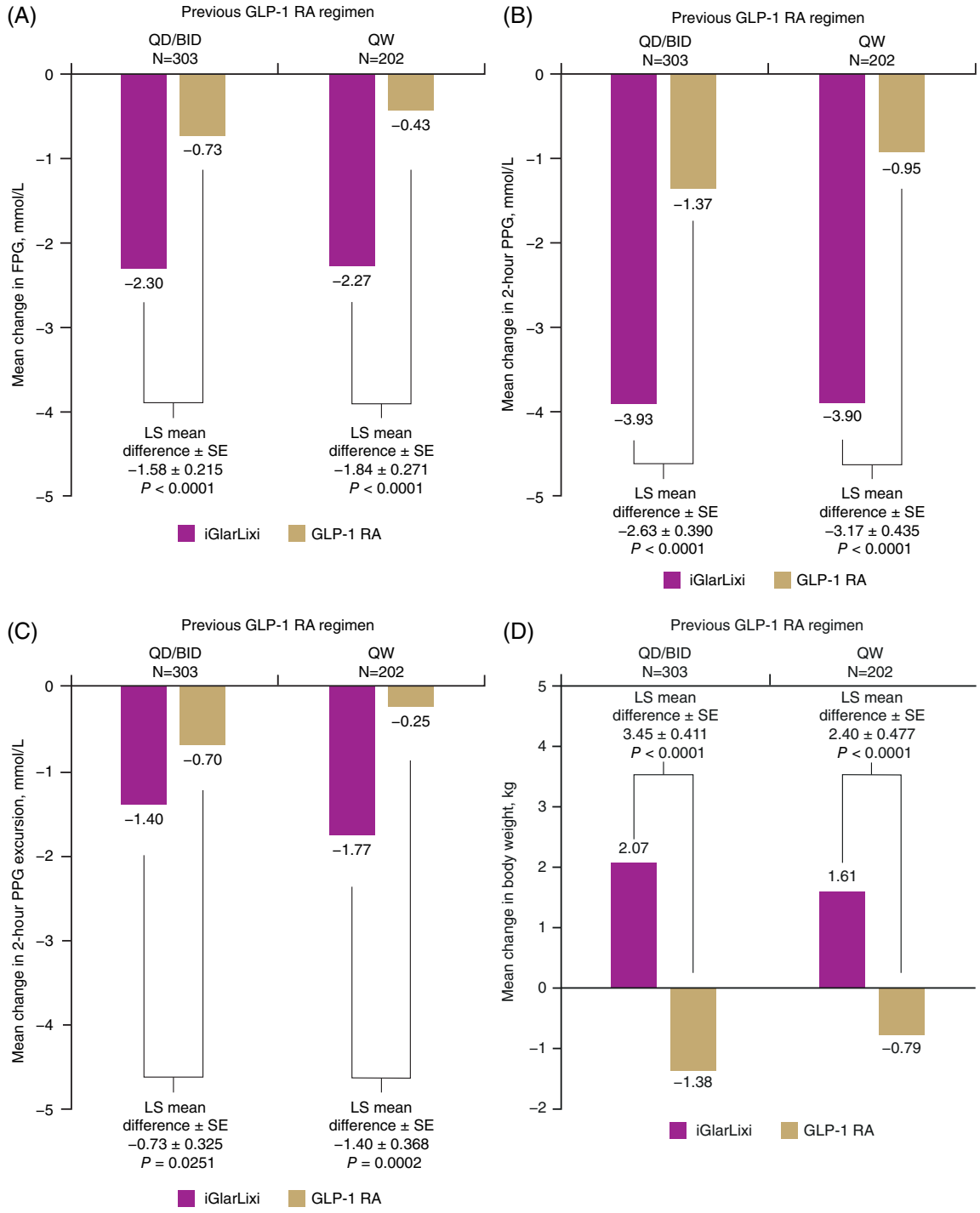

FIGURE 3 Mean change from baseline to Week 26 in (A) fasting plasma glucose (FPG), (B) 2-hour postprandial plasma glucose (PPG), (C) 2-hour PPG excursion, and (D) body weight by previous glucagon-like peptide 1 receptor agonist (GLP-1 RA) regimen subgroup, modified intention-to-treat population (mixed model repeated measures). *Abbreviations:* BID, twice daily; LS, least squares; QD, once daily; QW, once weekly; SE, standard error

remained on GLP-1 RAs, irrespective of screening HbA1c or previous GLP-1 RA regimen (Table 2). For each definition of hypoglycaemia, incidence and rates were highest in the QD/BID GLP-1 RA regimen subgroup.

3.7 | Dose ranges

The numbers of participants in the iGlarLixi group receiving each dose range of iGlar and Lixi are presented in Appendix S1. Slightly more

TABLE 2 Incidence and rates of any documented symptomatic hypoglycaemia by screening HbA1c and previous GLP-1 RA regimen subgroup: safety population

Screening HbA1c						
	Number of participants with events, n/N (%)			Events per participant year[a]		
	≥7.0 to ≤7.5 %; ≥53 to ≤58 mmol/mol (N = 168)	>7.5 to ≤8.0 %; >58 to ≤64 mmol/mol (N = 152)	>8.0 to ≤9.0 %; >64 to ≤75 mmol/mol (N = 191)	≥7.0 to ≤7.5 %; ≥53 to ≤58 mmol/mol (N = 168)	>7.5 to ≤8.0 %; >58 to ≤64 mmol/mol (N = 152)	>8.0 to ≤9.0 %; >64 to ≤75 mmol/mol (N = 191)
Documented symptomatic hypoglycaemia (≤3.9 mmol/L [≤70 mg/dL])						
iGlarLixi	22/86 (25.6)	17/72 (23.6)	32/97 (33.0)	1.17	1.09	2.20
GLP-1 RA	1/82 (1.2)	1/80 (1.3)	4/94 (4.3)	0.03	0.05	0.15
Documented symptomatic hypoglycaemia (<3.0 mmol/L [<54 mg/dL])						
iGlarLixi	11/86 (12.8)	3/72 (4.2)	10/97 (10.3)	0.37	0.09	0.26
GLP-1 RA	0/82	0/80	1/94 (1.1)	0	0	0.02

Previous GLP-1 RA regimen subgroup				
	Number of participants with events, n (%)		Events per participant year[a]	
	QD/BID regimen (N = 305)	QW regimen (N = 206)	QD/BID regimen (N = 305)	QW regimen (N = 206)
Documented symptomatic hypoglycaemia (≤3.9 mmol/L [≤70 mg/dL])				
iGlarLixi	46/152 (30.3)	25/103 (24.3)	1.80	1.13
GLP-1 RA	4/153 (2.6)	2/103 (1.9)	0.11	0.04
Documented symptomatic hypoglycaemia (<3.0 mmol/L [<54 mg/dL])				
iGlarLixi	15/152 (9.9)	9/103 (8.7)	0.27	0.21
GLP-1 RA	1/153 (0.7)	0/103	0.01	0

Abbreviations: GLP-1 RA, glucagon-like peptide 1 receptor agonist; HbA1c, glycated haemoglobin; BID, twice daily; QD, once daily; QW, once weekly.

[a]Calculated as number of events divided by total exposure +1 day in patient-years for daily formulation and number of events divided by total exposure +7 days in patient-years for weekly formulation.

participants previously on QD/BID regimens versus QW regimens received the maximum dose for iGlar (29.9% vs 21.8%) and Lixi (33.1% vs 26.7%). More participants with screening HbA1c >8.0 % to ≤9.0 % received the maximum doses of iGlar and Lixi (34.4% and 37.5%, respectively) compared with participants in the lower HbA1c subgroups (21%–22% received maximum iGlar dose; 26%–27% received maximum Lixi dose).

3.8 | Safety by previous GLP-1 RA regimen

Overall, 163 (63.9%) and 121 participants (47.3%) in the iGlarLixi and GLP-1 RA treatment arms, respectively, experienced an AE; 10 (3.9%) and nine participants (3.5%) experienced a serious AE, respectively. Rates of nausea, vomiting and diarrhoea were low, but were higher in those switching to iGlarLixi compared with those who continued GLP-1 RAs, irrespective of the previous GLP-1 RA regimen (Appendix S2). The incidence of nausea was 10.5% for those switching to iGlarLixi and 2.6% for those remaining on previous GLP-1 RA regimen amongst those on QD/BID GLP-1 RA regimens at screening, and 5.8% and 1.9%, respectively, amongst those on QW GLP-1 RAs. The incidence of vomiting was 4.6% for those switching to iGlarLixi and 0.7% for those remaining on the previous GLP-1 RA regimen amongst those on QD/BID GLP-1 RA regimens at screening, and 1.0% and 1.0%, respectively, amongst those on QW GLP-1 RAs. The incidence of diarrhoea was 5.9% for those switching to iGlarLixi and 3.3% for those remaining on a previous GLP-1 RA regimen, amongst those on QD/BID GLP-1 RA regimens at screening, and 4.9% and 1.0%, respectively, amongst those on QW GLP-1 RAs.

4 | DISCUSSION

In LixiLan-G, the titratable FRC iGlarLixi proved to be an effective and safe intensification treatment in people with T2D with insufficient glycaemic control in spite of maximal dose GLP-1 RA and OADs.[6] However, whether different baseline glycaemic control and/or different GLP-1 RA therapy may have had an impact on the response to switching to iGlarLixi is a relevant clinical question, particularly when translating these results into clinical practice. This post hoc analysis of the LixiLan-G results shows that switching to the FRC iGlarLixi does improve glycaemic outcomes compared with continuing GLP-1 RA therapy, irrespective of screening HbA1c or previous GLP-1 RA regimen. HbA1c target (<7 %) achievement in those switching to iGlarLixi occurred more than twice as often as in those remaining on GLP-1 RAs in each subgroup analysed, showing that in those insufficiently controlled on GLP-1 RAs, treatment intensification by switching to iGlarLixi is an effective option for reaching optimal glycaemic control. The same benefits were also observed whether switching to iGlarLixi from daily or QW GLP-1 RA regimens. These findings are particularly important as the availability of more weekly formulations of GLP-1 RAs have expanded GLP-1 RA usage,[7] yet not all people achieve glycaemic targets, indicating that intensification with basal insulin may be required. While a daily FRC regimen requires more injections than weekly GLP-1 RAs, it requires fewer injections than intensification with a separate basal insulin regimen. This analysis clearly demonstrates that switching from a weekly GLP-1 RA to daily FRC iGlarLixi is a highly effective and safe therapeutic option.

As expected, when an insulin-based therapy is initiated, participants who switched to iGlarLixi experienced modest mean weight gain of 2.1 kg. This is similar to the 2.0-kg weight increase observed with IDegLira, an FRC of insulin degludec and liraglutide, in adults with T2D uncontrolled on maximum dose GLP-1 RA therapy and OADs.[8] However, this study only included daily GLP-1 RAs, liraglutide QD and exenatide BID.

Individuals who switched to iGlarLixi had a higher rate of documented symptomatic hypoglycaemia over 26 weeks versus those who continued to receive their original GLP-1 RA therapy. Nevertheless, event rates for documented hypoglycaemia were generally low. Interestingly, there was no clinically meaningful difference in hypoglycaemia incidence and rates in the lowest screening HbA1c subgroup compared with the other HbA1c subgroups. While this group may be considered at a higher risk of hypoglycaemia as they are closer to target, recent evidence suggests there is not a simple correlation between lower HbA1c and greater hypoglycaemia risk, especially in T2D.[9,10] Indeed, higher HbA1c levels may increase the risk of hypoglycaemia.[11] Despite showing increased hypoglycaemia with iGlarLixi versus GLP-1 RAs, the hypoglycaemia risk reported in this study is consistent with previous findings of GLP-1 RA intensification with insulin-containing therapy. The LixiLan-L and LixiLan-O studies demonstrated that the risk of hypoglycaemia (<3.0 mmol/L [<54 mg/dL]) with iGlarLixi is not elevated above that seen when initiating insulin alone.[4,5]

The incidences of nausea, vomiting and diarrhoea were also low in both groups, although higher with iGlarLixi. Lixisenatide is a rapid-acting GLP-1 RA, in contrast to the longer-acting GLP-1 RAs liraglutide and exenatide that most participants were receiving prior to the study. Therefore, the slightly higher incidence of gastrointestinal AEs reported with iGlarLixi may be partially explained by the initiation of a different type of GLP-1 RA (lixisenatide) with different pharmacokinetic and pharmacodynamic properties in the iGlarLixi group versus continuation of prior stable treatment in the GLP-1 RA group.[7] Nevertheless, the frequency of gastrointestinal AEs with iGlarLixi was considerably lower than that reported with initiation of most other GLP-1 RAs administered individually. In contrast, in the DUAL-III study, 79.5% of the participants were previously treated with liraglutide, the GLP-1 RA component of IDegLira.[8] This may explain why switching to IDegLira in DUAL-III was not associated with increased nausea compared with continuing GLP-1 RA therapy.[8] In the present study, gastrointestinal AEs were not assessed over time, however, previous studies have shown that they usually occur early after treatment initiation and treatment intensification.[12,13]

Limitations of this study include that it was not designed or powered to test for superiority of iGlarLixi versus GLP-1 RA within these subgroups and the analysis did not include all possible GLP-1 RAs; for example, semaglutide was not included as it was only

approved after the study had started. The limitations of the main LixiLan-G study have been previously described, including the lack of an active comparator that included basal insulin. However, a strength of this analysis is that it did assess the switch to iGlarLixi from a variety of previous GLP-1 RAs, reflecting a diversity of real-world situations.

In conclusion, switching to iGlarLixi further improved glycaemic control in people with T2D who had suboptimal glycaemic control despite receiving the maximum tolerated dose of a GLP-1 RA with OADs, offering a simple and highly efficacious and well-tolerated treatment intensification option regardless of screening HbA1c or previous GLP-1 RA regimen.

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CONFLICT OF INTEREST

J.R. has been a consultant for Applied Therapeutics, Boehringer Ingelheim, Eli Lilly, Intarcia, Janssen, Novo Nordisk, Oramed and Sanofi, and has received grant/research support from Applied Therapeutics, AstraZeneca, Boehringer Ingelheim, Eli Lilly, Genentech, GlaxoSmithKline, Intarcia, Janssen, Lexicon, Merck, Novo Nordisk, Oramed, Pfizer and Sanofi. L.B. has been a consultant for AstraZeneca, Gilead Sciences, Janssen, Merck, Novo Nordisk and Sanofi, has received grant/research support (including to his institution) from Janssen, Lexicon, Merck, Novo Nordisk and Sanofi, and has been a speaker for Janssen, Novo Nordisk and Sanofi. V.R.A. has received clinical trial/research support from Applied Therapeutics, Fractyl/Premier, Novo Nordisk and Sanofi, has been a consultant for Applied Therapeutics, Novo Nordisk and Sanofi, and her spouse is an employee of Janssen. J.F. has been a consultant for Boehringer Ingelheim, Johnson & Johnson, Eli Lilly, Merck, Novo Nordisk and Sanofi, has received grant/research support from AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb, Eli Lilly, Johnson & Johnson, Merck, Novo Nordisk, Pfizer, Sanofi and Theracos, and has been a speaker for Merck and Sanofi. E.S., C.J. and E.N. are employees of Sanofi. S.D.P. has received grant/research support from AstraZeneca, Boehringer Ingelheim, Merck and Novartis, and honoraria from Abbott, AstraZeneca, Boehringer Ingelheim, Eli Lilly, Merck, Mundipharma, Novartis, Novo Nordisk, Sanofi, Servier and Takeda.

AUTHOR CONTRIBUTIONS

J.R., L.B., V.R.A., J.F., E.S., C.J., E.N. and S.D.P. contributed to the conception and design of the analysis, as well as interpretation of the data. C.J. performed the statistical analysis. All authors critically reviewed and revised drafts of the manuscript and provided final approval for submission.

PEER REVIEW

The peer review history for this article is available at https://publons.com/publon/10.1111/dom.14345.

DATA AVAILABILITY STATEMENT

The datasets generated and analysed during the current study are available from the corresponding author upon reasonable request. To gain access, data requestors will need to sign a data access agreement.

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REFERENCES

1. American Diabetes Association. 9. Pharmacologic Approaches to Glycemic Treatment: Standards of Medical Care in Diabetes - 2020. *Diabetes Care*. 2020;43(Suppl 1):S98-S110.
2. Davies M, D'Alessio D, Fradkin J, et al. Management of Hyperglycemia in Type 2 Diabetes, 2018. A Consensus Report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). *Diabetes Care*. 2018;41(12):2669-2701.
3. Polonsky W, Henry R. Poor medication adherence in type 2 diabetes: recognizing the scope of the problem and its key contributors. *Patient Prefer Adherence*. 2016;10:1299-1307.
4. 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 with oral agents: The LixiLan-O randomized trial. *Diabetes Care*. 2016;39(11):2026-2035.
5. Aroda V, 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;39:1972-1980.
6. Blonde L, Rosenstock J, Del Prato S, et al. Switching to iGlarLixi Versus continuing daily or weekly GLP-1 RA in Type 2 diabetes inadequately controlled by GLP-1 RA and oral antihyperglycemic therapy: The LixiLan-G randomized clinical trial. *Diabetes Care*. 2019;42(11):2108-2116.
7. Meier JJ. GLP-1 receptor agonists for individualized treatment of type 2 diabetes mellitus. *Nat Rev Endocrinol*. 2012;8(12):728-742.
8. Linjawi S, Bode BW, Chaykin LB, et al. The efficacy of IDegLira (Insulin degludec/liraglutide combination) in adults with type 2 diabetes inadequately controlled with a GLP-1 receptor agonist and oral therapy: DUAL III randomized clinical trial. *Diabetes Ther*. 2017;8(1):101-114.
9. Lipska KJ, Warton EM, Huang ES, et al. HbA1c and risk of severe hypoglycemia in type 2 diabetes: the Diabetes and Aging Study. *Diabetes Care*. 2013;36(11):3535-3542.
10. Malkani S, Frequency KA. predictors of self-reported hypoglycemia in insulin-treated diabetes. *J Diabetes Res*. 2017;2017:7425925.
11. Silbert R, Salcido-Montenegro A, Rodriguez-Gutierrez R, Katabi A, McCoy RG. hypoglycemia among patients with type 2 diabetes: epidemiology, risk factors, and prevention strategies. *Curr Diab Rep*. 2018;18(8):53.
12. Rayner C, Wu T, Aroda V, et al. Gastrointestinal adverse events with insulin glagine/lixisenatide fixed-ratio combination versus glucagon-like

peptide-1 receptor agonists in people with type 2 diabetes mellitus: a network meta-analysis. *Diabetes Obes Metab*. 2020;23(1):136-146.
13. Trujillo J, Roberts M, Dex T, Chao J, White J, LaSalle J. Low incidence of gastrointestinal adverse events over time with a fixed-ratio combination of insulin glargine and lixisenatide versus lixisenatide alone. *Diabetes Obes Metab*. 2018;20:2690-2694.

SUPPORTING INFORMATION

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

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