



Ultra-Rapid Lispro Efficacy and Safety Compared to Humalog® in Japanese Patients With Type 2 Diabetes: PRONTO-T2D Subpopulation Analysis

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ABSTRACT

Introduction: The aim of this study was to evaluate the efficacy and safety of ultra-rapid lispro (URLi) versus lispro in a subgroup analysis of Japanese adults with type 2 diabetes mellitus (T2DM) from the phase 3 PRONTO-T2D trial.

Methods: After an 8-week lead-in period during which patients transitioned to insulin lispro 3 times a day before main meals in association with basal insulin (glargine or degludec), the patients were randomized to 26 weeks of double-blind URLi or lispro injected immediately prior to meals. The primary endpoint was change in hemoglobin A1c (HbA1c) from baseline to week 26 between URLi and lispro. The multiplicity-adjusted objectives were 1- and 2-h postprandial glucose (PPG) excursions after a test meal and change in HbA1c from baseline to week 26 in the URLi and lispro groups.

Results: Results were obtained from prespecified exploratory analyses of 26-week data in

Japanese patients randomized to receive URLi ($n = 47$) or lispro ($n = 46$). Mean baseline HbA1c levels significantly improved during the lead-in period to a baseline value of 7.50% and 7.60% in patients subsequently randomized to the URLi and lispro treatment groups, respectively. At week 26, the least squares mean (LSM) difference in HbA1c between the URLi and lispro groups was 0.13% (95% confidence interval [CI] – 0.12 to 0.39) (1.4 mmol/mol, 95% CI – 1.3 to 4.2). Although there were no significant differences in PPG excursions at any time-point, numerically smaller PPG excursions were consistently observed from 30 min to 3 h during the mixed-meal tolerance test in patients on URLi compared to those on lispro. LSM differences in PPG excursions at week 26 were – 10.5 mg/dL (95% CI – 32.7 to 11.7) (– 0.58 mmol/L, 95% CI – 1.82 to 0.65) at 1 h and – 14.9 mg/dL (95% CI – 40.3 to 10.5) (– 0.83 mmol/L, 95% CI – 2.24 to 0.58) at 2 h. There were no significant differences between treatments in rates of severe/overall hypoglycemia or incidence of treatment-emergent adverse events.

Conclusions: URLi administered as prandial insulin in combination with basal insulin provides effective glycemic control when administered immediately before a meal in Japanese patients with T2DM. URLi was well tolerated in this population.

Trial Registration: ClinicalTrials.gov, NCT03214380.

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Key Summary Points

Why carry out this study?

The prevalence of diabetes in Japan is increasing and there is an medical need for the development and official approval of rapid-acting insulins.

We evaluated the efficacy and safety of ultra-rapid lispro (URLi) in comparison to Humalog® (lispro) in Japanese patients with T2DM in a phase 3, randomized, subpopulation analysis.

What was learned from the study?

URLi and lispro provide effective and comparable glycemic control (including postprandial glycemic control).

URLi provides effective glycemic control in Japanese patients with type 2 diabetes and is well tolerated.

INTRODUCTION

The vast majority of people with diabetes have type 2 diabetes mellitus (T2DM), and the increasing global prevalence of T2DM represents a worldwide health burden [1]. Adequate blood glucose control is important for preventing diabetic complications and cardiovascular disease, and for reducing the medical and public health burden of T2DM [1]. For patients with T2DM, reaching and maintaining glycemic goals remain challenging, with many patients experiencing difficulties [2, 3] achieving the target hemoglobin A1c (HbA1c) of < 7% [3]. In Japan, where the prevalence of diabetes is increasing [4], the mean HbA1c of patients with T2DM is 7.03% [5], with only approximately

50% of patients reaching the recommended target [5].

Control of both fasting and postprandial hyperglycemia is essential to reach HbA1c goals. It has been demonstrated that postprandial hyperglycemia contributes to overall glucose control as assessed by HbA1c, and increases the risk of micro- and macrovascular complications and death in diabetic patients [6–10]. There is substantial evidence to support the association of postprandial glucose (PPG) levels with the development of complications in T2DM [11]. However, control of postprandial hyperglycemia continues to be a challenge [12] in the overall treatment of T2DM patients, with increased PPG levels significantly associated with increased healthcare resource utilization [13]. Currently available rapid-acting insulins were developed to manage PPG levels [14–18] and have been found to be a superior treatment for lowering postprandial glycemic excursions [15,19].

Lispro (Humalog®; Eli Lilly and Company) is a commercially available, rapid-acting human insulin analogue indicated to improve glycemic control in patients with diabetes mellitus [20]. Fast-acting insulin aspart (Fiasp®; Eli Lilly and Company) is a formulation of the rapid-acting insulin analogue insulin aspart that was recently approved for the treatment of T2DM in Japan (September 2019). Ultra-rapid lispro (URLi; intervention study name LY900014) is a newly developed insulin lispro formulation that utilizes two enabling excipients, treprostinil and citrate, each with an independent mechanism, to accelerate the absorption of the insulin lispro. Treprostinil is used in microdose quantities in the formulation of URLi but is not detectable in clinical doses in the systemic circulation, nor is it associated with systemic effects. URLi was formulated to more closely mimic the physiological prandial insulin secretion pattern, and the expectation is that it will control PPG excursions more effectively than lispro.

PRONTO-T2D was a recent, prospective, randomized, double-blind phase 3 trial in adults with T2DM which compared URLi to lispro, in combination with insulin glargine or insulin degludec [21]. This pivotal study demonstrated

that URLi was non-inferior to lispro in maintaining glycemic control [21]. Here we describe a Japanese subpopulation analysis of the PRONTO-T2D trial. The aim of this subpopulation analysis was to evaluate the efficacy and safety of URLi administered at mealtime, in comparison to lispro, in Japanese patients with T2DM.

METHODS

Study Participants

The study design has been described previously [21]. Briefly, adults with clinically diagnosed T2DM (based on the World Health Organization classification [22]) for at least 1 year prior to screening and with HbA1c levels between 7.0% (53.0 mmol/mol) and 10.0% (85.8 mmol/mol) inclusive were eligible to participate. Exclusion criteria included hypoglycemia unawareness, as assessed by an investigator, ≥ 1 event of severe hypoglycemia requiring medical assistance, diabetic ketoacidosis or a hyperglycemic hyperosmolar state within 6 months prior to screening.

Study Design

PRONTO-T2D was a phase 3, prospective, randomized, double-blind, outpatient, multinational, multicenter, two-group, parallel, active-controlled study conducted in patients with T2DM which compared URLi to insulin lispro, in combination with basal insulin. URLi and lispro were administered immediately (0–2 min) prior to each meal in combination with insulin degludec or glargine. Patients were able to continue their therapy with metformin and/or sodium-glucose cotransporter-2 inhibitor throughout the study. Randomization was followed by 26 weeks of treatment and a 4-week safety follow-up period. Here we report the results of a prespecified subpopulation analysis of Japanese patients from the PRONTO-T2D trial. The study design is outlined in Fig. 1.

The study was conducted in accordance with the International Council for Harmonization Guidelines for Good Clinical Practice, including

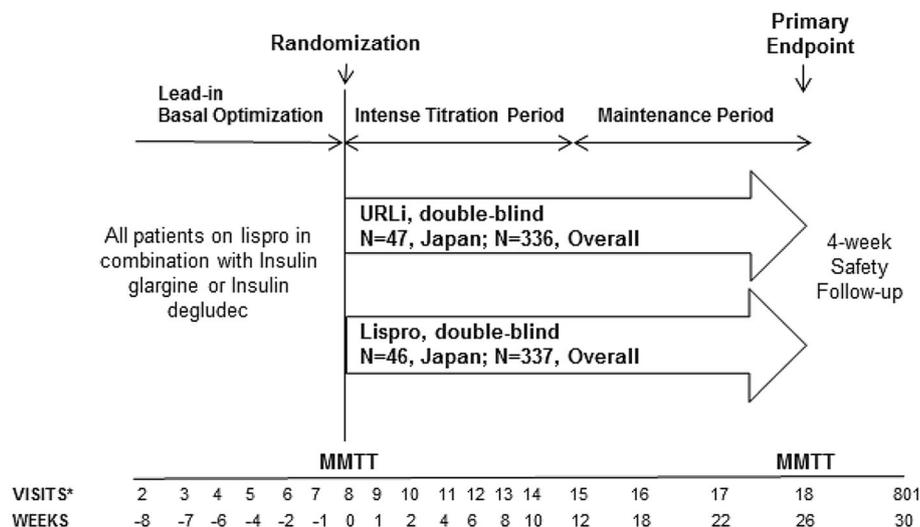
the Declaration of Helsinki and its later amendments, and the Council for International Organization of Medical Sciences International Ethical Guidelines. An Ethical Review Board at each site (Kobori Clinic, H.E.C. Science Clinic, Jinnouchi Hospital, Heiwadai Hospital, The Institute for Adult Diseases, Naka Memorial Clinic, Tomonaga Clinic, Nihonbashi Sakura Clinic, AMC Nishi-umeda Clinic, Manda Hospital, Fukuoka Red Cross Hospital, Shin Akasaka Clinic, Shinagawa East One Medical Clinic, Sasebo Chuo Hospital, Okuguchi Clinic of Internal Medicine, Sapporo Skin Clinic, Takatsuki Red Cross Hospital, Osaka City University Medical School Hospital, Goshogatani Home Clinic, Tokyo Women's Medical University Hospital) approved all procedures, and all subjects provided written, informed consent.

Study Interventions and Randomization

The study consisted of an 8-week lead-in period during which time patients transitioned to insulin lispro 3 times a day before main meals in combination with basal insulin (glargine or degludec). Following the lead-in period, patients were randomized to one of two treatment groups in a 1:1 ratio, URLi 100 U/mL or lispro 100 U/mL, administered 0–2 min prior to the start of each meal. Following randomization, the prandial insulin dose was adjusted as necessary during the initial 12 weeks in a treat-to-target manner to self-monitored blood glucose (SMBG) levels of 80 to < 110 mg/dL (4.4–6.1 mmol/L) fasting or premeal, 90–130 mg/dL (5.0–7.2 mmol/L) bedtime and < 140 mg/dL (< 7.8 mmol/L) 1–2 h postmeal. Patients were able to use the carbohydrate counting method or the pattern adjustment method to adjust their insulin dose. During weeks 12–26 of treatment, adjustments to prandial and basal insulin doses were only performed to maintain glycemic control or for safety reasons, such as hypoglycemia or unacceptable hyperglycemia.

Standardized Meal Test

All participants underwent a 4-h mixed-meal tolerance test (MMTT) at baseline and at the



*Visits 3, 4, 6, 9, 12, 14 were telephone visits

Fig. 1 Study design. Following a 1-week screening period and an 8-week lead-in period, Japanese patients were randomized in a 1:1 ratio to receive ultra-rapid lispro (*URLi*) or lispro for 26 weeks, administered immediately (0–2 min) prior to each meal in combination with insulin

degludec or glargine. All patients underwent a 4-h mixed-meal tolerance test (*MMTT*) at baseline (week 0, visit 8) and at the end of primary treatment period (week 26, visit 18). *N* Number of patients

end of the 26-week treatment period. The *MMTT* meal (700 kcal including approximately 100 g of carbohydrate) consisted of a liquid nutrition shake and had to be consumed within 15 min.

Self-Monitored Blood Glucose

All study participants were instructed to perform three sets of 10-point SMBG profiles prior to five visits (baseline, weeks 4, 8, 12, and 26). Participants were also instructed to measure a minimum of four SMBG readings daily (morning, midday and evening premeal and prebed-time), with additional SMBG readings as needed for glucose self-management.

Study Endpoints

The primary endpoint was the change in HbA1c from baseline to week 26. Key secondary endpoints were 1- and 2-h PPG excursions during the *MMTT*. Other secondary endpoints

included the percentage of patients who achieved the target HbA1c, 10-point SMBG values and safety measurements.

Statistical Analysis

The efficacy analysis was conducted as previously described for the overall population [21]. These methods were applied to the Japanese population in a prespecified subset analysis, although statistical power was not taken into consideration, and *p* values are provided as a reference.

Safety Analysis

Safety measures included primary adverse events (AEs), hypoglycemia and weight. When statistical comparisons were applied, the Fisher's exact test was employed. Severe hypoglycemia (an episode requiring assistance due to neurological impairment as confirmed by the investigator)

was reported as a severe AE (SAE) and summarized by rate and incidence.

RESULTS

Study Participants in the Japanese Subpopulation

The Japanese subpopulation comprised 93 patients of the 673 randomized patients in the overall patient population of the PRONTO-T2D trial. Of these 93 patients, 47 were randomized to the URLi treatment arm and 46 were randomized to the lispro treatment arm. All Japanese patients completed the study. Baseline patient characteristics are outlined in Table 1. Overall, baseline characteristics were similar between the treatment groups with the exception of gender: there were more males in the URLi treatment arm than in the lispro treatment arm (83.0 vs. 58.7%, respectively).

Efficacy

Glycated hemoglobin

The primary study endpoint was the change in HbA1c from baseline to week 26. For the overall patient population of the PRONTO-T2D trial, non-inferiority of URLi to lispro was confirmed in the change in HbA1c from baseline to week 26 [21] (the upper 95% confidence interval [CI] of least squares mean [LSM] difference was $< 0.4\%$, defined as the prespecified non-inferiority criteria for the overall population).

In the Japanese patients of our subanalysis, the mean HbA1c at study entry was 8.1% (64.5 mmol/mol) and 8.1% (65.3 mmol/mol) for patients randomized at baseline (i.e. end of lead-in period) to the URLi and lispro treatment arms, respectively. The mean HbA1c improved during the lead-in period, during which time all patients were treated with lispro plus basal insulin (degludec or glargine), to baseline values of 7.5% (58.5 mmol/mol) for patients randomized to the URLi treatment group and 7.6% (59.5 mmol/mol) for patients randomized to the lispro treatment group. The changes in the LSM from baseline to week 26 was -0.22%

(-2.4 mmol/mol) for the URLi group and -0.35% (-3.9 mmol/mol) for the lispro group. At week 26, the LSM difference between the URLi and lispro treatment groups was 0.13% (95% CI -0.12 to 0.39) (1.4 mmol/mol, 95% CI -1.3 to 4.2). HbA1c levels at baseline and at weeks 4, 8, 12 and 26 are shown in Fig. 2.

At week 26, the HbA1c target of $< 7.0\%$ was achieved by 15 of the 47 patients (31.91%) in the URLi treatment arm and by 14 of the 46 patients (30.43%) in the lispro treatment arm (odds ratio [OR] 1.10, 95% CI 0.42–2.87), and the HbA1c target of $\leq 6.5\%$ was achieved by eight (17.02%) and eight (17.39%) patients in these treatment arms, respectively (OR 0.99, 95% CI 0.33–2.96).

Meal Test/Postprandial Excursions

In this Japanese subpopulation, there were no statistically significant differences at week 26 in PPG excursions between the URLi and lispro treatment arms at 1 h postmeal (LSM differences -10.5 mg/dL, 95% CI -32.7 to 11.7 [-0.58 mmol/L, 95% CI -1.82 to 0.65]) or 2 h postmeal (LSM differences -14.9 mg/dL, 95% CI -40.3 to 10.5 [-0.83 mmol/L, 95% CI -2.24 to 0.58]). Although treatment with mealtime URLi and lispro did not result in significant differences at week 26 in terms of controlling PPG excursions, consistent numerically smaller excursions were observed for URLi at time-points ranging from 30 min to 3 h after the meal. The mean insulin dose during the MMTT at week 26 was similar between the URLi (8.9 U/mL [0.12 U/kg]) and lispro (10.7 U/mL [0.14 U/kg]) treatment groups. PPG excursions during the MMTT at week 26 for both treatment groups is shown in Fig. 3.

A reduction in the incremental area under the serum glucose concentration–time curve (iAUC), above the glucose level at the start of MMTT, was observed during the MMTT for URLi in comparison to lispro at all measured time intervals from 30 min to 4 h (0–30 min, 0–1 h, 0–2 h, 0–3 h, 0–4 h). Serum glucose iAUC at all time intervals during the 4-h MMTT at 26 weeks was statistically significantly lower in the URLi group than in the lispro group.

Table 1 Baseline characteristics in the subpopulation of Japanese patients from the PRONTO-T2D trial

Patient characteristics	Treatment arm		Total study population (<i>N</i> = 93)
	URLi (<i>N</i> = 47)	Lispro (<i>N</i> = 46)	
Age (years)	58.7 (9.6)	59.5 (9.3)	59.1 (9.4)
Gender, male, <i>n</i> (%)	39 (83.0)	27 (58.7)	66 (71.0)
Weight (kg)	73.3 (13.0)	73.2 (14.6)	73.2 (13.7)
Body mass index (kg/m ²)	26.2 (3.6)	27.8 (5.1)	27.0 (4.4)
Duration of T2DM (years)	17.3 (8.3)	16.2 (8.0)	16.8 (8.1)
HbA1c at study entry (%)	8.1 (0.8)	8.1 (0.7)	8.1 (0.7)
Baseline HbA1c (%)	7.5 (0.6)	7.6 (0.8)	7.6 (0.7)
Fasting serum glucose (mg/dL)	124.3 (30.5)	123.1 (29.3)	123.7 (29.7)
Metformin treatment, <i>n</i> (%)	24 (51.1)	21 (45.7)	45 (48.4)
SGLT-2 inhibitor treatment, <i>n</i> (%)	14 (29.8)	13 (28.3)	27 (29.0)
Bolus insulin at study entry, <i>n</i> (%)			
Aspart	16 (39.0)	19 (54.3)	35 (46.1)
Glulisine	10 (24.4)	6 (17.1)	16 (21.1)
Lispro 100 U/mL	15 (36.6)	10 (28.6)	25 (32.9)
Basal insulin at baseline, <i>n</i> (%)			
Degludec (QD)	21 (44.7)	21 (45.7)	42 (45.2)
Glargine (QD)	26 (55.3)	25 (54.3)	51 (54.8)
Prandial insulin dosing plan, <i>n</i> (%)			
Pattern adjustment	46 (97.9)	46 (100.0)	92 (98.9)
Carbohydrate counting	1 (2.1)	0 (0)	1 (1.1)

Values in table are presented as the mean with the standard deviation (SD) in parenthesis, unless otherwise indicated. *HbA1c* Hemoglobin A1c, *n* number of patients, *N* number of patients, *QD* once daily, *SGLT-2* sodium-glucose cotransporter-2, *T2DM* type 2 diabetes mellitus, *URLi* ultra-rapid lispro

Self-Monitored Blood Glucose

A time course of 10-point SMBG profiles at week 26 for both treatment groups is outlined in Fig. 4. At week 26, LSM differences for the morning postmeal glucose excursions were -26.8 mg/dL (95% CI -43.8 to -9.8) (-1.49 mmol/L) at 1 h postmeal and -21.9 mg/dL (95% CI -40.7 to -3.1) (-1.22 mmol/L) at 2 h postmeal; LSM differences for the midday postmeal glucose excursions were -9.2 mg/dL (95% CI -27.3 to 8.8) (-0.51 mmol/L) at 1 h postmeal and -0.6 mg/

dL (95% CI -21.1 to 20.0) (-0.03 mmol/L) at 2 h postmeal; and LSM differences for the evening postmeal glucose excursions were -13.3 mg/dL (95% CI -34.2 to 7.6) (-0.74 mmol/L) at 1 h postmeal and -8.4 mg/dL (95% CI -28.6 to 11.8) (-0.47 mmol/L) at 2 h postmeal.

Overall, daily average blood glucose levels in the 10-point SMBG profiles were similar between treatment groups, with the exception of significantly higher blood glucose levels in the lispro group compared to the URLi group at

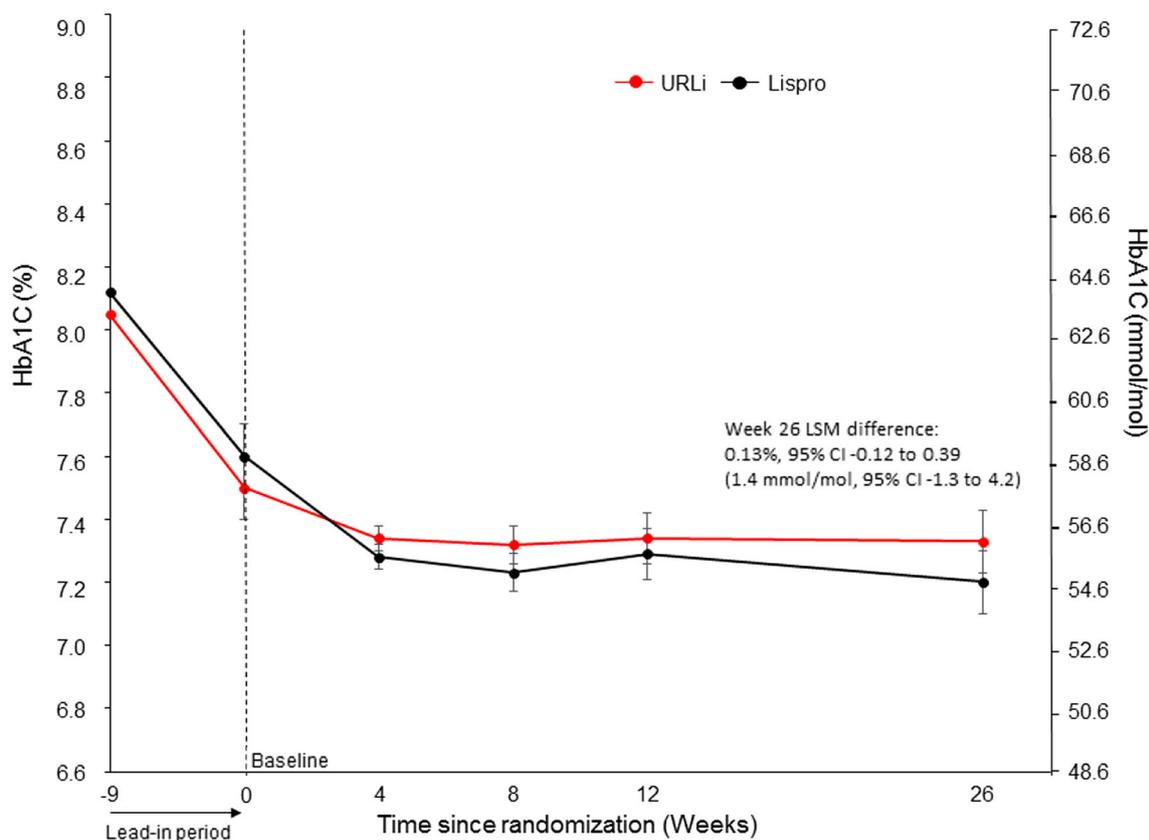


Fig. 2 Glycated hemoglobin (*HbA1c*) profile by visit during the lead-in period and 26 weeks of treatment in Japanese patients. HbA1c levels for patients subsequently randomized to the URLi and lispro treatment arms during the lead-in period and from baseline to week 26 are given

in percentage and in nanomoles per mole (mmol/mol). Data are presented as the mean at study entry and as the least squares mean (*LSM*) \pm standard error (*SE*) at all other time-points. *CI* Confidence interval

the morning postmeal time-points of 1 h (*LSM* difference -25.3 mg/dL [-1.41 mmol/L], $p = 0.001$) and 2 h (*LSM* difference -22.3 mg/dL [-1.24 mmol/L], $p = 0.005$) (Fig. 4).

Insulin Dose

The total daily basal insulin dose at baseline was 0.28 U/kg for URLi and 0.32 U/kg for lispro. At week 26, the daily basal insulin dose was 0.33 U/kg for both URLi and lispro. The ratio of prandial to total insulin dose at week 26 was similar between the URLi and lispro treatment groups (56 and 53%, respectively; $p = 0.663$).

Safety and Tolerability

A summary of AEs is outlined in Table 2. Overall, the incidence of treatment-emergent AEs (TEAEs) related to the study treatment and SAEs was low, and similar for both treatment groups. In addition, the majority of the TEAEs related to the study treatment were mild and resolved without dose adjustment. There were no discontinuations from the study, or from study treatment, due to an AE. At week 26, mean change in body weight from baseline was 1.2 kg in the URLi treatment group and 1.3 kg in the lispro treatment group.

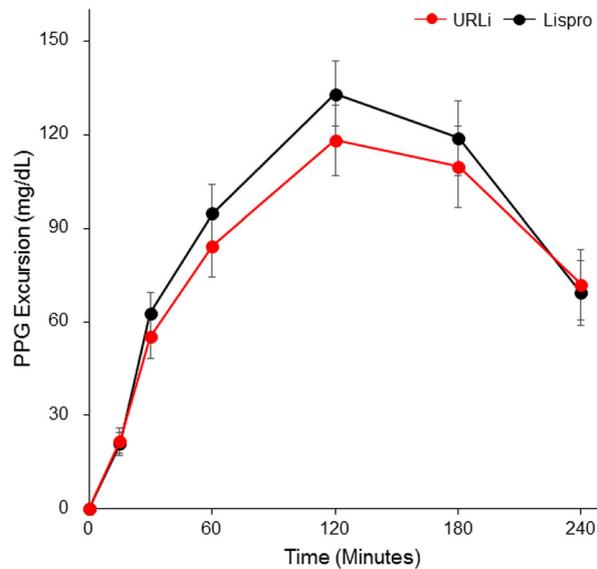


Fig. 3 Postprandial glycemic excursions during the MMTT at week 26 in Japanese patients. Postprandial glucose (PPG) excursions (mg/dL) following URLi or lispro treatment at time-points ranging from 15 min to 4 h during the MMTT are shown. Data are presented as LSM \pm SE

During the 26-week treatment period, no severe hypoglycemia was observed, and there were no significant differences between treatment groups in the incidence of documented symptomatic hypoglycemia and in the rate and

incidence of non-nocturnal hypoglycemia with glucose $<$ 54 mg/dL. The rate of documented symptomatic hypoglycemia (events/patients per 30 days) with glucose $<$ 54 mg/dL was significantly higher in the URLi treatment group than in the lispro treatment group (Table 3).

The rate and incidence of postprandial hypoglycemia at the time-points of \leq 2 h was statistically significantly higher in the URLi group than in the lispro group, but there were no significant differences in the late postprandial period ($>$ 4 h postmeal). No statistical differences were observed between the two treatments between 2 and 4 h (Fig. 5).

DISCUSSION

The PRONTO-T2D study demonstrated that URLi is non-inferior to lispro in terms of change in HbA1c following 26 weeks of treatment and that URLi is superior to lispro at reducing 1- and 2-h PPG excursions during the meal test [21]. In our subpopulation analysis of Japanese patients with T2DM, URLi demonstrated effective glycemic control when used in combination with basal insulin, with an acceptable safety profile. This is the first study to report the efficacy and safety of URLi compared to lispro in this patient population and provides valuable information for clinicians and policy-makers in Japan.

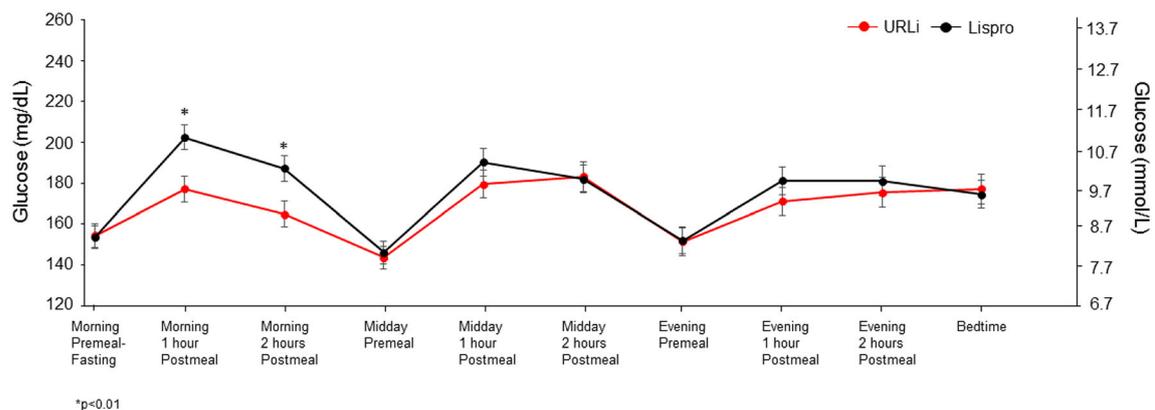


Fig. 4 Time course of 10-point self-monitored blood glucose (SMBG) profile at week 26 in Japanese patients. SMBG profiles (mg/dL and mmol/L) in URLi and lispro treatment groups are shown at the time-points of morning,

midday, evening and bedtime. Data are presented as LSM \pm SE. Asterisks indicates time-points at which there was a significant difference ($p <$ 0.01) between treatment groups

Table 2 Summary of adverse events between week 0 and week 26 in the subpopulation of Japanese patients from the PRONTO-T2D trial

Adverse event	Treatment arm	
	URLi (<i>N</i> = 47)	Lispro (<i>N</i> = 46)
Treatment-emergent adverse events	31 (66.0)	25 (54.3)
Treatment-emergent adverse events related to study treatment ^a	4 (8.5)	2 (4.3)
Injection site pain	2 (4.3)	0 (0)
Myalgia	1 (2.1)	0 (0)
Asthma	1 (2.1)	0 (0)
Diabetic retinopathy	0 (0)	1 (2.2)
Muscle spasm	0 (0)	1 (2.2)
Serious adverse events	4 (8.5)	1 (2.2)
Discontinuation from study treatment due to an adverse event	0 (0)	0 (0)
Discontinuation from study due to an adverse event	0 (0)	0 (0)
Deaths	0 (0)	0 (0)

Values in table are presented as a number with the percentage in parenthesis. Patients may be counted in more than one category

n Number of patients, *N* number of patients

^a Events that were considered to be related to study treatment as judged by the investigator

Table 3 Summary of hypoglycemia events between week 0 to week 26 in the subpopulation of Japanese patients from the PRONTO-T2D trial

Characteristic	Treatment arm	
	URLi (<i>N</i> = 47)	Lispro (<i>N</i> = 46)
Severe hypoglycemia, <i>n</i> (%)	0 (0)	0 (0)
Documented symptomatic hypoglycemia with glucose < 54 mg/dL, <i>n</i> (%)	16 (34.0)	9 (19.6)
Rate of documented symptomatic hypoglycemia with glucose < 54 mg/dL, events/patients/30 days, LS mean (SE)	0.32 (0.12)*	0.05 (0.02)
Non-nocturnal hypoglycemia with glucose < 54 mg/dL, <i>n</i> (%)	29 (61.7)	26 (56.5)
Rate of non-nocturnal hypoglycemia with glucose < 54 mg/dL, events/patients/year, LS mean (SE)	7.37 (1.9)	4.74 (1.4)

LS Least squares, *N* number of subjects in the population with baseline and post-baseline values at the specified time-point, *n* number of subjects with hypoglycemia, *SE* standard error

*Significant difference at $p < 0.05$ between URLi and lispro treatment groups

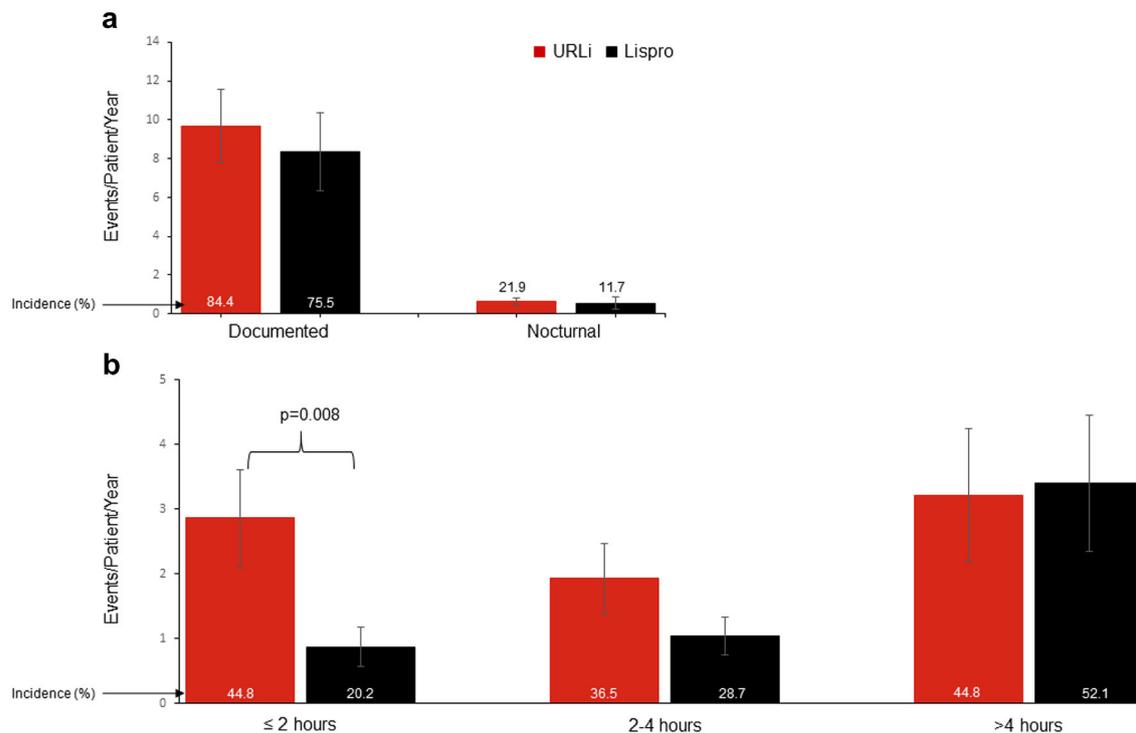


Fig. 5 Incidence and rate of hypoglycemia (with or without symptoms) from week 0 to week 26 in Japanese patients. Rate and incidence of documented and nocturnal hypoglycemia (blood glucose [BG] < 54 mg/dL) (a) and

symptomatic and asymptomatic postmeal hypoglycemia (BG < 54 mg/dL) (b). Data are presented as LSM + SE for event rate and LSM for incidence

As shown in the overall PRONTO-T2D study population, in this Japanese subpopulation URLi was comparable to lispro in terms of change in mean HbA1c levels. The upper limit of 95% CI of LSM differences between mealtime dosing of URLi and mealtime dosing of lispro was < 0.4%, which was the prespecified non-inferiority margin for the overall population [21]. Overall, consistent HbA1c profiles were observed between Japanese patients and the overall PRONTO-T2D study population, from study entry through week 26.

In the overall PRONTO-T2D patient population, URLi treatment was statistically significantly better at controlling PPG excursions during a MMTT in comparison to lispro at 1 and 2 h postmeal at week 26 [21]. This finding reflects the fast onset and short duration of action observed in URLi clinical pharmacology studies [23, 24]. In this Japanese patient subpopulation, we observed a consistent numerical trend for a PPG reduction with URLi treatment

in comparison to lispro from 30 min to 3 h following the MMTT. This observation is consistent with the findings in the overall population, in which the higher number of patients resulted in statistically significant PPG reductions [21]. The small number of Japanese patients limited the likelihood of obtaining the consistent statistical differences observed in the whole study population [21].

Overall, the daily average blood glucose levels in the 10-point SMBG profiles were similar between treatments, with the exception of blood glucose levels at the morning postmeal time-points of 1- and 2-h where the URLi treatment group showed lower PPG levels compared with the lispro treatment group. Importantly, the ratio of prandial to total insulin dose at week 26 was similar between the two groups. The SMBG results observed in this subgroup analysis is consistent with the SMBG profiles observed in the overall population where 10-point SMBG testing demonstrated

improved PPG control with significantly lower PPG levels after the morning meal and reduced daily mean PPG levels and excursions in the URLi group compared with the lispro group [21].

An important observation is that the overall trend in PPG excursions in the MMTT was consistent between the Japanese subpopulation and the overall PRONTO-T2D study population. In this exploratory analysis of Japanese patients, we observed consistently numerically smaller PPG excursions from 30 min to 3 h during the MMTT for mealtime URLi compared to lispro; LSM differences were -10.5 mg/dL at 1 h postmeal and -14.9 mg/dL at 2 h postmeal. By comparison, the estimated treatment differences between mealtime URLi and lispro for the overall population were -11.0 mg/dL at 1 h postmeal and -17.4 mg/dL at 2 h postmeal [21].

Overall, URLi was well tolerated by Japanese patients. The incidence of SAEs and TEAEs related to the study treatment was low and similar across treatment groups. Furthermore, there were no discontinuations from the study due to an AE, and no deaths.

It is well established that achieving glycemic control, as determined by HbA1c levels, is effective in reducing the risk of diabetes complications. In addition, epidemiology studies indicate elevated PPG levels increase the risk of cardiovascular disease [10, 25–28] and that controlling PPG excursions is essential for achieving recommended HbA1c goals [29,30]. In comparison to lispro, URLi may not only mimic the time-action profile of normal insulin secretion more closely, but it may also lower PPG excursions, with an acceptable safety profile, as described in the PRONTO-T2D trial [21]. Following approval in Europe [31], URLi was recently granted approval in Japan (March 2020) under the trade name Lyumjev [32].

A limitation of the study design is that the MMTT insulin dose may not have been fit for Japanese patients who were relatively lighter compared to patients in the overall population. As mentioned above, the 500-rule was used to calculate the MMTT insulin dose for the majority of Japanese patients on the pattern adjustment method, and one limitation of the 500-rule method is it does not account for body

weight. In addition, the small number of patients in this subpopulation analysis limited the likelihood of obtaining statistical differences in this population.

CONCLUSION

In conclusion, the results of this 26-week trial indicates that URLi is effective and comparable to lispro in terms of overall glycemic control when administered immediately before a meal in Japanese patients with T2DM. Furthermore, URLi was well tolerated, with an acceptable safety profile in this population.

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Compliance with Ethics Guidelines. The study was conducted in accordance with the International Council for Harmonization Guidelines for Good Clinical Practice including the Declaration of Helsinki and its later amendments and the Council for International Organisation of Medical Sciences International Ethical Guidelines. An Ethical Review Board at each site (Kobori Clinic, H.E.C. Science Clinic, Jinnouchi Hospital, Heiwadai Hospital, The Institute for Adult Diseases, Naka Memorial Clinic, Tomonaga Clinic, Nihonbashi Sakura Clinic, AMC Nishi-umeda Clinic, Manda Hospital, Fukuoka Red Cross Hospital, Shin Akasaka Clinic, Shinagawa East One Medical Clinic, Sasebo Chuo Hospital, Okuguchi Clinic of Internal Medicine, Sapporo Skin Clinic, Takatsuki Red Cross Hospital, Osaka City University Medical School Hospital, Goshogatani Home Clinic, Tokyo Women's Medical University Hospital) approved all procedures, and all subjects provided written, informed consent.

Data Availability. Eli Lilly and Company provides access to all individual participant data collected during the trial, after anonymization, with the exception of pharmacokinetic or genetic data. Data are available to request 6 months after the indication studied has been approved in the USA and EU and after primary publication acceptance, whichever is later. No expiration date of data requests is currently set once data are made available. Access is provided after a proposal has been approved by an independent review committee identified for this purpose and after receipt of a signed data sharing agreement. Data and documents, including the study protocol, statistical analysis plan, clinical study report and blank or annotated case report forms, will be provided in a secure data-sharing environment. For details on

submitting a request, see the instructions provided at www.vivli.org.

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