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ORIGINAL ARTICLE

WILEY

Comparing a daily versus weekly titration algorithm in people with type 2 diabetes switching from basal insulin to iGlarLixi in the LixiLan ONE CAN randomized trial

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Abstract

Aim: To compare the efficacy and safety of a simple daily titration algorithm compared with a weekly dose adjustment of iGlarLixi in people with type 2 diabetes.

Materials and Methods: LixiLan ONE CAN (NCT03767543), a randomized, 26-week, open-label, multicentre phase 3 trial conducted in Canada, involved 265 people with type 2 diabetes and an HbA1c of ≥7.5% to ≤ 10.5% or less (≥58 to ≤91 mmol/mol) on basal insulin for 6 months or longer. Participants were randomized 1:1 with instructions to self-titrate iGlarLixi daily (1 unit/day) or once weekly (2 or 4 units/week) to a common target fasting plasma glucose of 4.4 to 5.6 mmol/L (79 to 101 mg/dl). The primary objective was to show non-inferiority of the daily versus weekly titration algorithm.

Results: At 26 weeks, daily titration of iGlarLixi was not inferior to a weekly titration for both the prespecified primary endpoint of change in HbA1c from baseline (least square [LS] mean change: −1.24% vs. −0.92%, respectively; LS mean difference: 0.32%; 95% CI [0.07, 0.57]; $P < .0001$) and for the secondary endpoint of change in weight from baseline (LS mean change: −0.22 vs. +0.81 kg, respectively; LS mean difference: 1.03 kg; 95% CI [0.01, 2.06]; $P < .0001$). Indeed, for both the primary and secondary outcome, the daily titration of iGlarLixi was superior. There were no statistically significant differences in hypoglycaemia incidence between the two titration strategies during the 26-week study.

Conclusion: A daily titration algorithm for switching basal insulin to iGlarLixi was shown to be non-inferior and superior for glycaemic control and weight compared with weekly titration.

KEYWORDS
basal insulin, GLP-1 analogues, glycaemic control, phase III, randomized trial, type 2 diabetes

1 | INTRODUCTION

Suboptimal glycaemic control and therapeutic inertia continue to be challenges in the management of type 2 diabetes (T2D).[1-4] Titratable fixed-ratio combinations (FRCs) of a basal insulin and glucagon-like peptide-1 receptor agonist (GLP-1 RA) may be helpful for people with T2D to achieve and maintain HbA1c targets compared with each component used individually.[5-8] FRCs of basal insulin and GLP-1 RA reduce the need for multiple injections and lower HbA1c with less hypoglycaemia and weight gain compared with an insulin-only regimen and less gastrointestinal (GI)-related adverse effects (AEs) compared with the use of a GLP-1 RA.[9-13]

Titration of currently available FRCs of basal insulin and GLP-1 RAs typically follows weekly regimens that were implemented in clinical trials.[14] However, previous studies show that simpler, daily titration algorithms of insulin glargine can achieve similar or better glycaemic control than less frequent titration algorithms. For example, the INSIGHT study showed that insulin glargine 100 U/ml with 1 unit/day daily titration was more probable to achieve a lower HbA1c level than conventional titration of oral agents with no differences in hypoglycaemia, and that family physicians achieved similar results compared with specialists.[15] Similarly, the TITRATION study showed that insulin glargine 300 U/ml with 1 unit/day daily titration was effective and comparable with once weekly titration with a similar frequency of AEs between algorithms.[16] The objective of the LixiLan ONE CAN study was to compare the efficacy and safety of a once daily versus once weekly titration algorithm for iGlarLixi, an FRC of insulin glargine 100 U/ml and lixisenatide therapy, in people with T2D suboptimally controlled on basal insulin and oral antihyperglycaemic drugs (OADs).

2 | MATERIALS AND METHODS

2.1 | Study design and participants

LixiLan ONE CAN was an open-label, randomized, two treatment arms, parallel-group, 26-week, multicentre phase 3b study conducted in Canada (registered with ClinicalTrials.gov: NCT03767543). The study was conducted in accordance with consensus ethics principles derived from international ethics guidelines, including the Declaration of Helsinki and the International Council for Harmonization guidelines for Good Clinical Practice, and all applicable laws, rules and regulations. Informed consent was obtained prior to conducting any study-related procedures.

Study participants were aged 18 years or older with T2D having an HbA1c of ≥7.5% to ≤ 10.5% (≥58 to ≤91 mmol/mol) and a body mass index of 20 to 40 kg/m^2 (Figure S1). Participants had been treated for at least 6 months on 40 units or less per day basal insulin (including insulin glargine, degludec and others) with or without OADs. The OADs allowed at inclusion were metformin, insulin secretagogues, dipeptidyl peptidase-4 inhibitors (DPP-4is) and sodium-glucose co-transporter-2 inhibitors (SGLT2is), with no change in OAD dose for at least 2 months prior to randomization. Participants were excluded if they had a history of severe hypoglycaemia or hypoglycaemia unawareness; a history of metabolic acidosis, including diabetic ketoacidosis within 1 year prior to screening; or were on current treatment with a GLP-1 RA or previous treatment with known intolerance to GLP-1 RAs.

2.2 | Randomization and study treatment

Study participants were randomly assigned to self-titrate iGlarLixi using either a once daily or once weekly regimen targeting a fasting self-monitored plasma glucose (SMPG) level of 4.4-5.6 mmol/L (79-101 mg/dl). For all participants, basal insulin taken at inclusion was replaced by iGlarLixi, injected once a day 1 hour prior to the first meal of the day. For those transferring from once daily basal insulin, the iGlarLixi starting dose was 15 or 30 units if the basal insulin dose was less than 30 units or 30 or more units, respectively. For those transferring from twice daily basal insulin, the same starting dose rationale was applied after calculating 80% of the pretrial total daily basal insulin dose.

The following titration protocols were used. For the daily arm, if fasting SMPG values were 5.7 mmol/L or higher (≥103 mg/dl), the dose change was +1 unit; and if participants experienced one value less than 4.4 mmol/L (<79 mg/dl) or symptomatic hypoglycaemia, the dose change was −1 unit. For the weekly arm, fasting SMPG values were based on median values from the preceding 3 days: if values were more than 7.8 mmol/L (>140 mg/dl), the dose change was +4 units; if values were than 5.6 and 7.8 or less mmol/L (>101 and ≤140 mg/dl), the dose change was +2 units; and if participants experienced one value less than 4.4 mmol/L (<79 mg/dl), the dose change was −2 units. For both arms, dose changes were not required when fasting SMPG values were in the target range. Participants were instructed to self-measure fasting plasma glucose (FPG) levels before breakfast and before administration of glucose-lowering agents once daily, and if possible, whenever symptoms of hypoglycaemia were experienced. Administration of OADs taken at baseline continued at the same dose after randomization, except for DPP-4i, which was discontinued, and doses of other OADs could be reduced at the discretion of the investigator in response to biochemical or clinical hypoglycaemia. Additional oral glucose-lowering agents were not permitted to be added during the 26-week treatment period. Routine fasting SMPG was required to ensure that glycaemic variables remained below predefined threshold values. If the fasting SMPG values were above predefined threshold values, the investigator had to ensure that no reasonable explanation existed for insufficient glucose control. If no reasons could be found, appropriate actions failed, and a daily FRC dose of more than 60 units/20 μg was necessary to decrease fasting SMPG below the threshold values, then rescue therapy was introduced. It was recommended to add an injection of basal insulin when the FPG was the main contributor of hyperglycaemia.

Stratification factors at baseline included the use of SGLT2i, the use of DPP-4i, and a stratum for baseline HbA1c (<8.5% vs. ≥8.5%).

Of note, a cap on the SGLT2i stratum, initially set at a maximum of 20% of randomized subjects, was removed and the protocol amended after the start of participant recruitment.

2.3 | Outcomes

The primary endpoint was change in HbA1c from baseline to week 26. Key secondary endpoints included change in body weight from baseline to week 26, and the percentage of participants reaching the composite endpoint of HbA1c of 7.0% or less (≤53 mmol/mol) without body weight gain (defined as no increase ≥1 kg) and without hypoglycaemia (severe or documented symptomatic [<3.9 mmol/L]) at week 26. Safety analyses conducted on the safety population (defined as all randomized participants exposed to at least one dose of investigational medicinal product regardless of the amount of treatment administered) were performed to assess hypoglycaemia (percentage of participants who had ≥1 event and rate of events by type) and AEs. Hypoglycaemic event types were categorized according to American Diabetes Association definitions: level 1, documented symptomatic hypoglycaemia less than 3.9 mmol/L (<70 mg/dl); level 2, documented symptomatic hypoglycaemia less than 3.0 mmol/L (<54 mg/dl); and level 3, severe symptomatic hypoglycaemia requiring external assistance for recovery.[17]

2.4 | Statistical methods

The primary efficacy population was the modified intent-to-treat (mITT) population, which included all randomized participants who had both a baseline assessment and at least one postbaseline assessment HbA1c. The primary endpoint was analysed using a mixed-effect model with repeated measures (MMRM) under the missing at random framework. The MMRM model included titration method, randomization strata of HbA1c (<8.5%, ≥8.5%), DPP-4i use (Yes, No), SGLT2i use (Yes, No) and visit (week 12 and week 26). To show non-inferiority, the least square (LS) mean difference and 95% confidence interval (CI) were tabulated. Non-inferiority was shown when the lower confidence limit was greater than −0.4%. A statistical test for non-inferiority was also made and superiority was concluded when the lower confidence limit was greater than 0.0%.

Change in body weight was analysed similarly to the primary endpoint. Based on an hierarchical approach, if the primary endpoint was met and the lower limit of 95% CI for the difference was greater than −1.0 kg, then non-inferiority was shown.

No imputation was performed for the primary efficacy analysis of change in HbA1c or for the key secondary endpoint of change in body weight. In a sensitivity analysis, multiple imputation was used to determine the impact of missing HbA1c values and the results remained unchanged.

The composite secondary endpoint of an HbA1c of 7.0% or less (≤53 mmol/mol) without body weight gain and without hypoglycaemia (severe or documented symptomatic [<3.9 mmol/L]) was analysed using the mITT population. A generalized linear model procedure using a binomial distribution was used to evaluate non-inferiority and the difference in percentage of participants reaching the composite endpoint of an HbA1c of 7.0% or less without body weight gain and without hypoglycaemia. Class effects included titration group, randomization strata of HbA1c (<8.5%, ≥8.5%), DPP-4i use (Yes, No) and SGLT2i use (Yes, No). Based on an hierarchical approach, if the change in body weight secondary endpoint was met and the lower limit of 95% CI for the difference was greater than −5%, non-inferiority was shown.

Overall, testing for non-inferiority stopped once a non-significant test was encountered to control for multiplicity of *P* values. Hypothesis testing in this study was only for non-inferiority and superiority was shown based on 95% CI not crossing the origin.

3 | RESULTS

3.1 | Study population

Of the 398 participants screened, 265 were randomized in the LixiLan ONE CAN study from 11 March 2019 to 23 October 2020, with 132 in the daily arm and 133 in the weekly arm (Figure 1). Notably, the coronavirus disease 2019 (COVID-19) pandemic occurred during the study, and the number of participants discontinuing the study were comparable between both treatment arms. Of 265 randomized participants, 222 (83.8%) completed the study period and 43 (16.2%) participants did not complete the study period. AEs were the most common reason for study discontinuation (19 [7.2%] participants). A greater percentage of participants in the weekly titration group (12 [9.0%]) discontinued the study because of AEs compared with the daily titration group (seven [5.3%]). The percentage of participants who discontinued treatment because of treatment-emergent adverse events (TEAEs) were comparable across treatment groups, driven mostly by GI-related AEs (3.1% in the daily arm vs. 2.3% in the weekly arm), notably diarrhoea and nausea. Study discontinuation was also reported because of withdrawal of consent (seven [2.6%] participants), inability to meet eligibility (one [0.4%] participant) and other reasons that were not related to COVID-19 (16 [6.0%] participants).

Baseline demographics and disease characteristics of participants were balanced between the two arms (Table 1). At study entry, 61.1% of participants were taking insulin glargine (100 U/ml, 300 U/ml, or biosimilar), 26.4% were taking insulin degludec, and 12.5% were taking other basal insulins. Notably, 80.8% of people were taking two or more OADs at baseline and, overall, the study population was highly diverse, comprising 28.0% Asian and 12.1% Black participants.

3.2 | Glycaemic responses and change in body weight

As noted in Table 2, the LS mean reduction of HbA1c from baseline to week 26 was 1.24% (95% CI: 1.06, 1.42) and 0.92% (95% CI: 0.74,

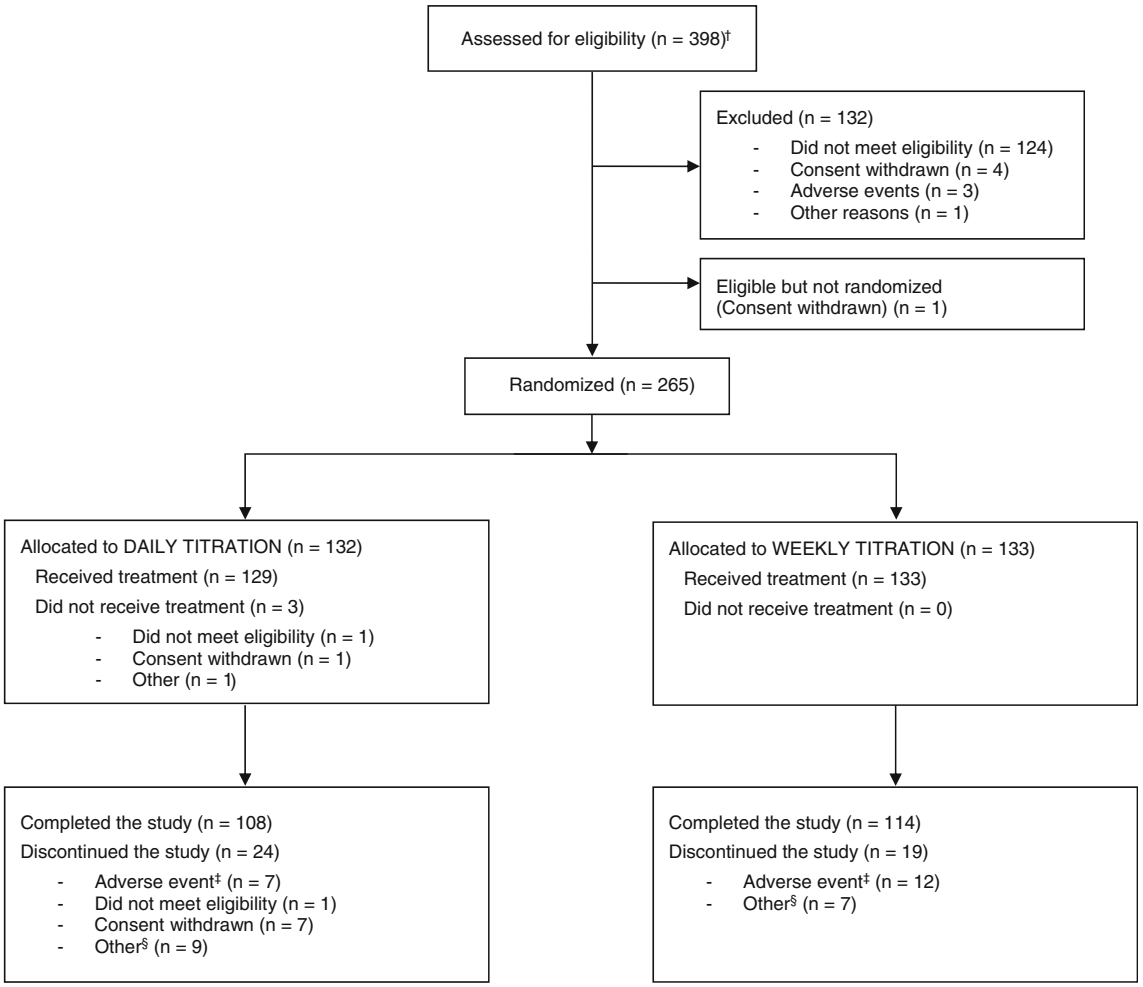


FIGURE 1 Study participants flowchart and disposition. COVID-19, coronavirus disease 2019. † One participant was entered as a duplicate and was not included in any summary. ‡ No participants stopped the study for an event related to COVID-19. § No participants stopped the study for other reasons related to COVID-19

1.10) for the daily titration and weekly titration arms, respectively. Thus, the HbA1c decreased 0.32% more (95% CI: 0.07, 0.57) in the daily versus the weekly titration arm, showing both non-inferiority ($P < .0001$) and superiority. A sensitivity analysis using multiple imputation confirmed the primary analysis result.

For the secondary endpoint of change in body weight from baseline to week 26, a reduction in body weight was observed in the daily titration arm, while an increase in body weight was observed in the weekly arm (Table 2). The LS mean difference between the two arms was 1.03 kg (95% CI: 0.01, 2.06; $P < .0001$), thus daily titration of iGlarLixi was shown to be non-inferior and superior to weekly titration.

For the composite secondary endpoint of an HbA1c of 7.0% or less without gain in body weight and without hypoglycaemia (severe or documented symptomatic [<3.9 mmol/L]), the LS mean difference between the two arms was −0.07 (95% CI: −0.13, 0.00; $P < .001$), showing statistical non-inferiority, and superiority, of daily titration compared with weekly titration (Table 2).

3.3 | Insulin dosage and FPG levels

Maintenance dose for iGlarLixi was reached sooner among those randomized to the once daily titration algorithm (Figure 2A). A mean dose of over 40 units was achieved by week 6 in the daily titration arm, and by week 15 in the weekly arm. The mean doses remained between 40 and 45 units for the remainder of the study in both groups and were not significantly different at the end of the treatment period.

Mean FPG levels decreased from baseline to week 12 and week 26 across both treatment arms (Figure 2B). Decreases in mean FPG were numerically greater, although not significantly different, in the daily arm compared with the weekly arm.

3.4 | Rescue therapy

The percentage of participants requiring a rescue therapy visit during the 26-week treatment period was low in both arms: four (3.2%) participants in the daily titration arm versus six (4.6%) participants the

TABLE 1 Participant demographics and disease characteristics of the randomized study population at baseline

iGlarLixi DAILY titration	iGlarLixi DAILY titration (n = 132)	iGlarLixi WEEKLY titration (n = 133)	Total (n = 265)
Age, mean, y (SD)	63.8 (11.6)	64.5 (10.4)	64.1 (11.0)
Age group, n (%)			
<50 y	17 (12.9)	14 (10.5)	31 (11.7)
≥50 and <65 y	46 (34.8)	47 (35.3)	93 (35.1)
≥65 and <75 y	48 (36.4)	49 (36.8)	97 (36.6)
≥75 y	21 (15.9)	23 (17.3)	44 (16.6)
Male, n (%)	84 (63.6)	81 (60.9)	165 (62.3)
Race, n (%)[a]			
Asian	33 (25.2)	41 (30.8)	74 (28.0)
Black	17 (13.0)	15 (11.3)	32 (12.1)
Indigenous	1 (0.8)	1 (0.8)	2 (0.8)
White	79 (60.3)	74 (55.6)	153 (58.0)
Unknown	1 (0.8)	2 (1.5)	3 (1.1)
HbA1c, mean, % (SD)	8.46 (0.75)	8.55 (0.85)	8.51 (0.81)
Duration of T2D, mean, y (SD)	15.8 (6.7)	17.3 (9.0)	16.5 (8.0)
BMI, mean, kg/m^2 (SD)[b]	29.65 (4.34)	28.87 (4.46)	29.26 (4.41)
BMI by category, n (%)[b]			
<30 kg/m^2	70 (56.0)	82 (64.6)	152 (60.3)
≥30 kg/m^2	55 (44.0)	45 (35.4)	100 (39.7)
Daily dose of basal insulin, mean, unit (SD)[c]	25.1 (10.1)	23.6 (9.8)	24.3 (9.9)
Type of OAD[d,e], n (%)			
Metformin	117 (88.6)	114 (85.7)	231 (87.2)
Insulin secretagogues	75 (56.8)	67 (50.4)	142 (53.6)
DPP-4i	80 (60.6)	78 (58.6)	158 (59.6)
SGLT2i	51 (38.6)	49 (36.8)	100 (37.7)
Number of OADs, n (%)			
No OADs	6 (4.5)	2 (1.5)	8 (3.0)
1 OAD	15 (11.4)	28 (21.1)	43 (16.2)
≥2 OADs	111 (84.1)	103 (77.4)	214 (80.8)

Abbreviations: BMI, body mass index; DPP-4i, dipeptidyl peptidase-4 inhibitors; OAD, oral antihyperglycaemic drug; SD, standard deviation; SGLT2i, sodium-glucose co-transporter-2 inhibitors; T2D, type 2 diabetes.
[a]The n value for the iGlarLixi DAILY arm was 131 in this instance.
[b]The n values for the iGlarLixi DAILY arm and the WEEKLY arm were 125 and 127, respectively, in this instance.
[c]The n values for the iGlarLixi DAILY arm and the WEEKLY arm were 128 and 127, respectively, in this instance.
[d]The n values for the iGlarLixi DAILY arm and the WEEKLY arm were 126 and 131, respectively, in this instance. Based on participants assuming at least one OAD. A participant could be counted in more than one OAD in case of assumption of more than one treatment.
[e]Administration of OADs taken at baseline continued after randomization at the same dose, except for DPP-4i, which was discontinued at randomization. Doses were reduced at the discretion of the investigator in response to biochemical or clinical hypoglycaemia. Additional oral glucose-lowering agents were not permitted.

weekly titration arm. Overall, one participant (0.8%) in the daily titration arm and three participants (2.3%) in the weekly titration arm reported a rescue therapy treatment.

3.5 | Hypoglycaemia and adverse events

There were no significant differences in the percentage of participants with any hypoglycaemia (Table 3). Incidences of severe hypoglycaemia episodes requiring external assistance for recovery were rare and similar between the daily and weekly groups.

Treatment arms were comparable with respect to AEs and the number of participants experiencing any TEAE leading to discontinuation was low (Table 3). The most common TEAEs (≥5% in overall participants) were nausea and diarrhoea and were balanced between the two arms.

4 | DISCUSSION

In the LixiLan ONE CAN randomized trial, a simple daily self-titration algorithm for iGlarLixi was shown to be an effective and safe

TABLE 2 Primary and key secondary outcomes after 26 weeks of treatment (mITT population)

Primary endpoint: Change in HbA1c from baseline to week 26							
	iGlarLixi DAILY titration (n = 125)			**iGlarLixi WEEKLY titration (n = 131)**			
	Baseline (n = 125)	**Week 26 (n = 116)**	**LS mean change from baseline to week 26**	**Baseline (n = 131)**	**Week 26 (n = 121)**	**LS mean change from baseline to week 26**	**LS mean change for weekly-daily**
HbA1c, mean, %	8.47 (SD: 0.76)	7.25 (SD: 0.94)	−1.24 (95% CI: −1.42, −1.06)	8.54 (SD: 0.85)	7.56 (SD: 1.10)	−0.92 (95% CI: −1.10, −0.74)	0.32* (SE: 0.13; 95% CI: 0.07, 0.57)
Secondary endpoint: Change in weight from baseline to week 26							
	iGlarLixi DAILY titration (n = 125)			**iGlarLixi WEEKLY titration (n = 131)**			
	Baseline (n = 125)	**Week 26 (n = 116)**	**LS mean change from baseline to week 26**	**Baseline (n = 131)**	**Week 26 (n = 118)**	**LS mean change from baseline to week 26**	**LS mean change for weekly-daily**
Body weight, mean, kg	83.13 (SD: 16.38)	83.19 (SD: 15.95)	−0.22 (95% CI: −0.95, 0.51)	80.86 (SD: 15.59)	82.77 (SD: 16.20)	0.81 (95% CI: 0.09, 1.53)	1.03** (SE: 0.52; 95% CI: 0.01, 2.06)
Secondary endpoint: Participants reaching composite of HbA1c ≤ 7.0% without body weight gain and without hypoglycaemia[a] at week 26							
	iGlarLixi DAILY titration (n = 125)			**iGlarLixi WEEKLY titration (n = 131)**			**LS mean difference for weekly-daily**
Participants, n (%)	19 (15.2)			10 (7.6)			NA
Composite endpoint, LSM, %	0.13 (95% CI: 0.08, 0.20)			0.06 (95% CI: 0.03, 0.12)			−0.07*** (SE: 0.04; 95% CI: −0.13, 0.00)

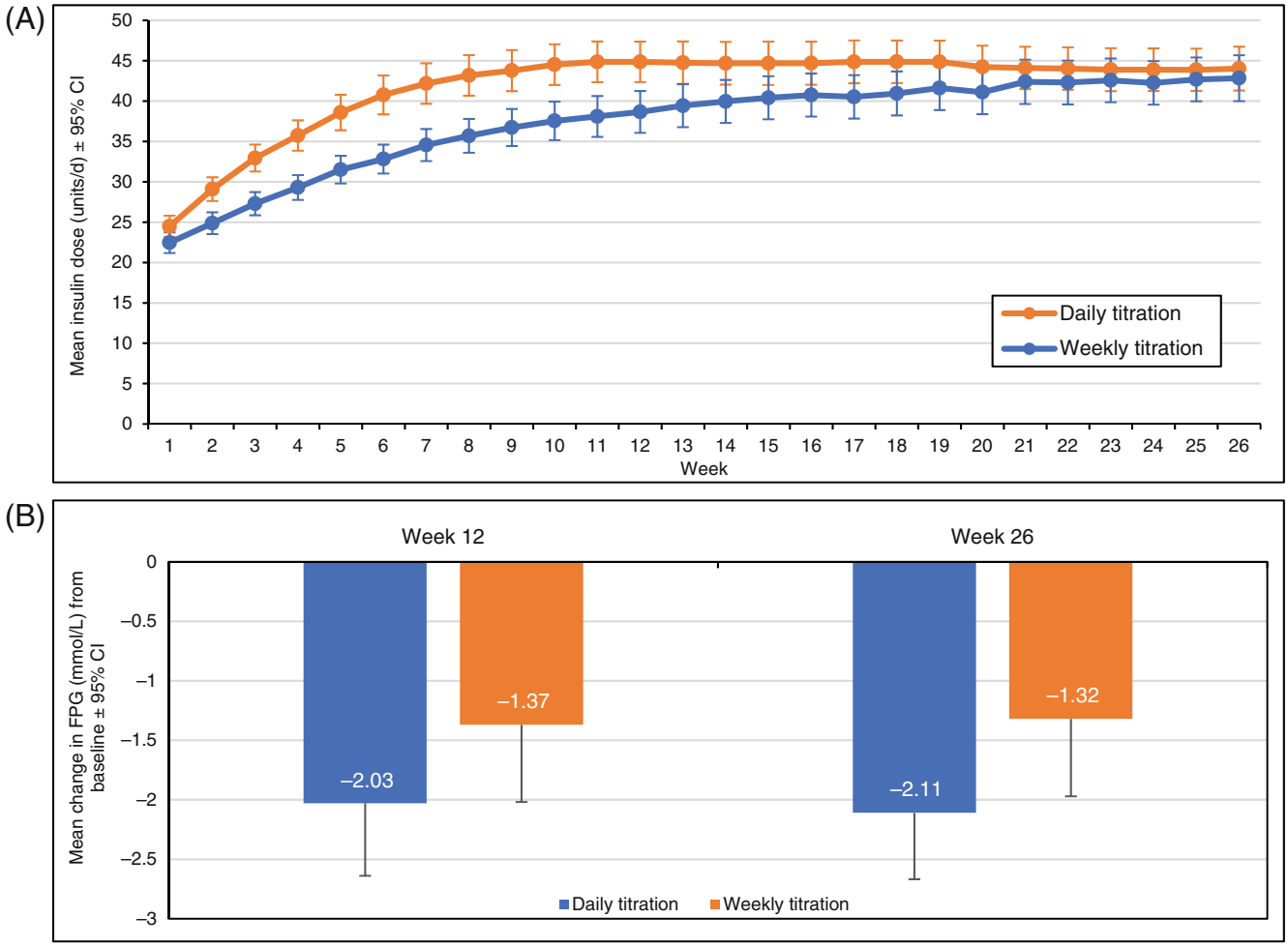
Abbreviations: CI, confidence interval; LS, least square; mITT, modified intent to treat; NA, not applicable; SD, standard deviation; SE, standard error.

[a]Severe or documented symptomatic (≤3.9 mmol/L).

*$P < .0001$ (the P value is based on the non-inferiority test with a non-inferiority margin of −0.4).

**$P < .0001$ (the P value is based on the non-inferiority test with a non-inferiority margin of −1).

***$P < .001$ (the P value for the difference is based on a test of non-inferiority where margin is 5.00%).



mITT population	iGlarLixi DAILY Titration (n = 125)			iGlarLixi WEEKLY Titration (n = 131)		
	Baseline (n = 106)	**Week 12** (n = 117)	**Week 26** (n = 114)	**Baseline** (n = 112)	**Week 12** (n = 118)	**Week 26** (n = 118)
FPG, mean (SD), mmol/L	8.37 (2.55)	6.33 (2.10)	6.48 (1.82)	8.43 (2.51)	7.08 (2.60)	7.20 (2.78)
FPG change from baseline, mean (95% CI), mmol/L	—	−2.03 (0.61)†	−2.11 (0.56)‡	—	−1.37 (0.65)‡	−1.32 (0.65)†

CI, confidence interval; FPG, fasting plasma glucose; mITT, modified intent to treat; SD, standard deviation.
† n value was 102 in this instance.
‡ n value was 101 in this instance.

FIGURE 2 A, Insulin glargine dosage per titration group (safety population), and B, Mean fasting plasma glucose (FPG) levels over the 26-week study period (mITT population). Presentation of the 95% confidence intervals is used for descriptive purposes only

alternative to weekly titration, while allowing participants to reach their maintenance dose earlier. Non-inferiority and superiority were shown for the daily titration regimen when compared with a weekly titration regimen in people with T2D for the primary endpoint, change in HbA1c from baseline to week 26, as well as the key secondary endpoints, change in body weight from baseline to week 26 and percentage of participants reaching the composite of an HbA1c of 7.0% or less without body weight gain and without hypoglycaemia (severe or documented symptomatic [<3.9 mmol/L]).

Daily self-titration algorithms can simplify regimen complexity, and as a result help people to manage their diabetes more conveniently and effectively.[2,15,16] In the LixiLan ONE CAN study, participants in the daily titration arm reached higher doses of iGlarLixi (mean dose >40 units) 9 weeks earlier than in the weekly titration arm. These results show that those who sequentially increased their dose every day increased their overall exposure to the treatment in the early phase of the trial more so than those in the weekly titration arm, which probably contributed to the greater HbA1c reductions, better

TABLE 3 Safety outcomes including hypoglycaemic events and AEs (safety population)

Hypoglycaemia	iGlarLixi DAILY titration (n = 129)		iGlarLixi WEEKLY titration (n = 133)	
	Incidence, n (%)	Event rate (patient-year)	Incidence, n (%)	Event rate (patient-year)
Any hypoglycaemia	84 (65.1)	13.55	81 (60.9)	10.33
Documented symptomatic hypoglycaemia	64 (49.6)	8.13	62 (46.6)	6.25
Level 1 hypoglycaemia[a]	75 (58.1)	8.48	67 (50.4)	6.12
Level 2 hypoglycaemia[a]	19 (14.7)	0.65	22 (16.5)	0.93
Level 3 hypoglycaemia[a]	2 (1.6)	0.03	3 (2.3)	0.05
AEs	**iGlarLixi DAILY titration (n = 129)**		**iGlarLixi WEEKLY titration (n = 133)**	
Any TEAE, n (%)	75 (58.1)		85 (63.9)	
Any severe TEAE, n (%)	8 (6.2)		7 (5.3)	
Any TEAE causing discontinuation, n (%)	5 (3.9)		6 (4.5)	
Any treatment-related TEAE, n (%)	34 (26.4)		33 (24.8)	
At least one GI event, n (%)	36 (27.9)		37 (27.8)	
GI TEAE in ≥5% of participants in any treatment group,n (%)				
Nausea	17 (13.2)		14 (10.5)	
Diarrhoea	8 (6.2)		10 (7.5)	

Abbreviations: AEs, adverse events; GI, gastrointestinal; TEAE, treatment-emergent adverse event.
[a]Hypoglycaemic events were categorized according to the American Diabetes Association definitions, where level 1 includes episodes with plasma glucose <3.9 mmol/L (<70 mg/dl) and ≥3.0 mmol/L (≥54 mg/dl); level 2 includes episodes with plasma glucose <3.0 mmol/L (<54 mg/dl); level 3 includes severe hypoglycaemia requiring external assistance for recovery.

weight effect and improvements in FPG levels observed with daily titration.

There were no significant differences in the percentage of participants with any hypoglycaemia, and hypoglycaemia in the LixiLan ONE CAN study was driven mostly by mild (<3.9 mmol/L [<70 mg/dl]) episodes, with severe (<3.0 mmol/L [<54 mg/dl] or hypoglycaemia requiring external assistance for recovery) episodes being rare and comparable between daily and weekly titration groups.

The LixiLan ONE CAN study included a broad demographic, allowing those on sulphonylureas or SGLT2is to participate, which previously was not permitted in registration trials. At study entry, 53.6% of participants (56.8% in the daily arm vs. 50.4% in the weekly arm) were taking insulin secretagogues including sulphonylureas, and 37.7% of participants (38.6% in the daily arm vs. 36.8% in the weekly arm) were taking SGLT2is, with the continued use of concomitant glucose-lowering medications being permitted after randomization. Although dosing adjustments were made at the discretion of investigators in response to hypoglycaemia throughout the study, the LixiLan ONE CAN study setting may be more representative of real-world clinical care, as participants may be on multiple OADs, some of which have a higher risk for hypoglycaemia, when treatment intensification occurs.

In the LixiLan ONE CAN study, nausea and diarrhoea were the most commonly reported TEAEs. Such GI-related AEs associated with GLP-1 RAs can be mitigated by slowly increasing exposure through uptitration regimens.[7,14] Notably, in the current study, despite the earlier exposure to higher dosages with the iGlarLixi daily titration regimen, GI-related AEs were mild and balanced between the groups.

Intensification of insulin treatment may involve the addition of bolus insulin for greater improvement in glycaemic control; however, this may add complexity in terms of more frequent monitoring and assessing the carbohydrate content of meals.[5,6,14] The LixiLan ONE CAN study, which involved older, insulin-experienced people with a suboptimally controlled long duration of T2D, showed that daily self-titration of iGlarLixi resulted in HbA1c lowering of more than 1%, with less weight gain and no significant difference in any hypoglycaemia incidence compared with weekly titration. This method of daily self-titration is less complicated than alternative methods of intensification involving multiple daily injections, requiring only once a day blood glucose monitoring, and replicating simplified basal insulin titration strategies already used in practice with less weight gain and hypoglycaemia risk. Such simple dosing algorithms may facilitate people with T2D in self-titrating their insulin, potentially improve adherence to dose escalations and help to achieve optimum doses in real-life scenarios.[7,14,18,19]

Participants in both groups were satisfied with their new treatment in the LixiLan ONE CAN study, as measured by Diabetes Treatment Satisfaction Questionnaire (change). Changes in treatment satisfaction scores at week 26 from baseline were comparable between groups, and similar results were reported for individual questions between treatment arms (Table S1). All participants in this study were taught to self-administer iGlarLixi using the prefilled pen, which was evaluated for usability in a substudy of LixiLan ONE CAN. Results

from participant and healthcare provider questionnaires as part of this substudy showed that the iGlarLixi pen was easy/very easy to use, thus supporting the ease of transitioning from self-administration of basal insulin to iGlarLixi.[20]

The limitations to the LixiLan ONE CAN study include its short duration and also that the COVID-19 pandemic was ongoing during the trial, which may have impacted study discontinuation and adherence. Nonetheless, protocol deviations because of COVID-19 were reported in 44 (16.6%) participants; none were critical, and most were related to study visit attendance and laboratory availability. Pandemic disruptions did not impact the overall quality or outcome of the trial. A sensitivity analysis performed in the population without trial impact (disruption) because of COVID-19 showed results consistent with those of the primary efficacy analysis. Moreover, no COVID-19 pandemic-related TEAEs, severe AEs or deaths were reported. The other limitations were that although statistical non-inferiority, and superiority, of daily versus weekly titration was achieved, at 26 weeks, mean HbA1c values remained 7.0% or higher (despite routine SMPG and dose adjustments), changes in body weight were minor and low proportions of participants met the composite secondary endpoint. While choosing an alternative titration approach might slightly improve overall efficacy, it might not warrant achievement of treatment goals. LixiLan ONE CAN was a treat-to-target trial where titration was participant driven, and the study design was that the strategies to achieve the glycaemic goals were too cautiously implemented for achieving those goals for most participants. Alternative treatment approaches may be necessary for some patients. Another limitation was the exclusion of people taking a basal insulin dose of more than 40 units/day. Also excluded were those not on insulin at baseline, which may potentially limit the generalizability of these findings to those earlier in their disease course, given the demographics of this study included those with long-standing suboptimally controlled T2D. Lastly, this trial solely involved Canadian study centres, although the trial enrolled a sizable proportion of non-White participants. Thus, more studies are needed in other populations to confirm the results from this study and to determine the feasibility of a once daily titration algorithm for iGlarLixi in other real-life settings.

In conclusion, results from the LixiLan ONE CAN study showed that a daily self-titration algorithm of iGlarLixi was efficacious and well tolerated by people with T2D.

AUTHOR CONTRIBUTIONS

HCG, IH, J-FY, JS, LAL, SBH designed the study and analysis HB. HCG, IH, J-FY, LAL, SBH recruited the patients and collected the data. HCG, IH, J-FY, JS, LAL, SBH prepared the data for analysis. HCG, IH, JS, LAL, performed the analysis. HB, HCG, IH, J-FY, LAL, SBH, JS, M-JT interpreted the data. HCG, IH, J-FY LAL, SBH wrote the first draft. All authors critically reviewed the manuscript. JS, IH are guarantors of the work and had full access to the data and take responsibility for the accuracy of the data and the data analysis. All authors approved the final draft of the manuscript for submission.

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CONFLICT OF INTEREST

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DATA AVAILABILITY STATEMENT

Data are available upon reasonable request.

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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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