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Summary

Poster book

LixilanONE CAN: Randomized Trial Comparing a Daily vs Weekly Titration Algorithm for Switching from Basal Insulin to iGlarLixi Fixed-Ratio Combination in People with T2DM in Canada

Irene Hramiak, MD, FRCP(C), MACP[a]; Hertzel C. Gerstein, MD, MSc, FRCPC[b]; Lawrence A. Leiter, MD, FRCPC, FACP, FACE, FAHA, FACC[c]; Jean-François Yale, MD, FRCPC[d]; Harpreet S. Bajaj, MD, MPH, ECNU, FACE[e]; John Stewart, MSc[f]; Marie-Josée Toutounji, BPharm[g]; Stewart B. Harris, CM, MD, MPH, FCFP, FACPM[h]

[a]Western University, London, Ontario, Canada; [b]McMaster University Department of Medicine, Hamilton, Ontario, Canada; [c]Li Ka Shing Knowledge Institute, St Michael's Hospital, University of Toronto, Toronto, Ontario, Canada; [d]McGill University Health Centre, Montreal, Quebec, Canada; [e]LMC Healthcare, Brampton, Ontario, Canada; [f]SANOFI, Laval, Quebec, Canada; [g]SANOFI, Laval, Quebec, Canada; [h]Western University, London, Ontario, Canada.

Disclosures and Acknowledgements

Disclosures

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John Stewart and **Marie-Josée Toutounji** are employees of Sanofi and may hold shares and/or stock options in the company.

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Introduction and Study Objective

- The combination of basal insulin with a GLP-1 RA may be helpful for people with T2DM to achieve and maintain HbA1c targets compared with each component used individually[1]
- Previous studies have demonstrated that daily (dosage increase of 1 U/day) and weekly (dosage increase once a week) titration algorithms of insulin glargine alone resulted in achieving HbA1c targets, with similar incidence of hypoglycemia events across groups
  - The Canadian INSIGHT study demonstrated that insulin glargine 100 U/mL with 1 U/day titration was more likely to achieve a lower HbA1c level than conventional titration with oral agents with no differences in hypoglycemia[2]
  - The TITRATION study demonstrated that insulin glargine 300 U/mL with 1 U/day titration was effective and comparable to once weekly titration with similar frequency of adverse events between algorithms[3]
- Simple insulin titration, which fixed-ratio combination therapies follow, has a greater chance of adherence and reaching optimum doses in real-life scenarios[1,4]

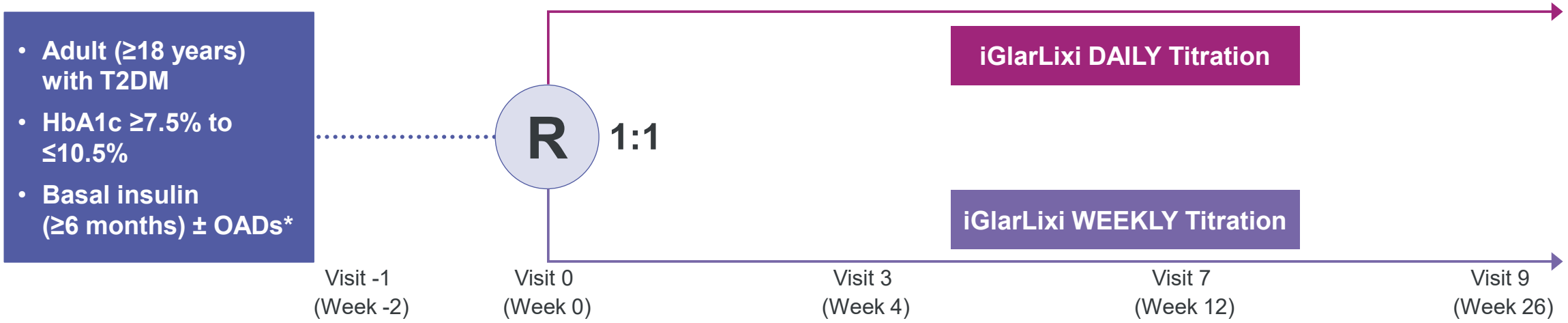
- **Objective: To evaluate whether a daily titration algorithm of iGlarLixi, a fixed-ratio combination of insulin glargine 100 U/mL and lixisenatide therapy, is non-inferior to a weekly titration algorithm**

GLP-1 RA: glucagon-like peptide-1 receptor agonist; HbA1c: glycated hemoglobin A1c; T2DM: type 2 diabetes mellitus; U: unit(s).

References: 1. American Diabetes Association. 9. Pharmacologic Approaches to Glycemic Treatment: *Standards of Medical Care in Diabetes-2021*. Diabetes Care. 2021 Jan;44(Suppl 1):S111-S124; 2. Gerstein HC, *et al*. *Diabetic Medicine* 2006;23(7):736–742; 3. Yale J-F, *et al*. *Can J Diabetes* 2017;41(5):478–484; 4. Haluzík M, *et al*. *Diabetes Ther* 11, 1029–1043 (2020).

LixilanONE CAN Study Design

- Randomized, 26-week, multicenter Phase 3 study (NCT03767543) in Canada
- T2DM and HbA1c ≥7.5% to ≤10.5% on ≤40 U/day basal insulin for ≥6 months



- **Primary endpoint:** Change in HbA1c (%) from baseline to Week 26
- **Secondary endpoints** included: change in body weight from baseline to Week 26, percentage of patients reaching HbA1c ≤7% with no body weight gain and/or hypoglycemia at Week 26, and insulin glargine dose at Week 26

* The basal insulin dose must be ≤40 U/day; the OADs allowed at inclusion were metformin, insulin secretagogues, DPP-4i, and SGLT2i.
DPP-4i: dipeptidyl peptidase 4 inhibitors; HbA1c: glycated hemoglobin A1c; OAD: oral antidiabetic drug; R: randomization; SGLT2i: sodium glucose co-transporter 2 inhibitors; T2DM: type 2 diabetes mellitus; U: unit(s).

LixilanONE CAN Study Titration Algorithms

- Participants were randomized (1:1) to receive iGlarLixi (1 hour before first meal of the day) to be titrated either:
  - Daily as noted below
  - Weekly as noted below

iGlarLixi DAILY Titration		iGlarLixi WEEKLY Titration	
Fasting SMPG	**Dose change**	**Fasting SMPG**	**Dose change**
≥5.7 mmol/L (≥103 mg/dL)	+1 U/day	>7.8 mmol/L (>140 mg/dL)	+4 U/day
		>5.6 and ≤7.8 mmol/L (>101 and ≤140 mg/dL)	+2 U/day
≤5.6 mmol/L (≤101 mg/dL)	No change	4.4 to 5.6 mmol/L (79 to 101 mg/dL)	No change
One value <4.4 mmol/L (<79 mg/dL) or symptomatic hypoglycemia	-1 U/day	One value <4.4 mmol/L (<79 mg/dL)	-2 U/day

SMPG: self-measured plasma glucose; U: unit(s).

LixilanONE CAN Baseline Demographics and Disease Characteristics

Randomized population	iGlarLixi DAILY Titration (N=132)	iGlarLixi WEEKLY Titration (N=133)
Age, mean, years (SD)	63.8 (11.6)	64.5 (10.4)
Age group, n (%)		
<50 years	17 (12.9)	14 (10.5)
≥50 and <65 years	46 (34.8)	47 (35.3)
≥65 and <75 years	48 (36.4)	49 (36.8)
≥75 years	21 (15.9)	23 (17.3)
Male, n (%)	84 (63.6)	81 (60.9)
HbA1c, mean, % (SD)	8.46 (0.75)	8.55 (0.85)
Duration of T2DM, mean, years (SD)	15.8 (6.7)	17.3 (9.0)
BMI, mean, kg/m^2 (SD)	29.7 (4.3)	28.9 (4.5)
BMI by category, n (%)		
<30 kg/m^2	70 (56.0)	82 (64.6)
≥30 kg/m^2	55 (44.0)	45 (35.4)
Daily dose of basal insulin, mean, unit (SD)	25.1 (10.1)	23.6 (9.8)
OAD, n (%)		
Metformin	117 (88.6)	114 (85.7)
DPP-4i	77 (58.3)	78 (58.6)
Insulin secretagogues	75 (56.8)	67 (50.4)
SGLT2i	50 (37.9)	49 (36.8)

BMI: body mass index; DPP-4i: dipeptidyl peptidase 4 inhibitors; HbA1c: glycated hemoglobin A1c; OAD: oral antidiabetic drug; SD: standard deviation; SGLT2i: sodium glucose co-transporter 2 inhibitors; T2DM: type 2 diabetes mellitus.

Daily Titration of iGlarLixi was Superior to a Weekly Titration for the Primary Endpoint of Change From Baseline in HbA1c at Week 26

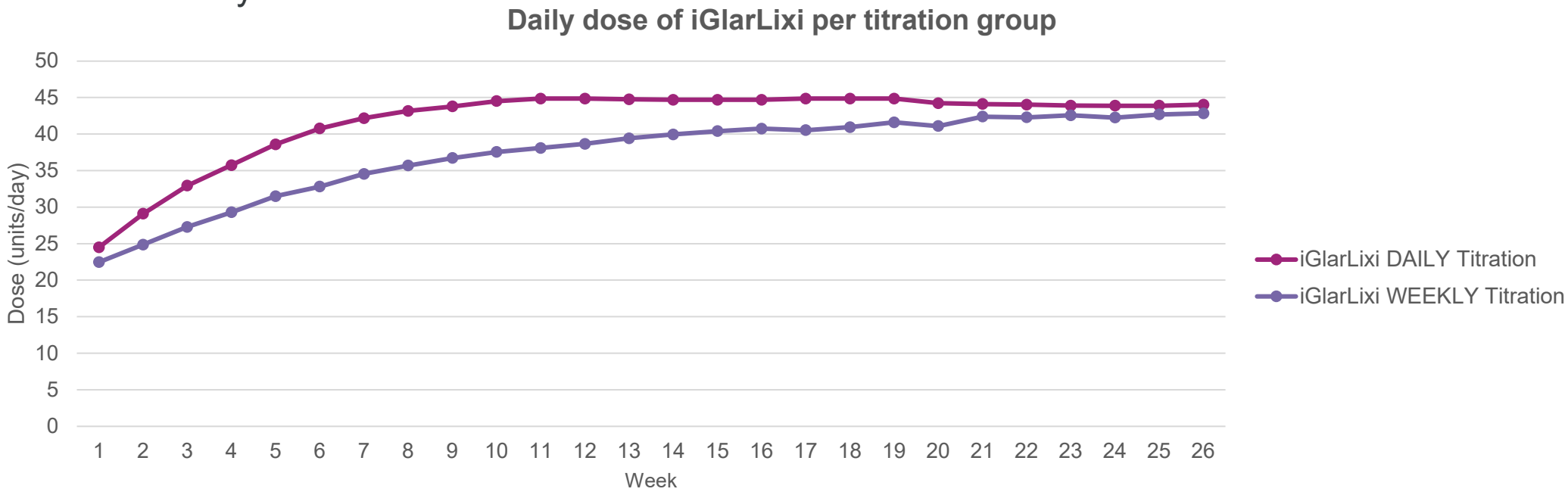
mITT population	iGlarLixi DAILY Titration			iGlarLixi WEEKLY Titration			LSM change for daily titration – weekly titration
	Baseline (N=132)	Week 26 (N=125)	LSM change from baseline to Week 26	Baseline (N=133)	Week 26 (N=131)	LSM change from baseline to Week 26	
Primary endpoint: Change in HbA1c from BL to Week 26, mean, %	8.5	7.3	-1.24 [95% CI: -1.42, -1.06]	8.6	7.6	-0.92 [95% CI: -1.10, -0.74]	-0.32* [95% CI: 0.07, 0.57]
Secondary endpoint: Change in weight from BL to Week 26, mean, kg	83.5	83.2	-0.22 [95% CI: -0.95, 0.51]	82.0	82.8	0.81 [95% CI: 0.09, 1.53]	-1.03* [95% CI: 0.01, 2.06]
* *p<0.0001* (non-inferiority).							

- For the secondary endpoint of change in weight from baseline to Week 26, daily titration of iGlarLixi was superior to a weekly titration
- The composite endpoint of HbA1c ≤7.0% and no weight gain OR hypoglycemia was achieved by a similar proportion of participants in the daily titration and weekly titration arms (LSM: 0.13 vs. 0.06, respectively; LSM difference: -0.07; 95% CI [-0.13, 0.00]; $p<0.001$ for non-inferiority).

BL: baseline; CI: confidence interval; HbA1c: glycated hemoglobin A1c; LSM: least squares mean; mITT: modified intent to treat.

Titration of the iGlarLixi Dose was Much Faster Among Those Randomized to the Daily Titration Algorithm

- In the safety population, a mean iGlarLixi dose of over 40 U was achieved by week 6 in the daily titration arm, and by week 15 in the weekly arm



Safety population	iGlarLixi DAILY Titration		iGlarLixi WEEKLY Titration	
	Week 1 (N=129)	Week 26 (N=99)	Week 1 (N=132)	Week 26 (N=101)
Insulin dose, mean, U/day	24.5	44.0	22.5	42.8

U: units.

Treatment Arms Were Comparable With Respect to Adverse Events and Hypoglycemia

AEs

Safety population	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)

Hypoglycemia

Safety population	iGlarLixi DAILY Titration (N=129)		iGlarLixi WEEKLY Titration (N=133)	
	Incidence, n (%)	Event rate (patient year)	Incidence, n (%)	Event rate (patient year)
Any hypo	84 (65.1)	13.55	81 (60.9)	10.33
Level 1 hypo†	75 (58.1)	8.48	67 (50.4)	6.12
Level 2 hypo†	19 (14.7)	0.65	22 (16.5)	0.93
Level 3 hypo†	2 (1.6)	0.03	3 (2.3)	0.05

*Most frequent AEs were nausea, diarrhea, vomiting and constipation; these were balanced across treatment arms.

† Level 1 includes episodes with plasma glucose <70 mg/dL (<3.9 mmol/L) and ≥54 mg/dL (≥3.0 mmol/L); level 2 includes episodes with plasma glucose <54 mg/dL (<3.0 mmol/L); level 3 includes severe hypoglycemia, defined as severe cognitive impairment requiring external assistance for recovery.
AEs: adverse events; GI: gastrointestinal; hypo: hypoglycemia; TEAE: treatment-emergent adverse event.
American Diabetes Association. 6. Glycemic Targets: *Standards of Medical Care in Diabetes-2021*. Diabetes Care. 2021 Jan;44(Suppl 1):S73-S84.

Discussion and Conclusion

- Daily iGlarLixi titration was non-inferior and superior to weekly titration for the primary endpoint of change in HbA1c from baseline to Week 26
- No difference in hypoglycemia and GI events was noted
- LixilanONE CAN demonstrated that a daily titration algorithm for iGlarLixi was safe and superior to weekly titration and allowed people with T2DM to reach their maintenance dose earlier

GI: gastrointestinal; HbA1c: glycated hemoglobin A1c; T2DM: type 2 diabetes mellitus.