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ORIGINAL ARTICLE

Ultra-Rapid Lispro results in accelerated insulin lispro absorption and faster early insulin action in comparison with Humalog® in Japanese patients with type 1 diabetes

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ABSTRACT

Aims/Introduction: Ultra-rapid lispro (URLi) is a novel ultra-rapid mealtime insulin. This study compared the pharmacokinetic and glucodynamic profiles, safety, and tolerability of URLi and lispro (Humalog®) in Japanese patients with type 1 diabetes mellitus.

Materials and Methods: This was a phase I, single center, randomized, patient- and investigator-blind, two-period, cross-over study. A total of 31 patients received a single subcutaneous 15-U dose of URLi or lispro before undergoing a euglycemic clamp procedure. Primary pharmacokinetic endpoints were the time to early half-maximal drug concentration and the area under the concentration versus time curve from 0 to 30 min postdose. The glucodynamic endpoints were the time to early half-maximal glucose infusion rate before time to maximum glucose infusion rate, and the time to onset of insulin action.

Results: URLi showed accelerated insulin lispro absorption compared with lispro, as shown by a decrease of 56% (URLi: 10.2 min, lispro: 23.3 min; $P < 0.0001$) in the early half-maximal drug concentration, and a 2.4-fold increase in the area under the concentration versus time curve from 0 to 30 min ($P < 0.0001$). The duration of insulin lispro exposure was 88 min shorter after URLi administration compared with lispro. URLi reduced the early half-maximal glucose infusion rate before time to maximum glucose infusion rate and the time to onset of insulin action significantly compared with lispro. The glucose infused within the first 30 min of the clamp was 2.16-fold greater with URLi compared with lispro. There was no difference in total exposure or glucose infused between treatments. All treatment-emergent adverse events were mild/moderate in severity.

Conclusions: In Japanese type 1 diabetes mellitus patients, URLi showed accelerated insulin lispro absorption, reduced late exposure, overall shorter duration and faster early insulin action compared with lispro.

INTRODUCTION

The development of rapid-acting insulins has been an important step in optimizing control of postprandial glycemic excursions. Such insulins are now indicated in patients with type 1 diabetes mellitus and insulin-requiring patients with type 2 diabetes mellitus[1]. Although rapid-acting insulins are superior at reducing postprandial glycemic excursions in comparison with regular insulin[2], there is a need to develop even faster acting insulin preparations to match carbohydrate absorption profiles and to more closely mimic physiological insulin release.

Lispro (Humalog®) is a commercially available, rapid-acting human insulin analog indicated to improve glycemic control in adults and children with diabetes mellitus[3]. Ultra-rapid lispro (URLi; LY900014) is a newly developed insulin lispro formulation utilizing two key enabling excipients, treprostinil and citrate, with independent mechanisms to accelerate the absorption of insulin lispro. Treprostinil is a prostacyclin analog

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approved for the treatment of pulmonary arterial hypertension[4]. A microdose of treprostinil in the URLi formulation is used to enhance insulin lispro absorption by local vasodilation. Sodium citrate was added to the URLi formulation to further enhance the absorption of insulin lispro. URLi was formulated to closely mimic the physiological prandial insulin secretion pattern, and is expected to effectively control postprandial glucose excursions.

The aim of the present study was to characterize the insulin lispro pharmacokinetic (PK) and glucodynamic (GD) profiles of URLi and lispro during a euglycemic clamp procedure in Japanese patients with type 1 diabetes mellitus. The results of this study may support further development of URLi in this population. The tolerability and safety of a single subcutaneous (s.c.) dose of both URLi and lispro were also evaluated.

METHODS

Participants

All patients provided written informed consent before participating. Japanese adults (aged ≥18 years) with type 1 diabetes mellitus for at least 1 year before screening, and with a body mass index between 18.5 and 30 kg/m^2, were eligible to participate in the study. Participants were also required to have glycated hemoglobin <9.0% at screening, with no episodes of severe hypoglycemia in the 6 months before study commencement. Participants were excluded if they had significant lipohypertrophy in the target abdominal injection area, regular or intended use of medications or nutritional supplements (other than insulin) that treat hyperglycemia or promote weight loss, use of systemic or inhaled glucocorticoid therapy, a history of renal impairment or deep vein thrombosis, proliferative retinopathy, maculopathy and/or severe neuropathy, or if their insulin regimen was changed in the 3 months before screening, or they required daily insulin treatment >1.5 U/kg. Participants were also excluded if they had any known allergies to insulin lispro, treprostinil, insulin glulisine, related compounds or any components of the formulation, or had a history of significant atopy.

Study design

This phase I, single center, randomized, patient- and investigator-blind, two-treatment, two-period, crossover study evaluated the PK and GD of URLi and lispro in Japanese patients with type 1 diabetes mellitus. The study protocol was approved by the Hakata Clinic Institutional Review Board, Fukuoka, Japan, and was carried out in accordance with the Declaration of Helsinki and good clinical practice guidelines.

An overview of the study design is outlined in Figure 1. Patients were randomized to one of two treatment sequences. The study included a screening period of up to 28 days, two inpatient treatment periods (over a period of 2 days), with 3–28 days washout between periods, and a follow-up visit at least 14 days after the last dose. Before each dosing visit, patients discontinued their basal insulin during a washout period of up to 3 days. Patients on multiple dose injections were required to discontinue basal insulin; insulin degludec or insulin glargine U300 within 72 h, insulin detemir or glargine within 48 h and neutral protamine Hagedorn insulin or other intermediate-acting insulin within 24 h, before each dosing visit. Any patients requiring bolus injection or bolus infusion through continuous subcutaneous insulin infusion were required to administer treatment no later than 6 h before dosing of the study drug.

After an overnight fast of at least 8 h for each treatment period, patients were connected to the clamp device (artificial pancreas STG-22; Nikkiso Co. Ltd., Tokyo, Japan) for a euglycemic glucose clamp, and for the start of the baseline run-in period before dosing. The run-in period ranged from 1 to 6 h, during which variable intravenous infusion of either glucose or insulin glulisine (Apidra) was used to obtain a steady blood glucose clamp target of 100 mg/dL (±20%). The target blood glucose level of 100 mg/dL (±20%) was kept at −60 to −30 min, followed by the target blood glucose level of 100 mg/dL (±10%) within the last 30 min before study drug administration without any glucose infusion. The study drug was administered after blood glucose levels remained stable, without any glucose infusion.

Patients received a 15-U s.c. dose of either lispro or URLi, as per the study schedule, and underwent the clamp procedure. At the onset of study insulin action, defined as a blood glucose drop to 5 mg/dL from baseline, a variable intravenous glucose infusion was initiated to keep blood glucose constant, and at the target level (100 mg/dL). The glucose infusion rate (GIR) was automatically adjusted by STG-22. The clamp procedure was continued for up to 10 h after dose or until blood glucose concentrations increased to >200 mg/dL without any glucose being administered for at least 30 min, whichever occurred earlier.

The GIR required to maintain blood glucose concentrations at the target level was recorded using a validated data capture system. Venous blood samples were collected before study drug dosing, and every 5 min postdose up to 60 min followed by increasing intervals (ranging from 10, 20, 30, 40 and 60 min) during the 10-h glucose clamp to determine the serum concentrations of insulin lispro. After the first treatment period, patients resumed their former insulin regimen, returning for the second dosing period within a 3- to 28-day interval. After study treatment completion, patients resumed their former insulin regimen. A follow-up visit or early discontinuation occurred at least 14 days after the last dose of the study drug.

Study treatments

URLi and lispro were both administered at a concentration of 100 U/mL in 3-mL cartridges, comprising 100 U/mL of insulin lispro in prefilled pens. For both compounds, the prefilled pens were used to administer 15-U through a single s.c. injection, as per the study design (Figure 1). A 15-U dose is within the clinical dose range[5,6], and provided measurable PK and GD profiles for both study insulins.

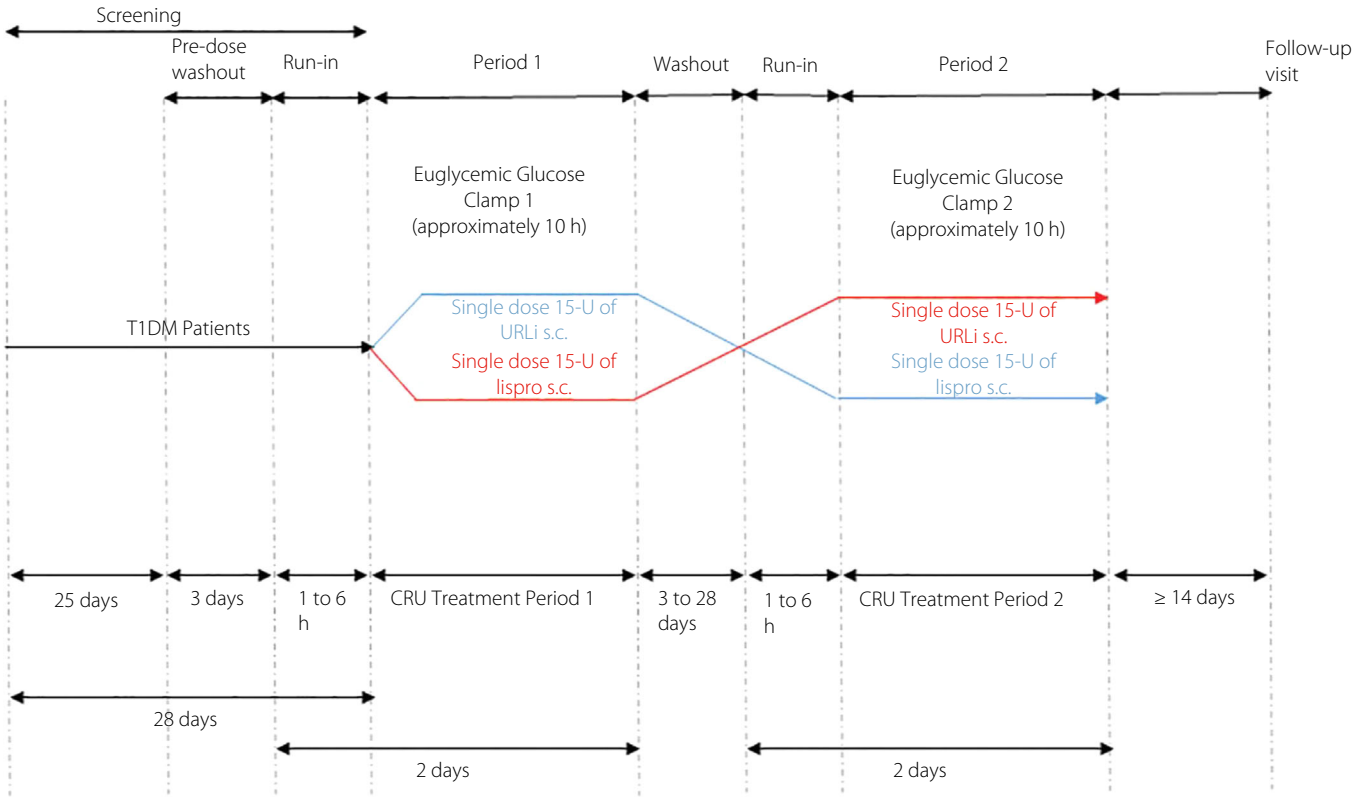

Figure 1 | Study design. Patients were randomized to one of two treatment sequences. In both periods, patients were discharged from the clinical research unit (CRU) after 1 day at the discretion of the investigator and after all assessments were completed. S.C., subcutaneous; T1DM, type 1 diabetes mellitus; URLi, ultra-rapid lispro.

Bioanalytical methods

Serum samples obtained during the study were analyzed for free insulin lispro using a validated enzyme-linked immunosorbent assay method. The lower limit of quantification was 50.0 pg/mL (8.6 pmol/L), and the upper limit of quantification was 2,000.0 pg/mL (344.4 pmol/L). Plasma samples were analyzed for treprostinil using a validated liquid chromatography tandem mass spectrometry method. The lower limit of quantification was 0.010 ng/mL, and the upper limit of quantification was 20.0 ng/mL.

Study end-points

The primary PK endpoints were time to early half-maximal serum concentration (early 50% t_{max}) and area under the concentration versus time curve from time 0 to 30 min postdose ($AUC_{[0–30\ min]}$). Secondary GD endpoints included time to early half-maximal GIR before time to maximum GIR (early 50% tR_{max}), total amount of glucose infused over the first 30 min and 1 h ($G_{tot[0–30\ min]}$ and $G_{tot[0–1\ h]}$, respectively), time to onset of insulin action (T_{onset}), as well as safety (adverse events [AEs] and tolerability analyses).

Pharmacokinetic and glucodynamic analyses

Patients who received at least one dose of the study drug and had measurable insulin lispro or treprostinil concentrations were included in the PK analysis. PK parameters were calculated using standard non-compartmental methods of analysis with Phoenix® version 8.0 and S-PLUS® version 8.2 (CERTARA, Princeton, NJ, USA).

Pharmacokinetic parameters included maximum observed drug concentration, time to maximum observed concentration (t_{max}), early 50% t_{max}, time to late half-maximal serum concentration (late 50% t_{max}), AUC from time 0 to 15 min ($AUC_{[0–15\ min]}$), AUC from time 0 to 30 min ($AUC_{[0–30\ min]}$), AUC from 0 to 1 h ($AUC_{[0–1\ h]}$), AUC from 2 to 10 h ($AUC_{[2–10\ h]}$), AUC from 3 to 10 h ($AUC_{[3–10\ h]}$) and AUC from time zero to infinity ($AUC_{[0–\infty]}$). The duration of time from study drug administration until the serum insulin lispro concentrations reached the lower limit of quantification in the terminal phase was also calculated.

Glucodynamics were assessed from the glucose clamp procedure, where the GIR over time was used as a measure of insulin effect. Patients who completed at least one clamp procedure were included in the GD analysis. A locally weighted scatterplot

smoothing function was applied to all individual GIR versus time profiles in each treatment group and/or period. Fitted data for each patient were used to calculate the following GD parameters: maximum GIR (R_{max}), time to maximum GIR (tR_{max}), early 50% tR_{max}, time to half-maximal GIR after time to maximum GIR (late 50% tR_{max}), time to onset of insulin action (T_{onset}), total amount of glucose infused (G_{tot}), G_{tot} over a period of 30 min ($G_{tot[0–30\ min]}$), G_{tot} over a period of 1 h ($G_{tot[0–1\ h]}$), G_{tot} over a period of 2 h ($G_{tot[0–2\ h]}$), G_{tot} from 2 h to the end of the clamp ($G_{tot[2\ h\text{-}END]}$), G_{tot} from 3 h to the end of the clamp ($G_{tot[3\ h\text{-}END]}$), G_{tot} from 4 h to the end of the clamp ($G_{tot[4\ h\text{-}END]}$) and duration of action calculated by subtracting T_{onset} from the time at the end of the clamp procedure.

Safety

The safety population consisted of all patients who received at least one dose of the study drug. Safety parameters included treatment-emergent AEs (TEAEs), injection-site assessments, clinical laboratory tests, vital signs, 12-lead electrocardiogram parameters and hypoglycemic events. Parameters were summarized using standard descriptive statistics.

Statistical analysis

Randomization was planned for up to 40 patients in order that approximately 28 patients completed the study. A total of 28 completing patients would provide approximately 92% power to show a 40% increase in the insulin lispro $AUC_{(0–30\ min)}$ between URLi and lispro. In addition, the study was adequately powered to evaluate the GD parameters. There was approximately 71% power to detect a 20% decrease in both T_{onset} and time to early half-maximal GIR before tR_{max} (early 50% tR_{max}), and approximately 81% power to detect at least a 40% increase in $G_{tot(0–30\ min)}$ and $G_{tot(0–1\ h)}$.

Log-transformed maximum observed drug concentration and AUC estimates for insulin lispro were evaluated to estimate least squares geometric means, ratios of geometric means between URLi and lispro, and their corresponding 95% confidence intervals (CIs) using the mixed-effects model. The same model without log transformation was used for the analysis of the PK time parameters (early 50% t_{max}, late 50% t_{max}, t_{max}, duration). Treatment ratios and 95% CIs for the ratios were calculated using Fieller's theorem. The above analyses were carried out on the population of patients who had evaluable PK data for, and completed, both study periods.

The GD statistical model was the same as that used for the analysis of PK parameters. The following factors were log-transformed before analysis: R_{max}, G_{tot}, $G_{tot(0–1\ h)}$ and $G_{tot(0–2\ h)}$. For GD parameters that had at least one patient with a value equal to 0, the parameter was analyzed untransformed, and treatment ratios and 95% CIs for ratios were calculated using Fieller's theorem. The same model without log transformation was used for the analysis of the GD time parameters (T_{onset}, tR_{max}, early 50% tR_{max} and late 50% tR_{max}). Treatment ratios and 95% CIs for the ratios were calculated using Fieller's theorem. The above analyses were carried out on the population of patients who completed, and had evaluable GD data, for both study periods.

Table 1 | Patient baseline characteristics and demographics

Characteristics	Total(n = 31)
No. Japanese patients	31
Mean age, years (SD)	39.5 (11.3)
Sex, *n* (%)	
Male	13 (41.9%)
Female	18 (58.1%)
Mean weight, kg (SD)	59.62 (8.29)
Mean body mass index, kg/m^2 (SD)	22.85 (2.44)
Mean HbA1c, % (SD)	7.55 (0.76)
Mean duration of type 1 diabetes mellitus, years (SD)	17.93 (11.95)
Previous insulin therapy, *n* (%)	
Insulin aspart	13 (41.9%)
Insulin glulisine	2 (6.5%)
Insulin lispro	7 (22.6%)
Insulin human injection, isophane	29 (93.5%)

HbA1c, glycated hemoglobin; SD, standard deviation.

RESULTS

Study participants

A total of 31 Japanese patients with type 1 diabetes mellitus were eligible for inclusion, with 30 patients completing the study. Due to a scheduling conflict, one patient withdrew consent after receiving a single administration of URLi, but before receiving a dose of lispro in the second period of the study. Data from this patient are included in the analyses. The mean age of participants was 39.5 years (standard deviation [SD] 11.3 years), with a mean type 1 diabetes mellitus duration of 17.9 years (SD 12.0 years). Mean bodyweight was 59.62 kg (SD 8.29 kg), mean body mass index was 22.85 kg/m^2 (SD 2.44 kg/m^2) and mean glycated hemoglobin 1c was 7.55% (SD 0.76%). Baseline patient demographics and insulin use are summarized in Table 1.

Insulin lispro pharmacokinetics

Early 50% t_{max} of insulin lispro was reduced by approximately 56%, a 13-min difference, after URLi treatment in comparison with lispro. A single 15-U dose of URLi showed accelerated insulin lispro absorption compared with a single 15-U dose of lispro, as shown by the following statistically significant changes: early 50% t_{max}, $P < 0.0001$; $AUC_{(0–15\ min)}$, $P < 0.0001$; $AUC_{(0–30\ min)}$, $P < 0.001$; and $AUC_{(0–1\ h)}$, $P = 0.0009$. The accelerated insulin lispro absorption increased the early serum insulin lispro exposure as the $AUC_{(0–15\ min)}$ was increased by 4.80-fold, $AUC_{(0–30\ min)}$ by 2.43-fold and $AUC_{(0–1\ h)}$ by 1.46-fold after URLi administration in comparison with lispro (Tables 2,3). Serum insulin lispro concentration profiles after a single 15-U dose of URLi and lispro are presented in Figure 2.

Similarly, the late insulin lispro exposure was statistically significantly reduced with URLi compared with lispro, evident by

Table 2 | Statistical analysis of insulin lispro pharmacokinetic parameters after administration of URLi and lispro

Parameter	URLi*N* = 31	Lispro*N* = 30	Ratio of Geometric LS means URLi vs Lispro (95% CI)	*P*-value
	Geometric LS means			
Early insulin lispro exposure				
$AUC_{(0–15\ min)}$ (pmol h/L)	102	21.2	4.80 (3.58, 6.43)	<0.0001
$AUC_{(0–30\ min)}$ (pmol h/L)	319	132	2.43 (1.92, 3.07)	<0.0001
$AUC_{(0–1\ h)}$ (pmol h/L)	770	526	1.46 (1.19, 1.80)	0.0009
Late insulin lispro exposure				
$AUC_{(2–10\ h)}$ (pmol h/L)	344	655	0.525 (0.34, 0.81)	0.0050
$AUC_{(3–10\ h)}$ (pmol h/L)	94.6	281	0.336 (0.19, 0.59)	0.0005
Overall insulin lispro exposure				
C_{max} (pmol/L)	1,091	930	1.17 (1.00, 1.37)	0.0478
$AUC_{(0–\infty)}$ (pmol h/L)	1,921	1,990	0.966 (0.80, 1.16)	0.7040

$AUC_{(0–\infty)}$ = area under the concentration vs time curve from time zero to infinity; $AUC_{(0–15\ min)}$ = area under the concentration vs time curve from time zero to 15 min postdose; $AUC_{(0–30\ min)}$ = area under the concentration vs time curve from time zero to 30 min postdose; $AUC_{(0–1\ h)}$ = area under the concentration vs time curve from time zero to 1 h postdose; $AUC_{(2–10\ h)}$ = area under the concentration vs time curve from time 2 to 10 h postdose; $AUC_{(3–10\ h)}$ = area under the concentration vs time curve from time 3 to 10 h postdose; C_{max} = maximum observed drug concentration; CI = confidence interval; LS = least squares; *N* = number of patients; PK = pharmacokinetic; URLi = ultra-rapid lispro. Model: Log (PK) = Period + Treatment + Sequence + Patient (Sequence) + Random Error, where Patient(Sequence) is fitted as a random effect.

Table 3 | Statistical analysis of insulin lispro pharmacokinetic time parameters after administration of ultra-rapid lispro and lispro

Parameter	URLi *n* = 31	Lispro *n* = 30	Difference in LS means URLi vs lispro (95% CI)	*P*-value	Ratio of LS means URLi vs lispro (95% CI)
	LS mean (*n*)				
t_{max} (h)	0.781 (31)	0.980 (30)	−0.199 (−0.38, −0.01)	0.0351	0.797 (0.63, 0.98)
Early 50% t_{max} (min)	10.2 (31)	23.3 (29)	−13.0 (−15.60, −10.50)	<0.0001	0.439 (0.37, 0.52)
Late 50% t_{max} (min)	120 (31)	148 (30)	−27.6 (−41.20, −14.10)	0.0003	0.813 (0.73, 0.90)
Duration (min)	373 (31)	461 (30)	−88.2 (−116.00, −60.00)	<0.0001	(0.75, 0.87)

Model: pharmacokinetic = period + treatment + sequence + patient (sequence) + random error, where patient (sequence) is fitted as a random effect. The confidence intervals (CI) for the ratio were calculated using the Fieller's theorem. *P*-value is for the test of the mean difference. Duration, time from study drug administration until the serum insulin lispro concentrations reached the lower limit of quantification; Early 50% t_{max}, time to early half-maximal drug concentration; Late 50% t_{max}, time to late half-maximal drug concentration; LS, least squares; t_{max}, time of maximum observed drug concentration; URLi, ultra-rapid lispro.

a 47.5% reduction in $AUC_{(2–10\ h)}$, and a 66.4% reduction in $AUC_{(3–10\ h)}$. The duration of insulin lispro exposure was 88 min shorter after URLi administration compared with lispro; however, total insulin exposure, $AUC_{(0–\infty)}$, was similar between the two treatments (Tables 2,3).

Treprostinil pharmacokinetics

After a single dose of URLi, there were no detectable concentrations of excipient treprostinil in the plasma from the 30 patients who completed the study.

Insulin lispro glucodynamics

The mean locally weighted scatterplot smoothing fits of weight-normalized glucose infusion profile is shown in Figure 3. URLi significantly reduced the time of onset of insulin action during the clamp (T_{onset}) by 27% and the early 50% tR_{max} by 26%, approximately 6.4 and 11 min difference, respectively. The faster action of URLi significantly increased the amount of glucose infused by the euglycemic clamp for URLi in comparison with lispro; 2.16-fold during the first 30 min and 1.28-fold over the first 2 h (Tables 4, 5).

In addition, the late 50% tR_{max} was significantly reduced by approximately 19% (50 min difference) after URLi administration in comparison with lispro. The glucose infused from 2, 3 and 4 h to the end of the clamp was significantly reduced by 20, 38 and 58%, respectively, after URLi treatment in comparison with lispro (Table 5). Overall, the duration of insulin action was 68 min shorter after URLi treatment in comparison with lispro (Table 5).

The R_{max} was significantly higher (approximately 15%) after URLi treatment compared with lispro; however, the G_{tot} was similar between treatments (Table 4).

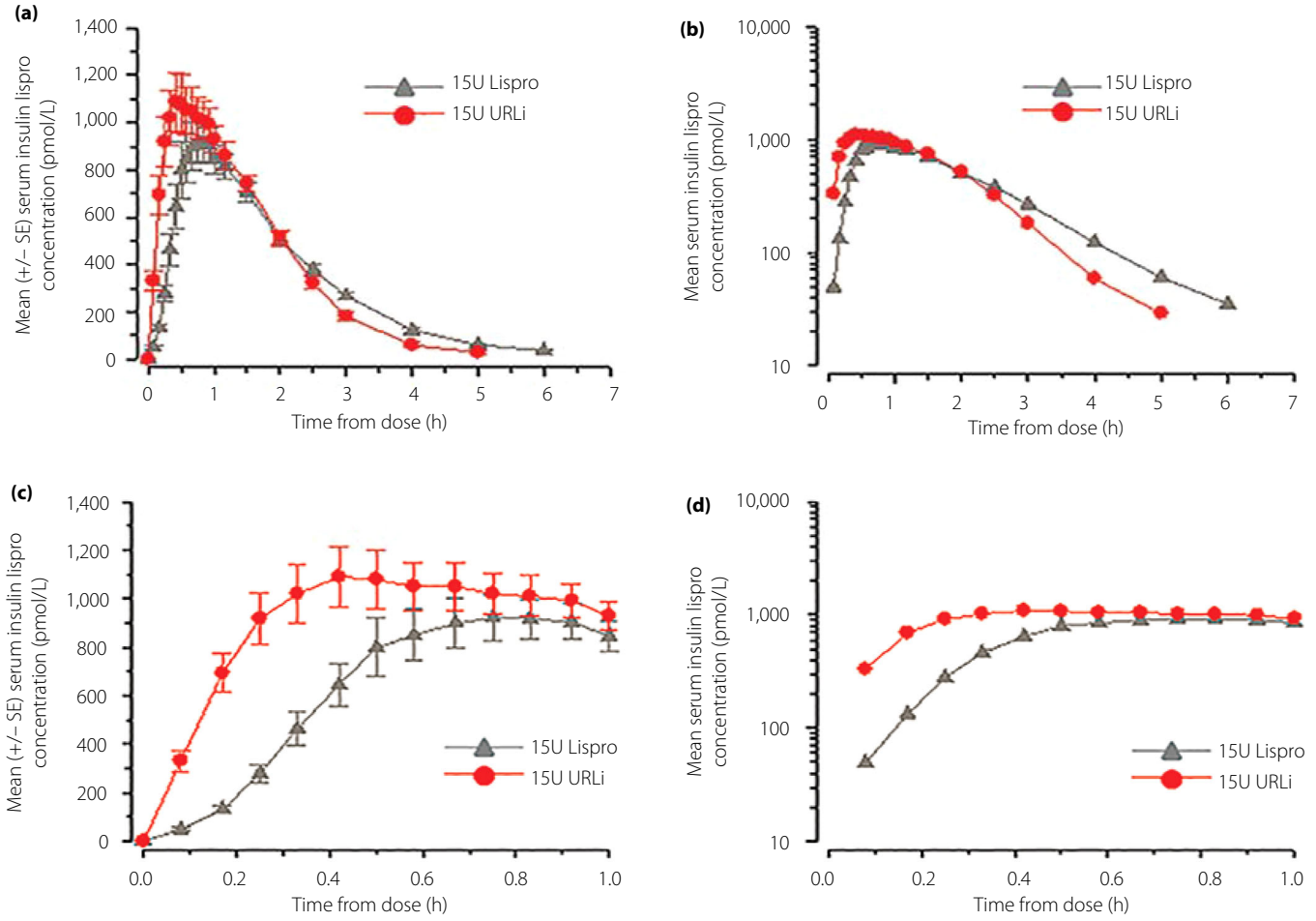

Figure 2 | Mean insulin lispro concentrations after administration of ultra-rapid lispro (URLi) and lispro. Mean insulin lispro concentration (±standard error) versus time by treatment after a 15-U subcutaneous (s.c.) dose of URLi and a 15-U s.c. dose of lispro for the duration of the clamp in (a) linear scale and (b) log scale; and for the first hour in (c) linear scale and (d) log scale.

Safety and tolerability

URLi and lispro, each administered at a single 15-U s.c. dose, were well tolerated by Japanese patients with type 1 diabetes mellitus in the present study, with no safety concerns. No deaths or serious AEs were reported, and no patient discontinued the study due to an AE.

Of the 31 patients who participated in the study, 10 (32.3%) reported a total of 25 TEAEs. Overall, the number of patients reporting a TEAE was comparable between treatment groups; URLi $n = 7$ (22.6%), lispro $n = 8$ (26.7%). The majority of TEAEs were mild in intensity; no severe TEAEs were reported. The most frequently reported TEAEs after URLi administration were headache ($n = 4$) and nausea ($n = 3$). Similarly, for lispro, the most commonly reported TEAE was headache ($n = 4$). One TEAE, injection-site erythema, was reported by one patient after URLi administration and was judged to be related to the study treatment. The injection-site erythema was mild in severity and occurred 1 h after injection, but was resolved approximately 9 h later.

DISCUSSION

We evaluated the PK and GD profiles of URLi and lispro, as well as their safety and tolerability in Japanese patients with type 1 diabetes mellitus, after a single s.c. dose using a euglycemic clamp, widely used to measure insulin action[7]. This is the first study to report the PK and GD profiles of this ultra-rapid insulin in Japanese patients.

We showed that URLi has accelerated insulin lispro absorption, with a reduction in late exposure, and an overall shorter PK duration compared with lispro in Japanese patients with type 1 diabetes mellitus. Although there was a leftward shift in the insulin lispro PK curve with URLi compared with lispro, there was no difference in the total exposure $AUC_{(0-\infty)}$ between the two treatments.

Consistent with the PK findings, URLi showed a faster early insulin action, a reduced late insulin action and a shorter duration of insulin action in Japanese patients with type 1 diabetes mellitus. A significantly faster onset of insulin action between URLi and lispro was observed, resulting in a significantly

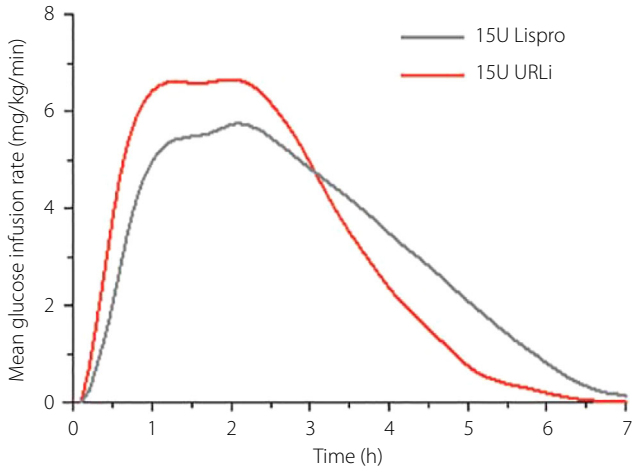

Figure 3 | Mean glucose infusion rates versus time comparing a single dose of ultra-rapid lispro (URLi) with lispro. Mean locally weighted scatterplot smoothing fits of weightnormalized glucose infusion rate versus time for a 15-U subcutaneous (s.c.) dose of URLi compared with a 15-U s.c. dose of lispro in Japanese patients with type 1 diabetes mellitus.

greater amount of glucose infused in the early part of the euglycemic clamp. This faster insulin action resulted in less late insulin action after URLi administration when compared with lispro. However, the overall glucose infused during the clamp was not significantly different between the two treatments.

Single s.c. doses of URLi and lispro were well tolerated by Japanese patients. No serious AEs were reported. The number of patients reporting a TEAE and the number of TEAEs reported were comparable between treatment groups. All TEAEs were mild or moderate in severity. Treprostinil is included in the URLi formulation to enhance insulin lispro absorption through local vasodilation. Treprostinil was undetectable in the plasma from Japanese patients after URLi administration and did not result in systemic effects.

A recent randomized, double-blind, two-period, cross-over study, with assessments using a euglycemic clamp, examined URLi and lispro in 41 white patients with type 1 diabetes mellitus[8]. Similar to the present findings in Japanese patients, accelerated insulin absorption, reduced late exposure and overall shorter duration of URLi compared with lispro were observed[8]. Specifically, early insulin lispro exposure was significantly greater in white patients administered URLi (7.2-fold in the first 15 min and 2.7-fold in the first 30 min, $P < 0.0001$) in comparison with treatment with lispro. Overall, the duration of exposure was 74 min shorter with URLi ($P < 0.0001$). In addition, early insulin action was increased 2.8-fold ($P < 0.001$) in the first 30 min for URLi compared with lispro. Late insulin action ($G_{tot[4\ h\text{-}END]}$) was reduced by 54% ($P < 0.0001$), and duration of action was 43.6 min shorter with URLi[8]. In alignment with our findings in Japanese patients, total insulin lispro exposure and glucose infused during the clamp did not differ, and tolerability was similar between URLi and lispro in white type 1 diabetes mellitus patients[8].

A direct comparison between faster acting insulin aspart and the present findings relating to URLi/lispro is not viable given these are independent clamp studies in different study participants, with varying study designs. In a recent phase I clamp study, faster acting insulin aspart was found to have earlier onset and higher early exposure compared with insulin aspart,

Table 4 | Statistical analysis of insulin lispro glucodynamic parameters after administration of ultra-rapid lispro and lispro

Parameter	URLi $n = 31$	Lispro $n = 30$	Ratio of Geometric LS means URLi vs lispro (95% CI)	*P*-value
	Geometric LS means			
Early insulin action[†,‡]				
$G_{tot(0–30\ min)}$ (mg/kg)	42.77	19.76	2.16 (1.68–2.86)	–
$G_{tot(0–1\ h)}$ (mg/kg)	191.84	122.12	1.57 (1.34–1.83)	<0.0001
$G_{tot(0–2\ h)}$ (mg/kg)	555.88	434.90	1.28 (1.09–1.49)	0.0033
Late insulin action[‡]				
$G_{tot(2\ h\text{-}END)}$ (mg/kg)	698.30	873.57	0.80 (0.72–0.88)	–
$G_{tot(3\ h\text{-}END)}$ (mg/kg)	334.32	541.15	0.62 (0.53–0.70)	–
$G_{tot(4\ h\text{-}END)}$ (mg/kg)	119.48	287.60	0.42 (0.31–0.51)	–
Total insulin action				
R_{max} (mg/kg/min)	6.85	5.97	1.15 (1.02–1.29)	0.0262
G_{tot} (mg/kg)	1,186.84	1,275.54	0.93 (0.79–1.09)	0.3652

CI, confidence interval; G_{tot}, weight-normalized total glucose infused during clamp; $G_{tot(0–1\ h)}$, weight-normalized glucose infused between time zero and 1 h; $G_{tot(0–2\ h)}$, weight-normalized glucose infused between time zero and 2 h; $G_{tot(0–30\ min)}$, weight-normalized glucose infused between time zero and 30 min; $G_{tot(2\ h\text{-}END)}$, weight-normalized glucose infused between time 2 h and the end of the clamp; $G_{tot(3\ h\text{-}END)}$, weight-normalized glucose infused between time 3 h and the end of the clamp; $G_{tot(4\ h\text{-}END)}$, weight-normalized glucose infused between time 4 h and the end of the clamp; LS, least squares; R_{max}, weight-normalized maximum glucose infusion rate; URLi, ultra-rapid lispro. [†]When glucodynamic parameters included 0, the analysis was carried out without log transformation. [‡]Least squares means; model: glucodynamic = period + treatment + sequence + patient (sequence) + random error, where patient (sequence) is fitted as a random effect.

Table 5 | Statistical analysis of insulin lispro glucodynamic time parameters after administration of ultra-rapid lispro and lispro

Parameter	URLi $n = 31$	Lispro $n = 30$	Difference in LS means URLi vs lispro (95% CI)	*P*-value	Ratio of LS means URLi vs lispro (95% CI)
	LS mean				
tR_{max} (min)	102.86	122.59	−19.73 (−33.94, −5.52)	0.0082	0.84 (0.74, 0.95)
Duration of action (min)	302.77	371.21	−68.44 (−97.88, −39.01)	<0.0001	0.82 (0.75, 0.89)
Early 50% tR_{max} (min)	29.85	40.45	−10.60 (−13.98, −7.21)	<0.0001	0.74 (0.68, 0.80)
Late 50% tR_{max} (min)	211.81	261.96	−50.15 (−66.93, −33.38)	<0.0001	0.81 (0.75, 0.87)
T_{onset} (min)	16.83	23.20	−6.37 (−9.71, −3.03)	0.0003	0.73 (0.62, 0.86)

Model: glucodynamic = period + treatment + sequence + patient (sequence) + random error, where patient (sequence) is fitted as a random effect The confidence interval (CI) for the ratio were calculated using the Fieller's theorem. *P*-value is for the test of the mean difference. Early 50% tR_{max}, time prior to tR_{max} when glucose infusion rate is half the maximum glucose infusion rate; Late 50% tR_{max}, time after tR_{max} when glucose infusion rate is half the maximum glucose infusion rate; LS, least squares; T_{onset}, time of first positive glucose infusion rate; tR_{max}, time of the maximum glucose infusion rate; URLi, ultra-rapid lispro.

with a greater early glucose-lowering effect and similar effectiveness[9]. A clamp study involving Japanese type 1 diabetes mellitus patients showed that faster acting insulin aspart showed faster onset, higher early exposure and a greater early glucose-lowering effect in comparison with insulin aspart[10].

A strength of the present study is the complete cross-over design, enabling each patient to act as his or her own control. In terms of limitations, the present study was carried out in well-controlled patients with type 1 diabetes mellitus, and therefore might not fully represent the results in other patient populations. This experimental method does not provide a direct measure of the postprandial glucose effect; however, the clamp procedure is the gold standard for assessing insulin action.

Overall, URLi showed accelerated insulin lispro absorption, reduced late exposure and overall shorter exposure duration in comparison with lispro. URLi displayed a faster early insulin action, a reduced late insulin action and a shorter duration of insulin action. Overall, there was no difference in the total exposure or glucose infused between the two treatments. Furthermore, URLi was well tolerated by Japanese patients with type 1 diabetes mellitus, with no differences in safety and tolerability observed between URLi and lispro. The accelerated absorption of insulin lispro shown with URLi could therefore optimizes the control of postprandial glucose of Japanese patients with type 1 diabetes mellitus who have been administered lispro.

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DISCLOSURE

Masanari Shiramoto declares no conflict of interest. His current affiliation is Kashiihara Hospital and this manuscript does not represent opinions of his current affiliation. Risa Nasu, Tomonori Oura, Makoto Imori and Kenji Ohwaki are employees of Eli Lilly Japan K.K, and Tomonori Oura and Makoto Imori are minor stockholders of Eli Lilly and Company.

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