





ORIGINAL ARTICLE

Impact of disease duration and β -cell reserve on the efficacy of switching to iGlarLixi in adults with type 2 diabetes on glucagon-like peptide-1 receptor agonist therapy: Exploratory analyses from the LixiLan-G trial

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Abstract

Aim: To evaluate the efficacy of iGlarLixi by C-peptide levels and duration of diabetes in an exploratory analysis of the LixiLan-G study.

Methods: LixiLan-G was a 26-week, randomized, open-label study in adults with type 2 diabetes (T2D) inadequately controlled while on a glucagon-like peptide-1 receptor agonist (GLP-1 RA), with metformin, with or without pioglitazone and/or a sodium-glucose co-transporter-2 inhibitor. This analysis investigated the efficacy of switching to iGlarLixi by fasting baseline quartile C-peptide levels and baseline quartile of duration of T2D compared with continued GLP-1 RA use.

Results: Change in glycosylated hemoglobin (HbA1c) from baseline to week 26 was significantly greater with iGlarLixi compared with continued GLP-1 RAs across all fasting C-peptide quartiles (−1.00% to −1.06% vs. −0.23% to −0.54% range, respectively) and irrespective of all T2D duration quartiles (−0.94% to −1.07% vs. −0.25% to −0.50% range). A significantly greater proportion of participants in the iGlarLixi arm achieved an HbA1c of <7% across all C-peptide quartiles (51%–73% range) than in the GLP-1 RA arm (19%–32% range). The greatest reductions in HbA1c in participants receiving iGlarLixi were observed in those with the shortest duration of disease, although consistently greater than reductions observed with continued GLP-1 RAs. Reductions in HbA1c were comparable across C-peptide quartiles within the iGlarLixi arm.

Conclusions: The results of this study suggest that iGlarLixi is an effective treatment option, irrespective of C-peptide levels or duration of diabetes, in adults with insufficiently controlled T2D receiving GLP-1 RAs.

KEYWORDS

beta cell function, clinical trials, GLP-1, randomized trial, type 2 diabetes

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1 | INTRODUCTION

Decline in β -cell function is a key factor that contributes to the worsening of glycaemic control and treatment failure in people with type 2 diabetes (T2D).^{1,2} By the time T2D is diagnosed, β -cell function has already declined by 50% and this decline continues at a rate of \sim 5% per year after diagnosis.³ Thus, it is important to understand the efficacy of therapies according to ranges of fasting C-peptide levels (as a measure of β -cell function) or duration of diabetes, as conceivably some glucose-lowering agents that primarily rely on β -cell stimulation may become less effective over time.⁴

Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) have been recommended by the American Diabetes Association as a first injectable treatment following the failure of oral agents.⁵ Long-acting GLP-1 RAs (once-daily [QD] liraglutide and once-weekly [QW] exenatide, dulaglutide, albiglutide and semaglutide) predominantly act on the endocrine pancreas to stimulate insulin secretion and inhibit glucagon secretion with a prominent effect on fasting plasma glucose (FPG), whereas short-acting GLP-1 RAs (lixisenatide and exenatide twice-daily [BID]) predominantly act by delaying gastric motility and reducing glucagon secretion to mainly improve postprandial hyperglycaemia.^{6–8} This delay of gastric emptying is maintained over time with short-acting GLP-1 RAs likely due to intermittent receptor binding, whereas following initiation of long-acting GLP-1 RAs, the gastric-slowing effect rapidly dissipates because of tachyphylaxis.^{7,8} Such non-insulin related actions of lixisenatide may contribute to its effectiveness, irrespective of β -cell function.⁹

iGlarLixi is a titratable, fixed-ratio combination of insulin glargine 100 units/mL (Gla-100) and the GLP-1 RA lixisenatide in 2 U:1 μ g and 3 U:1 μ g ratios, respectively. Efficacy of iGlarLixi has been shown in the LixiLan clinical development programme in adults with inadequately controlled T2D on oral glucose-lowering agents (LixiLan-O),¹⁰ basal insulin or metformin (LixiLan-L),¹¹ or GLP-1 RAs (LixiLan-G).¹²

This exploratory analysis of the LixiLan-G study was conducted in adults with T2D that was insufficiently controlled with GLP-1 RAs to investigate the efficacy and rates of symptomatic hypoglycaemia (glucose of $<$ 54 mg/dL) of iGlarLixi according to baseline fasting C-peptide level and duration of T2D.

2 | METHODS

2.1 | Study design

The LixiLan-G trial (ClinicalTrials.gov, NCT02787551) has been described elsewhere.¹² Briefly, LixiLan-G was a 26-week, randomized, open-label, active-controlled, parallel-group study in adults with T2D for \geq 1 year, inadequately controlled (glycated hemoglobin [HbA1c] between 7% and 9%) while on a maximum tolerated dose of either a QD or BID GLP-1 RA or a QW GLP-1 RA, with metformin, with or without pioglitazone and/or a sodium-glucose co-transporter-2

(SGLT2) inhibitor. Major exclusion criteria included a body mass index (BMI) of \leq 20 or $>$ 40 kg/m², a history of hypoglycaemia unawareness, previous treatment with insulin in the year before screening, or treatment with antidiabetic drugs within 3 months (excluding those previously described). Participants were randomized to continue their current GLP-1 RA treatment at the same maximally tolerated dose, or to switch to iGlarLixi, and were stratified by HbA1c at screening ($<$ 8% or \geq 8%) and by GLP-1 RA subtype at screening (QD, BID or QW formulation). The GLP-1 RAs included in this study were liraglutide 1.8 mg QD or 1.2 mg QD (if the 1.8 mg dose was not tolerated), exenatide 10 μ g BID or 5 μ g BID (if the 10 μ g dose was not tolerated), exenatide 2 mg QW, albiglutide 50 mg QW or 30 mg QW (if the 50 mg dose was not tolerated), and dulaglutide 1.5 mg QW or 0.75 mg QW (if the 1.5 mg dose was not tolerated). iGlarLixi was self-administered within 1 hour before the first meal of the day at an initial dose of 10 U daily (10 U Gla-100 and 5 μ g lixisenatide), and was titrated twice weekly during the first 8 weeks to a target FPG level of 80–100 mg/dL. From week 8 to 26 the dose was monitored once weekly and was adjusted to maintain an FPG level of 80–100 mg/dL; however, twice-weekly monitoring could be continued if the investigator deemed this appropriate. One of two SoloSTAR (Sanofi, Paris, France) pen injectors were used for self-administration of iGlarLixi, according to the insulin dose required. If the participant needed a dose of iGlarLixi between 10 and 40 U, a pen with a 2:1 ratio of insulin glargine to lixisenatide was dispensed. If a dose of 41–60 U was required by the participant, a pen with a 3:1 ratio of insulin glargine to lixisenatide was dispensed. If glucose parameters exceeded the threshold value defined for rescue therapy at the maximum defined daily dose of 60 U, the fixed-ratio combination dose was maintained at 60 U and a rescue therapy was added.

The study design is summarized in Figure S1. The study was conducted with good clinical practice as set out by 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.

2.2 | Outcomes and measurements

This exploratory analysis of the LixiLan-G trial investigated the efficacy of iGlarLixi by baseline quartile of fasting C-peptide levels and baseline quartile of T2D duration, as defined in Table 1.

The primary exploratory endpoint was the change in HbA1c level from baseline to week 26. Secondary exploratory outcomes included the proportion of participants achieving a target HbA1c of $<$ 7% and the change in FPG and postprandial glucose (PPG) concentrations from baseline to week 26 assessed by quartiles of C-peptide levels and T2D duration. The correlation of T2D duration with baseline C-peptide levels was evaluated, as was correlation of T2D duration with C-peptide:glucose ratios. Additionally, the percentage of participants

TABLE 1 Definitions of baseline fasting C-peptide concentration and T2D diabetes duration quartiles

Fasting C-peptide quartiles (nmol/L)		T2D duration quartiles (years)	
Q1	>1.21	Q1	≤6.5
Q2	≤1.21 to >0.94	Q2	>6.5 to ≤10
Q3	≤0.94 to >0.73	Q3	>10 to ≤14.6
Q4	≤0.73	Q4	>14.6

Abbreviations: Q, quartile; T2D, type 2 diabetes.

having hypoglycaemia with glucose of <54 mg/dL was analysed by C-peptide and duration of T2D quartile.

C-peptide levels were measured during a standardized meal test of ~ 600 kcal, composed of 50%-55% carbohydrate, 15%-20% protein and 25%-30% fat. Time points for assessment were at 30 minutes before the meal, before administration of investigational drugs, and at 0, 30, 60, 90 and 120 minutes after the meal.

2.3 | Statistical analysis

The modified intention-to-treat analysis population (all randomized participants with a baseline assessment and at least one postbaseline assessment of any primary or secondary efficacy variable) was used for efficacy analysis. A mixed-effect model with repeated measures was used for the analysis of change from baseline to 26 weeks in glycaemic parameters HbA1c, FPG and 2-hour PPG according to baseline C-peptide quartiles and T2D duration. The model included fixed effects of treatment arm (iGlarLixi, GLP-1 RA), randomization strata of HbA1c at screening (<8.0%, ≥8.0%), randomization strata of GLP-1 RA subtype at screening (QD/BID or QW formulation), scheduled visit, and treatment-by-visit interaction. Baseline of the corresponding outcome value-by-visit interaction was included as a covariate. All *P*-values for these analyses are nominal *P*-values without multiplicity adjustment.

The proportion of participants reaching glycaemic target was analysed using the Cochran–Mantel–Haenszel method weighted by randomization strata of HbA1c (<8.0, ≥8.0%) and randomization strata of GLP-1 RA subtype (QD/BID or QW formulation) at screening. The percentage of participants having hypoglycaemia with glucose of <54 mg/dL was analysed using the similar weighted Cochran–Mantel–Haenszel method. Participants were treated as non-responders if they had no HbA1c assessments at week 26 during the 26-week on-treatment period.

3 | RESULTS

3.1 | Characteristics of study participants

Of 514 randomized participants, 511 were treated, and 476 completed the 26-week treatment period. The modified intention-to-

treat population consisted of 505 participants (252 in the iGlarLixi arm and 253 in the GLP-1 RA arm). At baseline, participants with the lowest fasting C-peptide levels had a lower mean BMI, a longer duration of GLP-1 RA treatment, and were more likely to be receiving pioglitazone than those participants with the highest fasting C-peptide levels (Table 2). There was a significant negative correlation of decreasing fasting C-peptide concentrations with increasing duration of T2D (Figure 1). The negative correlation with T2D disease duration was observed for both fasting and postprandial C-peptide levels, as well as for C-peptide:glucose ratios (Table S1). No differences in baseline characteristics were observed between the iGlarLixi and GLP-1 RA arms across the baseline fasting C-peptide quartiles (Table 2).

At baseline, participants with the longest duration of T2D (Q4) had similar characteristics to those with the lowest fasting C-peptide levels, although those participants with the longest T2D durations were older. No differences in baseline characteristics were observed between the iGlarLixi and GLP-1 RA arms across the T2D duration quartiles (Table 2).

3.2 | Efficacy outcomes

3.2.1 | Change in HbA1c from baseline to week 26 by quartiles of C-peptide levels and duration of T2D

When analysed by fasting C-peptide quartiles, reductions in HbA1c from baseline to week 26 were greater in the iGlarLixi (–1.00% to –1.06% range) versus the GLP-1 RA (–0.23% to –0.54% range) arm across all fasting C-peptide quartiles, with the greatest differences observed in quartiles 3 and 4, which were the quartiles with the lower fasting C-peptide concentrations and longer diabetes durations (Figure 2A). Participants randomized to remain on GLP-1 RA treatment who were in the higher fasting C-peptide concentration quartiles (Q1 [>1.21 nmol/L] and Q2 [≤1.21 to >0.94 nmol/L]) had greater HbA1c reduction than those participants in the lower fasting C-peptide concentration quartiles (Q3 [≤0.94 to >0.73 nmol/L] and Q4 [≤0.73 nmol/L]). The reduction from baseline in HbA1c was comparable across all C-peptide quartiles within the iGlarLixi arm. Additionally, a greater proportion of participants in the iGlarLixi arm achieved an HbA1c of <7% across all C-peptide quartiles (51%-73% range) than in the GLP-1 RA arm (19%-32% range) (Figure 2B). In the iGlarLixi arm, a higher proportion of participants in the middle C-peptide quartiles (66% and 73%) achieved an HbA1c of <7% than those in the quartiles with the highest (51%) and lowest (56%) C-peptide concentrations. In the iGlarLixi arm, in the C-peptide quartile with the highest concentration, Q1 (>1.21 nmol/L), participants received a higher iGlarLixi dose than those in quartiles 2-4 (Table S2), possibly because of the higher BMI of participants within that quartile.

When analysed by T2D duration quartile, the change in HbA1c from baseline to week 26 was greater with iGlarLixi

TABLE 2 Baseline characteristics of study participants

	Fasting C-peptide quartile							
	Q1 (>1.21 nmol/L)		Q2 (≤1.21 to >0.94 nmol/L)		Q3 (≤0.94 to >0.73 nmol/L)		Q4 (≤0.73 nmol/L)	
	iGlarLixi (n = 60)	GLP-1 RA (n = 62)	iGlarLixi (n = 61)	GLP-1 RA (n = 61)	iGlarLixi (n = 64)	GLP-1 RA (n = 58)	iGlarLixi (n = 60)	GLP-1 RA (n = 62)
Demographics								
Age, mean ± SD, years	59.9 ± 9.9	58.2 ± 10.8	59.4 ± 9.6	60.5 ± 9.1	58.7 ± 8.1	59.7 ± 11.3	58.8 ± 10.8	61.0 ± 10.3
Male, n (%)	28 (46.7)	37 (59.7)	31 (50.8)	31 (50.8)	25 (39.1)	33 (56.9)	35 (58.3)	35 (56.5)
White, n (%)	58 (96.7)	61 (98.4)	59 (96.7)	54 (88.5)	57 (89.1)	57 (98.3)	55 (91.7)	58 (93.5)
Clinical characteristics, mean ± SD								
HbA1c, %	7.8 ± 0.6	7.8 ± 0.5	7.7 ± 0.6	7.8 ± 0.5	7.9 ± 0.6	7.8 ± 0.5	7.8 ± 0.7	7.8 ± 0.7
FPG, mmol/L	9.4 ± 2.4	9.5 ± 2.0	8.8 ± 1.8	9.4 ± 2.1	9.2 ± 2.3	9.6 ± 1.6	8.9 ± 2.1	9.4 ± 2.2
2-hour PPG, mmol/L [†]	13.8 ± 3.7	13.8 ± 3.4	13.0 ± 3.0	13.3 ± 3.5	14.5 ± 3.4	14.2 ± 3.4	13.5 ± 3.5	13.8 ± 2.6
BMI, kg/m ²	34.1 ± 3.9	34.9 ± 3.6	34.1 ± 3.5	33.9 ± 4.0	32.9 ± 4.0	32.7 ± 4.4	29.6 ± 4.4	30.1 ± 4.2
Fasting preprandial C-peptide, nmol/L [†]	1.5 ± 0.3	1.7 ± 0.5	1.1 ± 0.1	1.1 ± 0.1	0.8 ± 0.1	0.8 ± 0.1	0.6 ± 0.1	0.6 ± 0.1
Treatment at screening								
Duration of GLP-1 RA treatment, mean ± SD, years	1.52 ± 1.31	1.58 ± 1.38	1.64 ± 1.48	1.97 ± 2.14	2.21 ± 1.92	1.85 ± 1.65	2.21 ± 2.18	2.26 ± 2.13
GLP-1 RA formulation, n (%)								
OD/BID	30 (50.0%)	31 (50.0%)	40 (65.6%)	38 (62.3%)	37 (57.8%)	36 (62.1%)	38 (63.3%)	37 (59.7%)
QW	30 (50.0%)	31 (50.0%)	21 (34.4%)	23 (37.7%)	27 (42.2%)	22 (37.9%)	22 (36.7%)	25 (40.3%)
Pioglitazone use, n (%)	0	0	3 (4.9%)	5 (8.2%)	3 (4.7%)	6 (10.3%)	6 (10.0%)	10 (16.1%)
Yes								
SGLT2 inhibitor use, n (%)	6 (10.0%)	5 (8.1%)	3 (4.9%)	6 (9.8%)	6 (9.4%)	9 (15.5%)	11 (18.3%)	6 (9.7%)
Yes								
Duration of T2D quartile								
	Q1 (≤6.5 years)		Q2 (>6.5 to ≤10 years)		Q3 (>10 to ≤14.6 years)		Q4 (>14.6 years)	
	iGlarLixi (n = 65)	GLP-1 RA (n = 64)	iGlarLixi (n = 62)	GLP-1 RA (n = 66)	iGlarLixi (n = 68)	GLP-1 RA (n = 60)	iGlarLixi (n = 62)	GLP-1 RA (n = 67)
Demographics								
Age, mean ± SD, years	55.7 ± 9.6	54.8 ± 10.2	58.5 ± 8.0	57.9 ± 8.8	58.5 ± 10.3	59.3 ± 9.0	64.5 ± 8.4	67.7 ± 8.5
Male, n (%)	31 (47.7)	28 (43.8)	34 (54.8)	41 (62.1)	32 (47.1)	31 (51.7)	29 (46.8)	44 (65.7)
White, n (%)	63 (96.9)	61 (95.3)	58 (93.5)	64 (97.0)	63 (92.6)	58 (96.7)	57 (91.9)	61 (91.0)
Clinical characteristics, mean ± SD								
HbA1c, %	7.8 ± 0.6	7.7 ± 0.6	7.8 ± 0.6	7.8 ± 0.5	7.8 ± 0.6	7.9 ± 0.5	7.7 ± 0.6	7.8 ± 0.6
FPG, mmol/L	8.7 ± 1.9	9.3 ± 2.0	9.3 ± 2.3	9.5 ± 1.7	9.5 ± 2.1	9.8 ± 2.0	8.9 ± 2.3	9.2 ± 2.0

TABLE 2 (Continued)

	Duration of T2D quartile							
	Q1 (≤6.5 years)		Q2 (>6.5 to ≤10 years)		Q3 (>10 to ≤14.6 years)		Q4 (>14.6 years)	
	iGlarLixi (n = 65)	GLP-1 RA (n = 64)	iGlarLixi (n = 62)	GLP-1 RA (n = 66)	iGlarLixi (n = 68)	GLP-1 RA (n = 60)	iGlarLixi (n = 62)	GLP-1 RA (n = 67)
2-hour PPG, mmol/L [†]	13.2 ± 3.7	13.9 ± 3.5	12.9 ± 2.9	13.5 ± 3.5	14.3 ± 3.3	14.4 ± 2.8	14.4 ± 3.5	13.2 ± 3.1
BMI, kg/m ²	33.8 ± 3.9	34.0 ± 4.4	32.5 ± 4.4	33.2 ± 4.6	33.1 ± 4.5	33.0 ± 4.2	31.7 ± 4.6	31.6 ± 4.0
Fasting preprandial C-peptide, nmol/L [†]	1.1 ± 0.4	1.2 ± 0.6	1.0 ± 0.40	1.0 ± 0.4	1.0 ± 0.4	1.1 ± 0.5	0.9 ± 0.4	0.9 ± 0.4
Treatment at screening								
Duration of GLP-1 RA treatment, mean ± SD, years	1.4 ± 1.2	1.5 ± 1.3	1.7 ± 1.3	1.8 ± 1.7	1.9 ± 1.8	2.1 ± 1.9	2.6 ± 2.3	2.3 ± 2.4
GLP-1 RA formulation, n (%)								
OD/BID	39 (60.0)	29 (45.3)	32 (51.6)	42 (63.6)	42 (61.8)	46 (76.7)	40 (64.5)	37 (55.2)
QW	26 (40.0)	35 (54.7)	30 (48.4)	24 (36.4)	26 (38.2)	14 (23.3)	22 (35.5)	30 (44.8)
Pioglitazone use, n (%)								
Yes	0	1 (1.6)	2 (3.2)	4 (6.1)	5 (7.4)	6 (10.0)	5 (8.1)	11 (16.4)
SGLT2 inhibitor use, n (%)								
Yes	5 (7.7)	8 (12.5)	5 (8.1)	5 (7.6)	7 (10.3)	4 (6.7)	9 (14.5)	9 (13.4)

[†]Baseline data for 2-hour PPG and 30-min preprandial C-peptide reported values are from participants with available data in each arm; data were not available in ≤12% of participants.

Abbreviations: BID, twice daily; BMI, body mass index; FPG, fasting plasma glucose; GLP-1 RA, glucagon-like peptide-1 receptor agonist; OD, once daily; PPG, postprandial glucose; QW, every week; SD, standard deviation; SGLT2, sodium-glucose co-transporter-2.

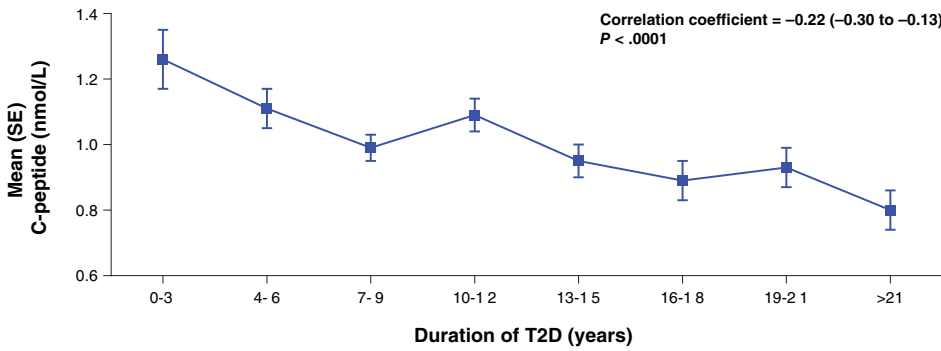


FIGURE 1 Correlation between duration of T2D and fasting C-peptide concentration at study baseline. Correlation coefficient based on Pearson correlation. Abbreviation: SE, standard error

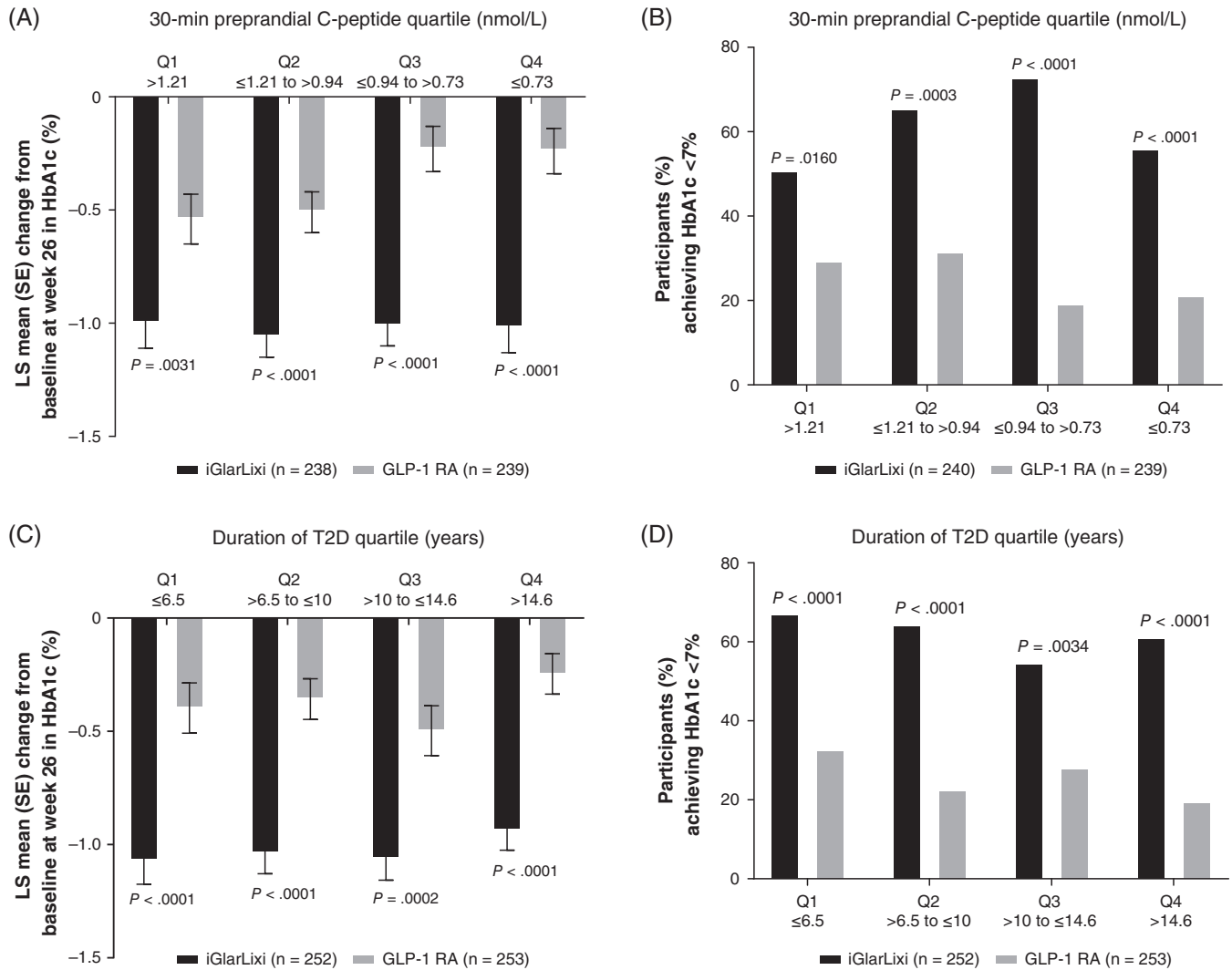


FIGURE 2 Mean HbA1c change from baseline to week 26 (A and C) and proportion of participants at target HbA1c of <7% (B and D) by fasting C-peptide quartiles and duration of T2D quartiles, respectively. Abbreviations: GLP-1 RA, glucagon-like peptide-1 receptor agonist; LS, least squares; SE, standard error

(-0.94% to -1.07% range) compared with continued GLP-1 RA therapy (-0.25% to -0.50% range) across all duration of T2D quartiles, with greater reductions from baseline in HbA1c in the quartiles with shorter T2D duration for both the iGlarLixi and GLP-1 RA arms (Q1-3 vs. Q4) (Figure 2C). Within the GLP-1 RA arm, participants in Q4 (T2D duration >14.6 years) had a smaller

HbA1c reduction (Figure 2C), and a smaller proportion of participants achieved an HbA1c of <7% (Figure 2D) than those in Q1 (T2D duration ≤ 6.5 years). A greater proportion of patients in the iGlarLixi arm achieved an HbA1c of <7% across all T2D duration quartiles (55%-67% range) than in the GLP-1 RA arm (20%-33% range) (Figure 2D).

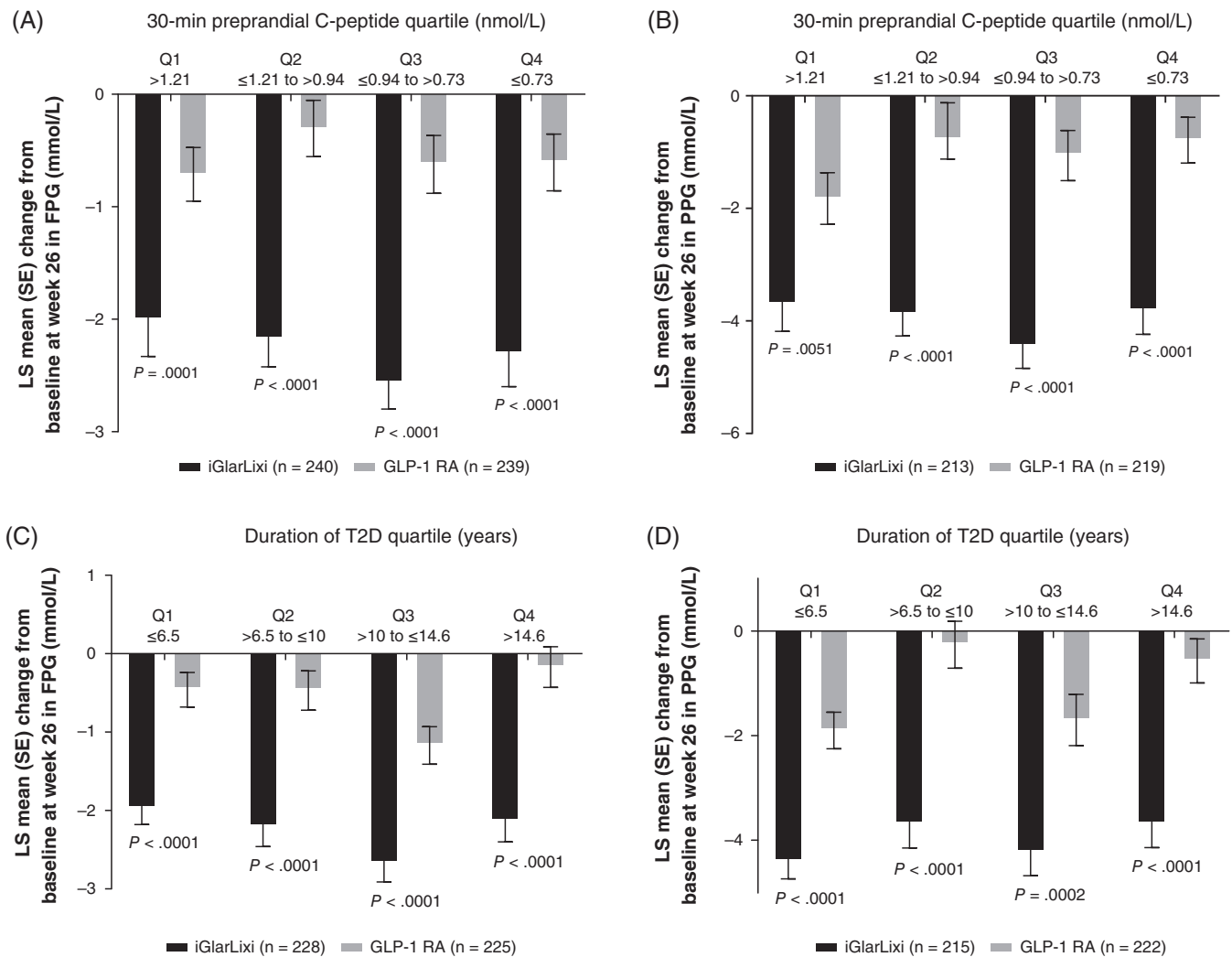


FIGURE 3 Mean change from baseline to week 26 for FPG (A and C) and PPG (B and D) by fasting C-peptide quartiles and duration of T2D quartiles, respectively. Abbreviations: FPG, fasting plasma glucose; GLP-1 RA, glucagon-like peptide-1 receptor agonist; LS, least squares; PPG, postprandial glucose; SE, standard error

3.2.2 | Change in FPG and PPG from baseline to week 26 by quartiles of C-peptide levels and duration of T2D

In the iGlarLixi arm, the reduction from baseline in FPG and PPG was similar across all fasting C-peptide quartiles and was greater than the reductions for the GLP-1 RA arm (Figure 3A,B). In the GLP-1 RA arm, the greatest reduction from baseline in FPG and PPG was observed in the highest C-peptide concentration quartile (Q1).

In the iGlarLixi arm, the reductions from baseline in FPG and PPG were similar across all T2D duration quartiles and were greater than the reductions seen in the GLP-1 RA arm (Figure 3C,D). Within the iGlarLixi arm, in the quartile with the longest diabetes duration (Q4 [>14.6 years]), it was noted that participants received a lower iGlarLixi dose than those in quartiles 1-3 (Table S2); those participants with the longest diabetes duration also had a lower mean BMI (Table 2).

3.3 | Hypoglycaemia

The rates of symptomatic hypoglycaemia (<54 mg/dL) were higher in the iGlarLixi versus the GLP-1 RA arm across all baseline fasting C-peptide and duration of T2D quartiles (Table S3). In the iGlarLixi arm, hypoglycaemia rates were highest in participants in the baseline fasting C-peptide quartile Q1 (>1.21 nmol/L) who also had the highest iGlarLixi doses, and highest in those in the duration of T2D quartile Q4 (>14.6 years) who also had the lowest iGlarLixi doses (Table S3).

4 | DISCUSSION

In these exploratory analyses of the LixiLan-G trial, the beneficial effect of iGlarLixi was maintained across all categories of baseline fasting C-peptide levels and T2D duration. However, in the GLP-1 RA arm, the reduction in HbA1c tended to be less pronounced in

participants with lower C-peptide levels and in those with a longer duration of T2D. For GLP-1 RA, the quartiles with the highest C-peptide levels and shortest duration of T2D were associated with the greatest reduction from baseline in HbA1c and also the greatest proportion of participants achieving an HbA1c of <7%. Rates of symptomatic hypoglycaemia (<54 mg/dL) were higher in the iGlarLixi versus the GLP-1 RA arm across all baseline fasting C-peptide and duration of T2D quartiles.

Consistent with other studies,^{13–15} in the current analyses, duration of T2D negatively correlated with C-peptide levels. In a 6-year follow-up of the UK Prospective Diabetes Study, in newly diagnosed patients with T2D, progressive β -cell dysfunction was associated with worse outcomes for glycaemic control.¹⁶ Thus, with worsening glycaemic control and declining β -cell function, new therapeutic approaches that do not rely solely on the proportion of functioning β -cells should be considered. Owing to the progression of T2D and the associated decline in β -cell function, it is estimated that ~20%–30% of patients¹⁷ will eventually require insulin to achieve glycaemic control. However, barriers to insulin initiation exist at both patient and physician levels.¹⁸ Concomitant therapies, such as GLP-1 RAs, which have been shown to reduce the burden of adverse side effects of insulin therapy such as weight gain,¹⁹ and do not themselves cause hypoglycaemia,²⁰ may help people achieve their therapeutic goals.

The observed efficacy difference of iGlarLixi compared with continuation of a GLP-1 RA across all baseline C-peptide levels and T2D duration categories in this analysis is likely because of the combination of the short-acting GLP-1 RA, lixisenatide, with Gla-100. These two agents work through multiple different complementary mechanisms, with Gla-100 mainly providing control over nocturnal and fasting hyperglycaemia, and lixisenatide exerting an effect on postprandial hyperglycaemia that is mediated primarily by a deceleration in gastric emptying, likely facilitated by non-continuous receptor engagement. This durable glucose-lowering effect of lixisenatide, independent of the severity of β -cell dysfunction, or duration of T2D, has been consistently shown in the LixiLan-L (duration of T2D only), GetGoal-M and GetGoal-S trials.^{9,21} The persistent glucose-lowering effect irrespective of residual β -cell function of lixisenatide is also supported by the results of a mechanistic study performed in patients with total pancreatectomy, in which significant PPG reductions through the slowing of gastric emptying and reductions of postprandial glucagon responses were shown with lixisenatide administration.²²

The preserved efficacy in terms of HbA1c, FPG and PPG lowering with iGlarLixi highlights the potential value of therapies with β -cell independent mechanisms of action to treat long-standing T2D. It has been suggested that long-acting GLP-1 RAs that rely more on residual functioning β -cells may be less effective in people with advanced stages of T2D.^{7,23} In a prospective study, participants with a clinical diagnosis of T2D ($n = 620$) and an HbA1c of $\geq 7.5\%$ who initiated GLP-1 RA therapy (liraglutide [64%], exenatide BID [27%] and exenatide QW [9%]), clinical markers of low β -cell function (low C-peptide level and positive for islet autoantibodies) were associated with a reduced response to GLP-1 RA therapy.⁴ In an analysis of the overall LixiLan-G study, no differences were observed in efficacy in

terms of reduction of HbA1c, FPG and PPG according to the type of GLP-1 RA used (40% were weekly dosing and 60% were daily dosing).²⁴

Despite initial highly effective glucose-lowering responses with most GLP-1 RAs, including weekly formulations, as T2D progresses glucose control may become insufficient and additional intervention with basal insulin may be needed. In the current study, iGlarLixi showed a greater effect in reducing HbA1c over continued GLP-1 RA use. Notably, iGlarLixi was consistently effective across all baseline fasting C-peptide quartiles and T2D duration quartiles, suggesting the combination to be a valuable therapeutic approach for people not achieving target glycaemic control with GLP-1 RA treatment. This is in line with the results of other studies that have showed that combined therapy of basal insulin and GLP-1 RA is highly effective at minimizing the risk of hyperglycaemia.^{25–27}

The DUAL III study, which evaluated a fixed-ratio formulation of insulin degludec and liraglutide (IDegLira), showed a similarly robust reduction in HbA1c as observed in the current study, in a population of adults inadequately controlled on liraglutide QD or exenatide BID, but the study did not include weekly GLP-1 RAs.²⁸ It would be interesting if similar exploratory analyses were performed on the data from DUAL III according to T2D duration to determine whether the efficacy of IDegLira would be preserved over a longer duration of T2D.

There are a number of limitations associated with the current analysis. The exploratory nature of these analyses renders the data hypothesis-generating, although consistent with previous findings. The open-label nature of the study could also lead to the introduction of bias; however, a masked study was not feasible. Another limitation to consider is the lack of an active comparator, such as basal insulin, in the main study.

The study also has a number of strengths. The availability of C-peptide data has allowed for analysis of the relationship of HbA1c outcomes to both this marker of β -cell function and duration of T2D. There were no differences between participant baseline characteristics in this study, even after stratifying participants by T2D duration subcategories and allowing for inclusion of adults with a diabetes duration of more than 15 years. In addition, sensitivity analyses showed that no differences were observed in the study results after exclusion of participants on SGLT2 inhibitor therapy: correlations between duration of T2D and C-peptide:glucose ratios, and duration of T2D and C-peptide concentrations, were maintained.

In adults with T2D whose HbA1c is suboptimally controlled on a GLP-1 RA therapy, switching to a fixed-ratio combination of basal insulin and GLP-1 RA is a clinically relevant option, particularly given the increasing number of people who receive GLP-1 RAs as their first injectable and who may not achieve glycaemic targets. The results of this analysis indicate that switching to iGlarLixi is an effective and simple treatment option in adults with insufficiently controlled T2D receiving GLP-1 RAs, irrespective of β -cell function or duration of T2D.

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CONFLICT OF INTEREST

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AUTHOR CONTRIBUTIONS

All authors were involved in analysis and interpretation of data, and in the drafting and revising of the manuscript for intellectual content. All authors have approved the final version of the manuscript for publication and agree to be accountable for all aspects of the work.

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REFERENCES

1. Bretzel RG, Eckhard M, Landgraf W, Owens DR, Linn T. Initiating insulin therapy in type 2 diabetic patients failing on oral hypoglycemic

agents: basal or prandial insulin? The APOLLO trial and beyond. *Diabetes Care*. 2009;32(suppl. 2):S260-S265.

2. Butler AE, Janson J, Bonner-Weir S, Ritzel R, Rizza RA, Butler PC. Beta-cell deficit and increased beta-cell apoptosis in humans with type 2 diabetes. *Diabetes*. 2003;52:102-110.
3. Saisho Y. Beta-cell dysfunction: its critical role in prevention and management of type 2 diabetes. *World J Diabetes*. 2015;6:109-124.
4. Jones AG, McDonald TJ, Shields BM, et al. Markers of beta-cell failure predict poor glycemic response to GLP-1 receptor agonist therapy in type 2 diabetes. *Diabetes Care*. 2016;39:250-257.
5. American Diabetes Association. Pharmacologic approaches to glycemic treatment: standards of medical care in diabetes-2018. *Diabetes Care*. 2018;41:S73-S85.
6. Guo XH. The value of short- and long-acting glucagon-like peptide-1 agonists in the management of type 2 diabetes mellitus: experience with exenatide. *Curr Med Res Opin*. 2016;32:61-76.
7. Meier JJ. GLP-1 receptor agonists for individualized treatment of type 2 diabetes mellitus. *Nat Rev Endocrinol*. 2012;8:728-742.
8. Uccellatore A, Genovese S, Dicembrini I, Mannucci E, Ceriello A. Comparison review of short-acting and long-acting glucagon-like peptide-1 receptor agonists. *Diabetes Ther*. 2015;6:239-256.
9. Yabe D, Ambos A, Cariou B, et al. Efficacy of lixisenatide in patients with type 2 diabetes: a post hoc analysis of patients with diverse beta-cell function in the GetGoal-M and GetGoal-S trials. *J Diabetes Complications*. 2016;30:1385-1392.
10. Rosenstock J, Aronson R, Grunberger G, et al. Benefits of LixiLan, a titratable fixed-ratio combination of insulin glargine plus lixisenatide, versus insulin glargine and lixisenatide monocomponents in type 2 diabetes inadequately controlled on oral agents: the LixiLan-O randomized trial. *Diabetes Care*. 2016;39:2026-2035.
11. Aroda VR, Rosenstock J, Wysham C, et al. Efficacy and safety of LixiLan, a titratable fixed-ratio combination of insulin glargine plus lixisenatide in type 2 diabetes inadequately controlled on basal insulin and metformin: the LixiLan-L randomized trial. *Diabetes Care*. 2016;39:1972-1980.
12. 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;42:2108-2116.
13. Bacha F, Gungor N, Lee S, Arslanian SA. Progressive deterioration of beta-cell function in obese youth with type 2 diabetes. *Pediatr Diabetes*. 2013;14:106-111.
14. Bo S, Cavallo-Perin P, Gentile L, Repetti E, Pagano G. Relationship of residual beta-cell function, metabolic control and chronic complications in type 2 diabetes mellitus. *Acta Diabetol*. 2000;37:125-129.
15. Prando R, Odetti P, Melga P, Giusti R, Ciuchi E, Cheli V. Progressive deterioration of beta-cell function in nonobese type 2 diabetic subjects. Postprandial plasma C-peptide level is an indication of insulin dependency. *Diabetes Metab*. 1996;22:185-191.
16. U.K. Prospective Diabetes Study Group. U.K. prospective diabetes study 16: overview of 6 years' therapy of type II diabetes: a progressive disease. *Diabetes*. 1995;44:1249-1258.
17. Garg SK, Rewers AH, Akturk HK. Ever-increasing insulin-requiring patients globally. *Diabetes Technol Ther*. 2018;20:S21-S24.
18. Peyrot M, Rubin RR, Khunti K. Addressing barriers to initiation of insulin in patients with type 2 diabetes. *Prim Care Diabetes*. 2010;4(suppl. 1):S11-S18.
19. Swinnen SG, Hoekstra JB, DeVries JH. Insulin therapy for type 2 diabetes. *Diabetes Care*. 2009;32(suppl. 2):S253-S259.
20. Onoviran OF, Li D, Toombs Smith S, Raji MA. Effects of glucagon-like peptide 1 receptor agonists on comorbidities in older patients with diabetes mellitus. *Ther Adv Chronic Dis*. 2019;10:2040622319862691.

21. Wysham C, Bonadonna RC, Aroda VR, et al. Consistent findings in glycaemic control, body weight and hypoglycaemia with iGlarLixi (insulin glargine/lixisenatide titratable fixed-ratio combination) vs insulin glargine across baseline HbA1c, BMI and diabetes duration categories in the LixiLan-L trial. *Diabetes Obes Metab.* 2017;19:1408-1415.
22. Juel CTB, Lund A, Hansen CP, et al. *The Glucagon-like Peptide-1 Receptor Agonist Lixisenatide Reduces Postprandial Glucose Excursions in Totally Pancreatectomized Patients.* San Diego, CA: American Diabetes Association, 77th Scientific Sessions; 2017.
23. Yabe D, Seino Y. Defining the role of GLP-1 receptor agonists for individualized treatment of type 2 diabetes. *Expert Rev Endocrinol Metab.* 2014;9:659-670.
24. Rosenstock J, Blonde L, Del Prato S, et al. *Switching to iGlarLixi vs Continued Treatment of GLP-1 RA: Comparative Analysis by Daily or Weekly GLP-1 RAs in the LixiLan-G trial.* San Francisco, CA: American Diabetes Association (ADA) 79th Scientific Sessions; 2019.
25. Davies MJ, D'Alessio DA, 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;41:2669-2701.
26. Maiorino MI, Chiodini P, Bellastella G, Capuano A, Esposito K, Giugliano D. Insulin and glucagon-like peptide 1 receptor agonist combination therapy in type 2 diabetes: a systematic review and meta-analysis of randomized controlled trials. *Diabetes Care.* 2017;40:614-624.
27. Wysham CH, Lin J, Kuritzky L. Safety and efficacy of a glucagon-like peptide-1 receptor agonist added to basal insulin therapy versus basal insulin with or without a rapid-acting insulin in patients with type 2 diabetes: results of a meta-analysis. *Postgrad Med.* 2017;129:436-445.
28. 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;8:101-114.

SUPPORTING INFORMATION

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

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