SUPPLEMENTARY DATA

Efficacy and Safety of 1:1 Fixed Ratio Combination of Insulin Glargine/Lixisenatide (iGlarLixi) versus Lixisenatide in Japanese Patients with Type 2 Diabetes Mellitus Inadequately Controlled on Oral Antidiabetic Drugs: The LixiLan JP-O1 Randomized Clinical Trial

Contents

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Supplementary Table 1— iGlarLixi dose titration algorithm

Median of fasting SMPG from the last 3 measurements (mmol/L)	Dose titration of iGlarLixi (dose steps [units/µg]/day)
>7.8	+2
>5.6 and ≤7.8	+1
Glycemic target: ≥4.4 and ≤5.6	No change
≥3.3 and <4.4	−2
<3.3 or occurrence of 2 (or more) symptomatic hypoglycemic episodes or 1 severe hypoglycemic episode (requiring assistance) documented in the preceding week	−3 or more or at the discretion of the investigator or medically qualified designee

iGlarLixi, insulin glargine/lixisenatide fixed ratio combination; SMPG, self-monitored plasma glucose.

Supplementary Table 2—Efficacy end points at week 52

Parameter	iGlarLixi (n = 161)	Lixi (n = 160)
HbA_{1c}, % [mmol/mol]		
Baseline	8.39 ± 0.64 [68 ± 7.0]	8.38 ± 0.63 [68 ± 6.9]
Week 52	6.86 ± 0.80 [51 ± 8.7]	8.02 ± 1.05 [64 ± 11.5]
Change from baseline	−1.53 ± 0.92 [−16.7 ± 10.1]	−0.36 ± 1.11 [−3.9 ± 12.1]
HbA_{1c} <7% [53 mmol/mol], n (%)		
Week 52	99 (61.5)	25 (15.6)
HbA_{1c} ≤6.5% [48 mmol/mol], n (%)		
Week 52	66 (41.0)	7 (4.4)
FPG, mmol/L		
Baseline	9.83 ± 1.61	9.62 ± 1.71
Week 52	7.53 ± 1.75	9.71 ± 2.24
Change from baseline	−2.30 ± 1.76	0.07 ± 2.29
Average 7-point SMPG, mmol/L		
Baseline	11.39 ± 1.98	11.26 ± 2.00
Week 52	8.43 ± 1.74	10.65 ± 2.56
Change from baseline	−2.96 ± 2.31	−0.55 ± 2.62
Body weight, kg		
Baseline	72.26 ± 14.80	72.95 ± 14.87
Week 52	73.26 ± 14.96	71.46 ± 15.02
Change from baseline	1.00 ± 2.97	−1.53 ± 2.32
HbA_{1c} <7% with no weight gain, n (%)		
Week 52	47 (29.2)	24 (15.0)
Daily iGlar dose*, units		
Day 1	5.00 ± 0.00	
Week 52	17.01 ± 4.04	
Change from day 1	12.01 ± 4.04	
Patients requiring rescue therapy, n (%)		
Week 52	3 (1.9)	37 (23.1)

Data are shown as mean ± SD unless otherwise indicated. Includes only patients for whom both baseline and week 52 (LOCF) measurements are available for continuous end points. Patients were treated as non-responders if they had no assessments at week 52 (LOCF) for categorical end points. Analysis included measurements obtained before the introduction of rescue medication and up to 14 days for HbA_{1c}, 1 day for FPG, 0 day for average 7-point SMPG and iGlar dose, and 3 days for body weight after the last injection of open-label study drug. Number of patients analyzed at week 52: n (iGlarLixi) = 161 and n (Lixi) = 157 for FPG; n (iGlarLixi) = 160 and n (Lixi) = 148 for average 7-point SMPG; n (iGlarLixi) = 161 and n (Lixi) = 157 for body weight. iGlarLixi, insulin glargine/lixisenatide fixed ratio combination; Lixi, lixisenatide; FPG, fasting plasma glucose; SMPG, self-monitored plasma glucose; iGlar, insulin glargine; SD, standard deviation; LOCF, last observation carried forward. *Dose of first injection of open-label study drug was considered as average daily insulin dose at day 1. Since iGlarLixi contains a 1:1 fixed ratio combination of iGlar (units) and Lixi (μg), results in iGlarLixi group are considered as results of Lixi dose (μg).

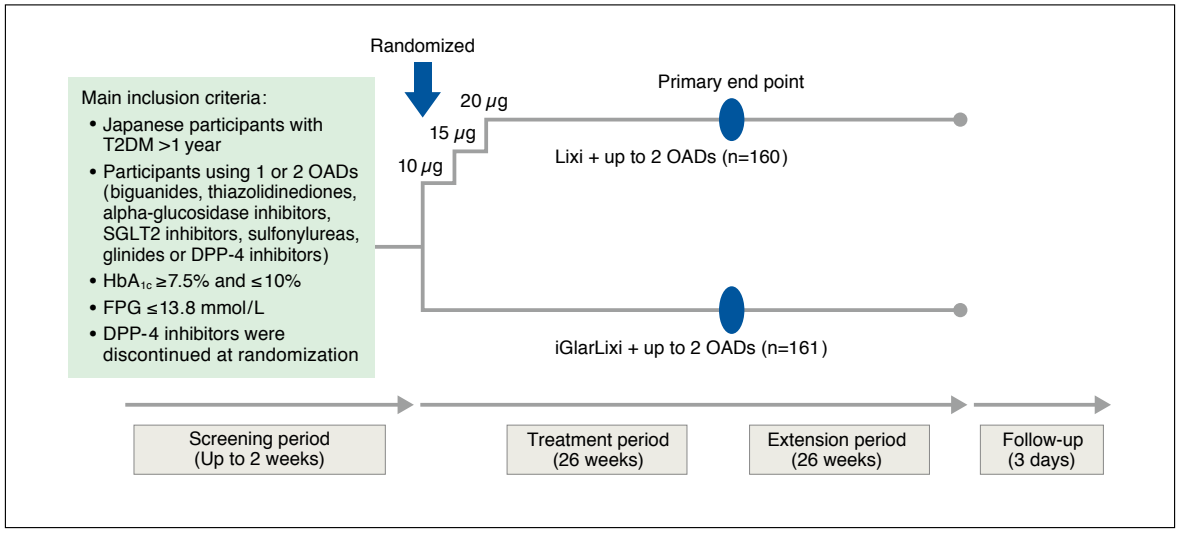
Supplementary Table 3—Summary of serious TEAEs

Serious TEAE by organ class and PT*, n (%)	iGlarLixi (n = 161)		Lixi (n = 160)	
	Week 26	Week 52	Week 26	Week 52
Any serious TEAE	5 (3.1)	7 (4.3)	4 (2.5)	13 (8.1)
Infections and infestations	0	0	0	4 (2.5)
Appendicitis	0	0	0	1 (0.6)
Liver abscess	0	0	0	1 (0.6)
Pneumonia	0	0	0	1 (0.6)
Pyelonephritis	0	0	0	1 (0.6)
Neoplasms benign, malignant and unspecified (incl. cysts and polyps)	2 (1.2)	2 (1.2)	0	0
Benign neoplasm of skin	1 (0.6)	1 (0.6)	0	0
Tongue neoplasm malignant stage unspecified	1 (0.6)	1 (0.6)	0	0
Metabolism and nutrition disorders	0	0	1 (0.6)	1 (0.6)
Diabetes mellitus inadequate control	0	0	1 (0.6)	1 (0.6)
Cardiac disorders	1 (0.6)	1 (0.6)	1 (0.6)	3 (1.9)
Myocardial ischaemia	1 (0.6)	1 (0.6)	0	0
Angina pectoris	0	0	0	1 (0.6)
Cardiac failure congestive	0	0	1 (0.6)	1 (0.6)
Coronary artery stenosis	0	0	0	1 (0.6)
Respiratory, thoracic and mediastinal disorders	0	0	1 (0.6)	1 (0.6)
Pulmonary alveolar haemorrhage	0	0	1 (0.6)	1 (0.6)
Gastrointestinal disorders	0	0	1 (0.6)	1 (0.6)
Pancreatitis acute	0	0	1 (0.6)	1 (0.6)
Hepatobiliary disorders	1 (0.6)	1 (0.6)	0	1 (0.6)
Bile duct stone	1 (0.6)	1 (0.6)	0	0
Jaundice cholestatic	0	0	0	1 (0.6)
Skin and subcutaneous tissue disorders	1 (0.6)	1 (0.6)	0	0
Skin ulcer	1 (0.6)	1 (0.6)	0	0
Musculoskeletal and connective tissues disorders	0	1 (0.6)	0	1 (0.6)
Osteoarthritis	0	1 (0.6)	0	1 (0.6)
Congenital, familial and genetic disorders	1 (0.6)	1 (0.6)	0	0
Atrial septal defect	1 (0.6)	1 (0.6)	0	0
Injury, poisoning and procedural complications	0	1 (0.6)	1 (0.6)	3 (1.9)
Fractured ischium	0	1 (0.6)	0	0
Cardiac contusion	0	0	1 (0.6)	1 (0.6)
Femoral neck fracture	0	0	0	1 (0.6)
Humerus fracture	0	0	0	1 (0.6)
Sternal fracture	0	0	1 (0.6)	1 (0.6)

Table shows time from first injection of open-label study drug up to 3 days after the last injection of open-label study drug regardless of introduction of rescue therapy. For 26-week treatment period, last injection of open-label study drug was at or before week 26 visit (or day 183 if week 26 visit was missing). iGlarLixi, insulin glargine/lixisenatide fixed ratio combination; Lixi, lixisenatide; TEAE, treatment-emergent adverse event; PT, preferred term.

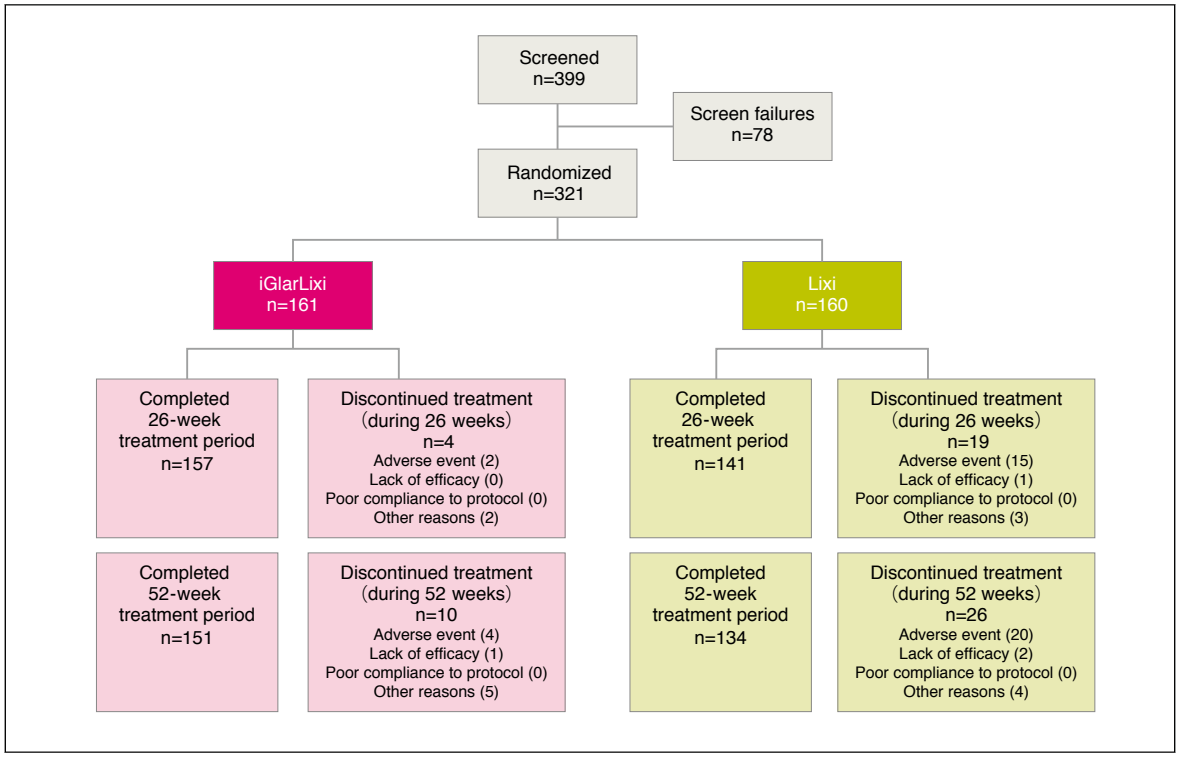
* Based on Medical Dictionary for Regulatory Activities Version 20.1.

Supplementary Fig. 1—Study design.



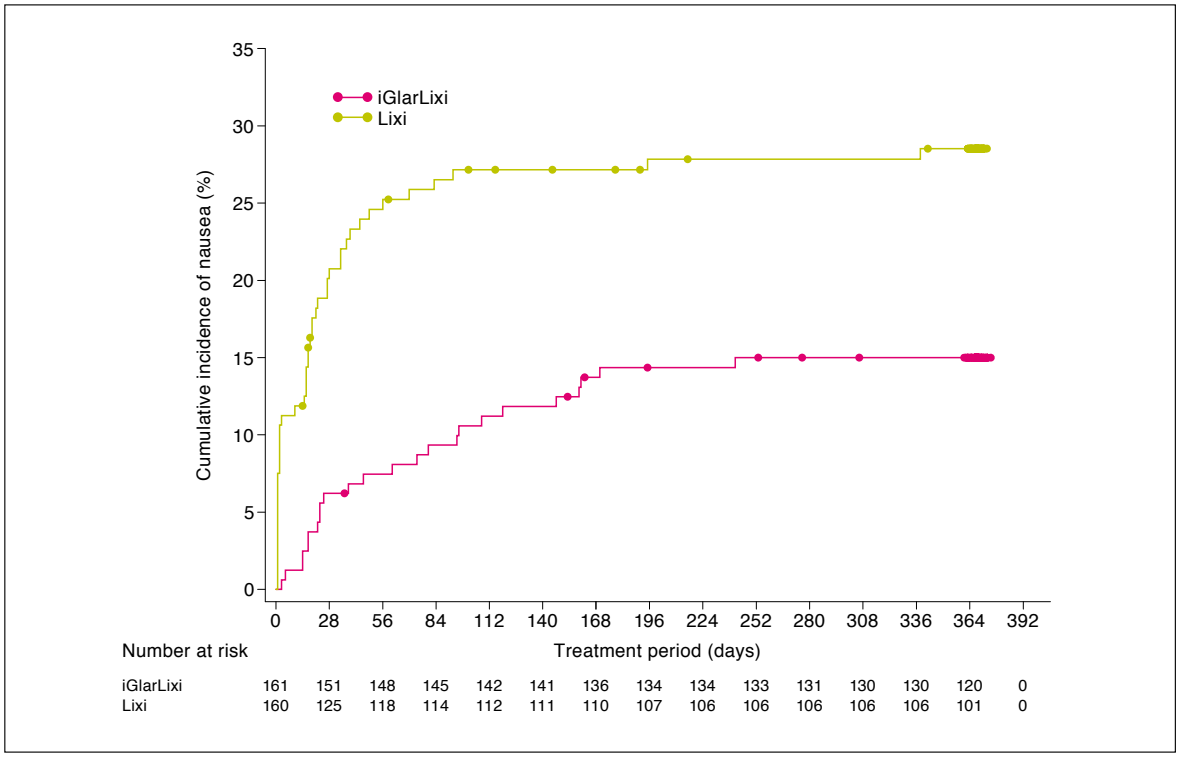
T2DM, type 2 diabetes mellitus; OAD, oral antidiabetic drug; SGLT2, sodium glucose cotransporter-2; DPP-4, dipeptidyl peptidase 4; FPG, fasting plasma glucose; Lixi, lixisenatide; iGlarLixi, insulin glargine/lixisenatide fixed ratio combination.

Supplementary Fig. 2—Patient flowchart: screening, randomization, and discontinuation.



iGlarLixi, insulin glargine/lixisenatide fixed ratio combination; Lixi, lixisenatide.

Supplementary Fig. 3—Incidence of nausea throughout the study.



The 52-week treatment period is defined as the time from the first injection of open-label study drug up to 3 days after the last injection of open-label study drug regardless of the introduction of rescue therapy. iGlarLixi, insulin glargine/lixisenatide fixed ratio combination; Lixi, lixisenatide.