Original Research

Evaluation of the Pharmacokinetic Profile of Ultra Rapid Lispro Administered Subcutaneously at Different Injection Sites

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ABSTRACT

Purpose: Ultra rapid lispro (URLi) is a novel insulin lispro formulation developed to more closely match physiological insulin secretion and improve postprandial glucose control. This study compared the pharmacokinetic profile and glucodynamic response of URLi when administered subcutaneously into the abdomen, upper arm, or thigh. An intravenous (IV) bolus administration was included to determine the absolute bioavailability at each injection site.

Methods: In this Phase I, randomized, open-label, 4-period, crossover study, healthy subjects received a single dose of 15 U URLi subcutaneously into the abdomen, upper arm, or thigh, or by intravenous injection. Serum insulin lispro concentrations and glucodynamic response during a 10-hour euglycemic clamp procedure were assessed after URLi administration.

Findings: Total insulin lispro exposure was similar for the abdomen, upper arm, and thigh, and absolute bioavailability was ~65% at each subcutaneous (SC) injection site. Total and peak insulin action were similar across these SC injection sites. The onset of appearance was <1 minute, and the time to early half-maximal drug concentration occurred at ~10 minutes across these three SC injection sites. Onset of insulin action occurred at ~22 minutes, and the early insulin action (for the first hour) was also similar across these SC injection sites. URLi was well tolerated after single SC injections and IV bolus administration.

Implications: The pharmacokinetic and glucodynamic profiles of URLi were similar after a single SC dose into the abdomen, upper arm, or thigh. The rate of insulin lispro absorption and early insulin action were maintained regardless of the SC injection site. The current study supports SC injection of URLi into the abdomen, upper arm, and thigh. ClinicalTrials.gov identifier: NCT03232983. (*Clin Ther.* 2022;44:836–845.)

Key words: Euglycemic glucose clamp, Glucodynamics, Injection site, Insulin lispro, Pharmacokinetics, Ultra rapid insulin.

INTRODUCTION

An important component of diabetes management to achieve an optimal glucose control, which can be measured through glycosylated hemoglobin or time in target glucose range,[1] is the use of rapid-acting insulin as a bolus insulin or in continuous subcutaneous (SC) insulin infusion systems.[2,3] Despite advancements, effectively and consistently controlling postprandial glucose (PPG) levels while avoiding hypoglycemia remains a clinical challenge.[4–6] Rapid-acting insulin analogues were developed to be absorbed more rapidly and have a faster onset of action compared with regular human insulin.[7,8] Although rapid-acting insulins have shown superiority over regular insulin at reducing postprandial glycemic excursions, they cannot always

Accepted for publication April 6, 2022
https://doi.org/10.1016/j.clinthera.2022.04.001
0149-2918/$ - see front matter

match carbohydrate absorption profiles, and a need remained to develop faster, ultra rapid–acting insulin that more closely mimics the endogenous insulin response to food intake.[9]

Ultra rapid lispro (URLi) is a novel insulin lispro formulation developed to more closely match physiological prandial insulin secretion and improve PPG control, and was first approved as Lyumjev® (Eli Lilly and Company, Indianapolis, IN, USA) in the United States, the European Union, and Japan in 2020 and in Canada in 2021. URLi contains 2 locally acting excipients, treprostinil and citrate, which act independently to accelerate the absorption of insulin lispro from the site of injection. Microdoses of treprostinil induce local vasodilation,[10] while citrate increases vascular permeability.[11] In clinical studies, URLi has exhibited ultra-rapid pharmacokinetic (PK) and glucodynamic (GD) profiles with an accelerated insulin lispro absorption and faster onset of action compared with Humalog® (Eli Lilly and Company) in healthy subjects[12] and patients with type 1 diabetes (T1DM)[13] and type 2 diabetes (T2DM).[14] Phase III studies have shown that URLi is superior to Humalog for PPG control in patients with T1DM[15,16] and T2DM.[17]

The preferred site of insulin injection varies among people with diabetes due to practical and anatomical reasons.[18] It is recommended that patients rotate insulin injection sites, and they may inject insulin at different regions of the body.[19] However, different anatomical regions could have differences in absorption rates due to SC blood flow and anthropometry.[20] Because the key attribute of URLi is the accelerated insulin absorption and faster insulin action, which provide a better match to carbohydrate absorption, understanding the PK and GD properties when administered at different tissue sites is important.

The aim of the present study was to compare the PK and GD variables of URLi in healthy subjects after SC injection into the abdomen, upper arm, or thigh, or after intravenous (IV) injection.

PARTICIPANTS AND METHODS

Study Design

This was a Phase I, open-label, 4-period, randomized, crossover, up to 10-hour euglycemic clamp study in healthy subjects. The study was conducted at a single center (Lilly-NUS Centre for Clinical Pharmacology, Singapore) in accordance with the principles of the Declaration of Helsinki (2000), the International Conference on Harmonisation Guidelines for Good Clinical Practice, and guidelines on bioavailability trials.[21,22] Institutional review board approval and written informed consent from all subjects were obtained before any evaluations or study procedures. This study was registered at ClinicalTrials.gov as NCT03232983.

An overview of the study design is outlined in Figure 1. Patients were randomized to 1 of 4 treatment sequences comprising single doses of 15 U of U100 URLi (Eli Lilly and Company) administered subcutaneously into the abdomen, thigh, or upper arm (deltoid), or by IV injection. The study included a screening period (≤28 days) followed by 4 inpatient treatment periods (3 days each) and a ≥14-day follow-up period. At least 3 days of washout occurred between each treatment period.

Participants

Eligible participants were overtly healthy men and women based on medical history, aged 21 to 65 years, body weight ≥45 kg, and body mass index 18.0 to 30.0 kg/m^2. The main exclusion criteria were smoking, history of any medical or psychiatric illness, abnormal cardiac parameters or vital signs deemed clinically relevant by the investigator, allergies to any components of URLi, or use of prescription or nonprescription medication (apart from vitamin/mineral supplements, occasional paracetamol, thyroid replacement medication, or contraceptives).

Bioanalytical Methods

Serum-free insulin lispro was analyzed by using a validated ELISA specific for insulin lispro (Charles River Laboratories Montreal, Senneville, Quebec, Canada). Blood samples for PK analysis were collected at time 2.5, 5, 10, 15, 20, 25, 30, 40, 60, 70, 90, 120, 150, 180, and 210 minutes, and every 60 minutes from 240 to 600 minutes after drug administration. The lower limit of quantitation was 50.0 pg/mL (8.6 pmol/L), and the inter-assay accuracy (percent relative error) and inter-assay precision (percent relative SD) were ≤12%. Quantification of insulin lispro was not affected by the presence of lipemic serum, hemolyzed serum, treprostinil (1 ng/mL), or human insulin (1722 pmol/L).

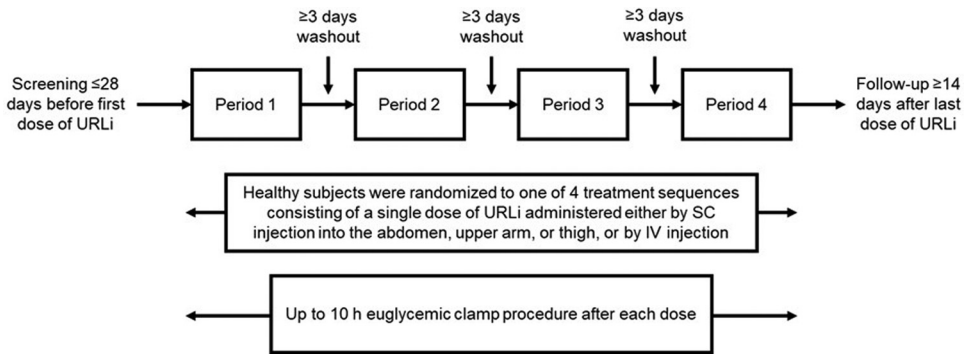

Figure 1. Study design. The trial consisted of 6 visits: screening (≤28 days before enrollment), 4 treatment visits for dosing and clamp procedures (periods 1–4) with a washout period of at least 3 days between visits, and follow-up visit with a washout period of at least 14 days after the last dose. A total of 24 of 28 subjects completed all study periods. Single doses of 15 U ultra rapid lispro (URLi) were administered either subcutaneously in the abdomen, thigh, or upper arm, or intravenously. An up to 10-hour euglycemic clamp procedure was performed after each dose. IV = intravenous; SC = subcutaneous.

Euglycemic Clamp Procedure

At each dosing visit, subjects fasted for at least 8 hours before administration of URLi. After administration, subjects underwent a euglycemic clamp procedure for up to 10 hours. Baseline fasting blood glucose levels were calculated for each subject as the mean of blood glucose concentrations at 10, 20, and 30 minutes before URLi administration. After drug administration, the glucose infusion was initiated at the time that the blood glucose dropped by 5 mg/dL (0.3 mmol/L) below the individual subject's fasting baseline, which was then used as the target blood glucose level for the euglycemic glucose clamp procedure. The time when the clamp was initiated was defined as the onset of insulin action. The clamp procedure was not performed in subjects with baseline blood glucose targets ≤63 mg/dL (3.5 mmol/L). After onset of insulin action, the glucose infusion rate (GIR) was adjusted manually to maintain the predetermined target blood glucose concentration for each individual subject. Blood glucose was maintained at target by variable infusion of IV 20% D-glucose (dextrose) solution. The GIR was recorded throughout the clamp procedure by the clamp operator and reflected the activity of the administered dose of insulin. The clamp operator was blinded to randomization. Blood samples were collected and measured for blood glucose every 2.5 minutes for the first 30 minutes, every 5 minutes from 30 to 120 minutes, every 10 minutes from 120 to 480 minutes, and every 20 minutes from 480 to 600 minutes after URLi injection.

Glucose levels were measured by using glucose analyzers (YSI 23000 STAT Plus Glucose and Lactate Analyzer, YSI Inc, Yellow Springs, OH, USA). The clamp was discontinued if the GIR fell to 0 for at least 30 minutes.

The variability (%CV) in the glucose target during the euglycemic clamp was consistent between treatment arms and similar to data reported for short-acting insulins (Supplemental Table 1).[23]

PK Analyses

PK analyses were conducted by using standard noncompartmental methods of analysis with Phoenix version 7.0 (Certara USA Inc, Princeton, NJ, USA) and S-PLUS version 8.2 (TIBCO Software, Palo Alto, CA, USA).

Free serum insulin lispro concentrations were used to calculate PK parameters, including C_{max}, $AUC_{0-\infty}$, and T_{max}. Insulin lispro absorption was characterized by time to early half-maximal drug concentration (early 50% T_{max}), and the onset of appearance, defined as time that serum insulin lispro reached the lower limit of quantitation. The determination of onset of appearance used a linear interpolation between the time of dosing (zero insulin lispro concentration) and the time of the first quantifiable insulin lispro.

The absolute bioavailability was calculated by using the ratio of the insulin lispro $AUC_{0-\infty}$ after SC injection into the abdomen, or upper arm, or thigh to the insulin lispro $AUC_{0-\infty}$ after IV administration.

GD Analyses

GD parameters were derived from the GIR during the glucose clamp procedure, using Phoenix version 6.4 and S-PLUS version 8.2. A locally weighted scatterplot smoothing function using a span of 0.2 was applied to all individual GIR versus time profiles in each treatment group using S-PLUS software version 8.2. The fitted data for each subject were used to calculate the following GD parameters: maximum GIR (R_{max}), time of maximum GIR (TR_{max}), total amount of glucose infused over the duration of the clamp procedure (G_{tot}), total amount of glucose infused over the first 30 minutes ($G_{tot[0-30min]}$), and total amount of glucose infused over 1 hour ($G_{tot[0-1h]}$). Time to onset of insulin action was based on the raw observed GIR data.

Safety and Tolerability Assessments

Safety and tolerability assessments included adverse events, clinical laboratory parameters, vital signs, ECGs, and hypoglycemic events. In addition, injection site assessment (erythema, pain, induration, edema, and itching) was performed at protocol-defined time points: immediately after injection, and 1, 4, and 10 hours after injection. Any injection site reaction findings were also recorded as adverse events.

Statistical Analysis

General Considerations

Unless otherwise specified, testing for significance was done at an α level of 0.1 with two-sided CIs. Statistical significance was claimed if the P value of a test was <0.1. For selected analyses in which no P values were calculated, statistical significance was claimed if the corresponding 90% CI did not contain 0 (difference between treatment groups) or did not contain 1 (ratio of treatment groups).

Sample Size Considerations

A sample size of 22 completing subjects was estimated to provide the two-sided 90% CIs of the ratios of geometric means for $AUC_{0-\infty}$ after SC injection into the thigh and upper arm, compared with the abdomen, to be within ~0.8 to 1.25 when the observed ratio is 1. This calculation is based on the assumption of a log-normal distribution and an estimate of intrasubject log-scale SD of 0.2.

PK and GD Statistical Methods

All relevant PK and GD parameters were log transformed, except for the time parameters. For log-transformed end points $AUC_{0-\infty}$, C_{max}, G_{tot}, and R_{max}, geometric least squares means (LSM), ratios of geometric LSM, and their corresponding 90% CIs were estimated for each injection site using the statistical model that includes injection site, period, and sequence as fixed effects, and subject within sequence as a random effect. Data from the upper arm, thigh, and abdomen injection sites were included in the same model. The same model without log transformation was used for the analysis of the time parameters T_{max} and TR_{max}. The LSM, injection site differences in LSM, and the corresponding 90% CIs for the injection site differences were estimated from the model. The ratios between injection sites and 90% CIs for the ratios were calculated by using Fieller's theorem. A nonparametric approach was used to test the median of injection site differences for time parameters using the Wilcoxon signed rank test and approximate 90% CIs.

RESULTS

Demographic Characteristics

A total of 28 healthy male subjects, aged between 24 and 63 years (mean [SD], 39.8 [8.6] years) and with a mean (SD) body mass index of 24.3 (3.08) kg/m^2, participated in this study. All subjects were Asian.

Twenty-four subjects completed the study. Four subjects discontinued the study: one due to subject's decision, one after experiencing redness and swelling over the cannulation site (physician's decision), one after cannulation issues (physician's decision), and one due to work commitments. No subject discontinued the study due to an adverse event considered related to the study treatment.

PK Parameters

The mean insulin lispro concentration versus time profiles after SC injection into the abdomen and upper arm are superimposable, whereas the profile was marginally broader after injection into the thigh (Figure 2). Overall insulin lispro exposure ($AUC_{0-\infty}$) was consistent between all 3 injection sites. The 90% CI for the ratio of $AUC_{0-\infty}$ mean values between (thigh or upper arm) and the abdomen included 1 and were

Table I. Statistical comparison between subcutaneous injection sites (upper arm/abdomen and thigh/abdomen).

Parameter	Injection Site	N	Geometric Least Squares Means	Ratio of Geometric Least Squares Means (Thigh or Upper Arm vs Abdomen)	90% CI for the Ratio (Lower, Upper)
Pharmacokinetics					
$AUC_{0-\infty}$, pmol·h/L	Abdomen	25	1744		
	Upper arm	26	1799	1.03	0.99, 1.07
	Thigh	26	1744	1.00	0.96, 1.04
C_{max}, pmol/L	Abdomen	25	731		
	Upper arm	26	762	1.04	0.92, 1.18
	Thigh	26	608	0.83	0.74, 0.94
Glucodynamics					
G_{tot}, mg/kg	Abdomen	25	1516		
	Upper arm	26	1658	1.09	1.00, 1.20
	Thigh	26	1729	1.14	1.04, 1.25
R_{max}, mg/kg/min	Abdomen	25	6.52		
	Upper arm	26	6.86	1.05	0.96, 1.15
	Thigh	26	6.73	1.03	0.94, 1.13

G_{tot} = total amount of glucose infused over the duration of the clamp procedure; R_{max} = maximum glucose infusion rate.

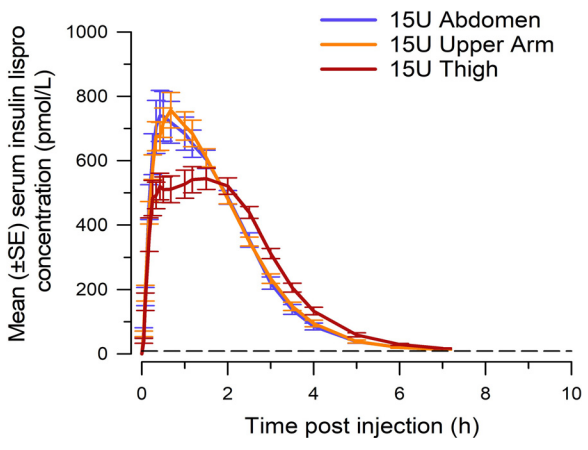

Figure 2. Arithmetic mean (SE) serum concentration versus time profiles for single subcutaneous injections of 15 U ultra rapid lispro into the abdomen, upper arm, or thigh of healthy subjects.

contained within 0.8 to 1.25 for both comparisons (Table I). C_{max} was similar between the abdomen and upper arm but slightly lower (17%–20%) for the thigh. The 90% CI treatment ratio between the upper arm and abdomen for C_{max} was contained within 0.8 to 1.25; however, the lower limit of the 90% CI of the ratio between thigh and abdomen was 0.737 and fell outside the 0.8 to 1.25 limits. The median (minimum–maximum) time of C_{max} (T_{max}) occurred at 0.67 hour (0.25–2.5 hours) for the abdomen, 0.67 hour (0.25–2.0 hours) for the upper arm, and 1.5 hours (0.17–2.5 hours) for the thigh.

Mean treatment ratios (%CV) for $AUC_{0-\infty}$ for the abdomen, upper arm, or thigh compared with IV administration were 0.65 (18), 0.65 (14), and 0.64 (19), respectively. Thus, absolute bioavailability of URLi was ~65% after SC administration in all 3 injection regions. The observed mean PK time profiles after IV administration or SC administration into the abdomen, upper arm, and thigh of URLi are shown in Supplemental Figure 1.

GD Responses

After SC injection of URLi into the abdomen, thigh, or upper arm, the mean GIR profiles were comparable (Figure 3). The maximum GIR (R_{max}) and total insulin action (G_{tot}) were similar across injection sites with the 90% CI for the ratio of means including 1 and contained within 0.8 to 1.25 for both

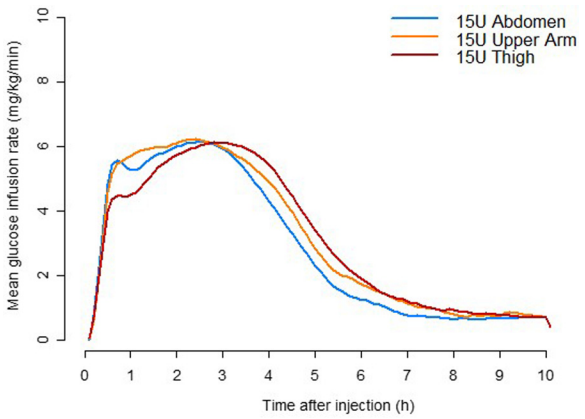

Figure 3. Arithmetic mean locally weighted scatterplot smoothing–fitted glucose infusion rate profiles during euglycemic clamps for single SC injections of 15 U ultra rapid lispro into the abdomen, upper arm, or thigh of healthy subjects.

comparisons between (thigh or upper arm) and the abdomen (Table I). The median (minimum–maximum) TR_{max} occurred at 96 minutes (30–216 minutes) for the abdomen, 123 minutes (36–228 minutes) for the upper arm, and 168 minutes (30–234 minutes) for the thigh.

Early Insulin Lispro Exposure and Insulin Action

The insulin lispro concentration time profiles for the different injection sites overlapped during the first 30 minutes after dosing (Figure 2). The time to early half-maximal drug concentration (early 50% T_{max}) across injection sites was similar, occurring at ~10 minutes after SC injection (Table II). The median onset of appearance was 0.79 minute for the abdomen, 0.48 minute for the upper arm, and 1.16 minutes for the thigh. Although there were differences in the medians between injection sites, the range for the onset of appearance for these injection sites overlapped. Thus, the average onset of appearance of insulin lispro across all injection sites following URLi SC injection was ~1 minute.

The early insulin action was also similar between SC injection sites, as shown by the overlap of the GIR during the first hour after injection (Figure 3). Correspondingly, the onset of insulin action occurred at approximately the same time (abdomen, 22.8 minutes; upper arm, 22.8 minutes; and thigh, 19.8 minutes). In addition, the amount of glucose infused in the first 30 minutes ($G_{tot\ [0\text{-}30min]}$) and in the first hour ($G_{tot\ [0\text{-}1h]}$) of the clamp was comparable across the injection sites (Table II).

Endogenous Insulin Secretion (C-peptide)

Mean C-peptide profiles during the euglycemic clamp were similar across the SC injection sites after a 15 U dose of URLi (Supplemental Figure 2).

Safety and Tolerability

A total of 75 treatment-emergent adverse events (TEAEs) were reported by 23 subjects. All TEAEs were mild in severity, and no serious adverse events were reported. The frequency of TEAEs was comparable between the three SC injection sites and IV administration. The majority of TEAEs were related to study procedures, mainly bruising, pain, swelling, and erythema associated with blood sampling cannulation and infusion catheter sites.

Five subjects reported TEAEs deemed to be related to study treatment: mild headache was reported by 1 subject; mild transient injection site pain was reported by 3 subjects after SC administration (abdomen and upper arm); and mild transient injection site pruritus was reported by 1 subject.

No hypoglycemic events were reported during the study. No clinically relevant alterations in laboratory parameters, vital signs, or ECGs were observed.

DISCUSSION

This study is the first, to the best of our knowledge, to compare the PK and GD effects of a single SC injection of URLi at different injection sites of the body. After a single SC injection of URLi into the upper arm, thigh, or abdomen, the insulin exposure and insulin action were similar across these injection sites. Importantly, the rate of absorption of insulin lispro and early insulin action of URLi were maintained regardless of SC injection site.

The inclusion of an IV study arm enabled the determination of absolute bioavailability of URLi, which was ~65% for all three SC injection sites. This is consistent with the reported absolute bioavailability of Humalog, which was 55% to 77% for SC doses between 0.1 and 0.2 U/kg.[24]

After SC injection of URLi into the abdomen, upper arm, or thigh, the total insulin lispro exposure was similar across the injection sites. This is consistent with other mealtime insulins, such

Table II. Summary of the pharmacokinetic parameters for insulin absorption and glucodynamic parameters for early insulin action after a single subcutaneous injection of 15 U ultra rapid lispro into the abdomen, upper arm, or thigh of healthy subjects. Data are %CV geometric mean unless otherwise stated.

Parameter	Abdomen (n = 25)	Upper Arm (n = 26)	Thigh (n = 26)
Pharmacokinetics			
Early 50% T_{max}, min*	9.8 (5.8–15.2)	9.1 (4.6–15.4)	10.9 (3.9–29.9)†
Onset of appearance, min*	0.8 (0.1–3.5)	0.5 (0.1–3.4)	1.2 (0.1–3.7)
Glucodynamics			
T_{onset}, min*	22.8 (2.4–30)	22.8 (2.4–42)	19.8 (7.8–45)
$G_{tot\ (0–30min)}$, mg/kg	37 (97)	33.2 (147)	28 (186)
$G_{tot\ (0–1h)}$, mg/kg	181 (58)	183 (51)	148 (77)

Early 50% T_{max} = time to early half-maximal drug concentration; $G_{tot\ (0–30min)}$ = total amount of glucose infused over the first 30 minutes; $G_{tot\ (0–1h)}$ = total amount of glucose infused over the first hour; Onset of appearance = time that serum insulin lispro reached the lower level of quantification; T_{onset} = time to onset of insulin action.

* Median (minimum–maximum).

† N = 25.

as Humalog,[25] regular insulin, NovoRapid® (Novo Nordisk, Bagsværd, Copenhagen),[26] Fiasp® (Novo Nordisk),[27] and Apidra® (sanofi-aventis U.S. LLC, Bridgewater, NJ, USA).[28] Consistent with a similar total insulin lispro exposure, the total insulin action after URLi was also similar across the injection sites.

The C_{max} was lower after injection into the thigh compared with abdomen and upper arm injections, but this was not observed with the GD response, as the R_{max} was similar across these injection sites.

It has generally been observed that insulin absorption is slower in the thigh than from the abdomen.[20] This has been attributed to differences in absorption rate between injection sites, which have been shown to vary due to differences in SC blood flow and anthropometry. Within this study, the median T_{max} and TR_{max} occurred later in the thigh compared with the abdomen or upper arm after injection of URLi, but the range for both the T_{max} and TR_{max} overlapped across these injection sites. Importantly, numerous clinical studies with ultra-rapid mealtime insulins have shown that timing of the T_{max} is not correlated with postprandial glucose lowering.[29–32] Rather, the faster rate of insulin absorption, as measured by the timing of the early 50% T_{max}, or the amount of early insulin exposure, resulted in a greater postprandial glucose lowering. Consistent with this finding, T_{max} was not significantly different after SC injection of URLi compared with Humalog in patients with T1DM[31] and was significantly later with URLi compared with Humalog in patients with T2DM.[32] In contrast, the timing of the early 50% T_{max} occurred earlier and there was a greater amount of insulin exposure within the first hour after dosing with URLi versus Humalog.[12–14,33] This has resulted in a consistent improvement in postprandial glucose lowering with URLi compared with Humalog in adults with T1DM or T2DM.[16,17,31,32] Similarly, a faster rise in the insulin lispro concentration in the first 15 minutes was observed after URLi administration in adults with T1DM compared with endogenous insulin levels in healthy subjects following the same test meal.[33] This faster rise in insulin lispro concentration resulted in a numerically greater PPG lowering at 1 hour after a test meal with URLi compared with what was observed in healthy subjects. These results show that a faster rate of insulin absorption results in greater PPG lowering, rather than differences in T_{max} or R_{max}.

Within this study, the onset of insulin lispro appearance was <1 minute, and the early 50% T_{max} was comparable between injection sites, occurring at ~10 minutes postdose. The onset of insulin action and early insulin activity ($G_{tot\ [0–30min]}$ and $G_{tot\ [0–1h]}$) were also similar across injection sites. Thus, there were no differences in the early insulin exposure or insulin action between the abdomen, upper arm, or thigh.

We would therefore expect similar glucose lowering when URLi is injected into the abdomen, upper arm, or thigh.

Although Humalog was not included in this study, we can compare the data within this study as URLi has consistently shown a faster insulin lispro absorption and earlier insulin action compared with Humalog.[12–14] In a dose range study conducted in healthy subjects,[12] a single 15 U SC dose of URLi administered into the abdomen had an onset of appearance at ~1 minute, 3.9 minutes faster than Humalog, and the early 50% T_{max} occurred at 13.6 minutes, which was 14 minutes faster than Humalog. The timing of the onset of appearance and early 50% T_{max} are consistent with the present findings and infers that the ultra-rapid action of URLi is maintained for all injection sites studied.

In some patients, buttocks is a preferred injection site for SC injection of insulin as described by the American Association of Diabetes Educators and in a pan-European epidemiologic study of insulin injection technique in patients with diabetes.[34] In the Phase III studies evaluating URLi in patients with T1DM and T2DM (PRONTO-T1D and PRONTO-T2D), patients were encouraged to rotate injection sites and allowed for injection in the abdomen, thigh, upper arm, and buttocks.[16,17] Although the buttocks was not studied as a site of injection in this study, the abdomen, upper arm, thigh, and buttocks can be used in SC injection of URLi according to the dosage and administration of the prescribing information,[35] which is consistent with the recommendations for Humalog[24] and NovoRapid.[36]

Although the present study was conducted in healthy subjects, the results are applicable to patients with T1DM and T2DM. Clinical pharmacology studies comparing the PK and GD profiles of URLi versus Humalog have been conducted in healthy subjects[12] and patients with T1DM[13] and T2DM.[14] Across the studied dose range and study populations, including elderly patients with T1DM,[13] URLi consistently exhibited a faster absorption, reduced late exposure, and overall shorter exposure duration compared with Humalog.[33] Similarly, URLi showed earlier insulin action while reducing late insulin action, resulting in a shorter duration of insulin action compared with Humalog across the study populations (healthy subjects and patients with T1DM and T2DM) and dose range reflected in the individual studies and in the pooled analysis.[37] Also, although all participants in the study were male, the data are expected to be representative of both male and female subjects because no difference in sex has been identified with URLi in previous studies.[35] Despite the euglycemic clamp being the gold standard for assessing insulin action, a limitation of this procedure is that it does not measure the glucose-lowering effects of the insulin after oral carbohydrate intake.

Strengths of this study were the crossover design, which enabled patients to act as their own control; the inclusion of a washout period between dosing periods, which ensured no presence of previously administered study drug; and the use of a specific assay to measure insulin lispro concentrations, ensuring no interference from endogenous insulin.

CONCLUSIONS

This study showed that the PK and GD profiles of URLi in healthy subjects were similar after SC injection of 15 U of URLi into the upper arm or thigh, compared with injection into the abdomen. The rate of insulin lispro absorption and early insulin action were maintained regardless of the SC injection site. The current study supports SC injection of URLi into the abdomen, upper arm, and thigh. This allows patients to inject at their preferred site while maintaining the rapid absorption with URLi.

DECLARATION OF INTEREST

All authors are employees and shareholders of Eli Lilly and Company. Ms LaBell is a shareholder of Johnson & Johnson and Novartis, outside of the submitted work. The authors have indicated that they have no other conflicts of interest regarding the content of this article.

Eli Lilly and Company was involved in the study design; collection, analysis, and interpretation of data; preparation of the manuscript; and decision to submit the article for publication.

ACKNOWLEDGMENTS

Eli Lilly and Company funded the study.

The authors thank the study participants and investigators. The authors also thank Michelle Yi Xiu Lim (Eli Lilly and Company) for study operational oversight and Alastair Knights (Eli Lilly and Company) for medical writing and editing assistance.

Dr Leohr, Ms Dellva, and Dr Linnebjerg were involved in the study design; Dr Linnebjerg was involved in medical monitoring; Dr Leohr, Dr Coutant

and Ms LaBell conducted data analyses; and Ms Dellva was involved in the statistical analysis. All authors participated in the interpretation of the study results and in the drafting and critical revision of the manuscript. All authors approved the final version of the manuscript to be published.

DATA SHARING

Eli Lilly and Company provides access to all individual participant data collected during the trial, after anonymization, with the exception of PK or genetic data. Data are available to request 6 months after the indication studied has been approved in the United States and European Union 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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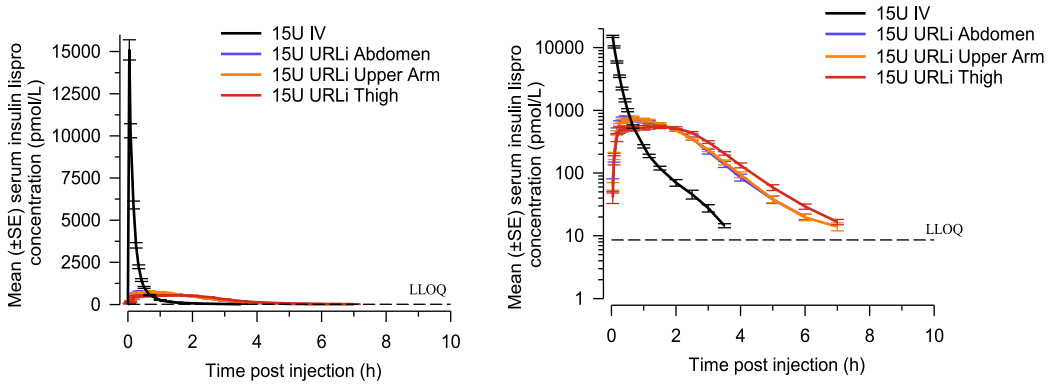
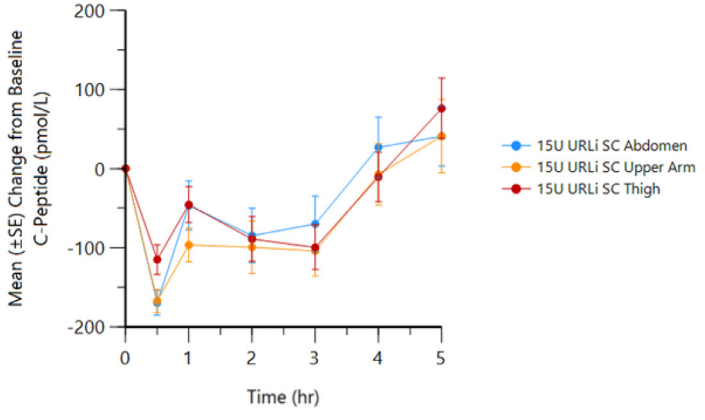
APPENDIX



Abbreviations: SC = subcutaneous; IV = intravenous; SE = standard error; U = units; URLi = ultra rapid lispro.

Supplementary Figure 1. Arithmetic mean (±SE) serum insulin lispro concentration-versus-time profiles for single IV and SC injections of 15 U URLi in healthy subjects

Abbreviations: SC = subcutaneous; IV = intravenous; SE = standard error; U = units; URLi = ultra rapid lispro.



Abbreviations: SC = subcutaneous; SE = standard error; U = units; URLi = ultra rapid lispro.

Supplementary Figure 2. Arithmetic mean (±SE) C-peptide concentration profiles for single SC injections of 15 U URLi in healthy subjects

Abbreviations: SC = subcutaneous; SE = standard error; U = units; URLi = ultra rapid lispro.

Supplementary Table 1. Mean glucose level for each participant and % CV of individual glucose level during clamp procedures

Treatment	N	Mean (mg/dL)	%CV
15U URLi IV	28	81.1	7.1
15U URLi SC Abdomen	25	80.1	8.1
15U URLi SC Upper Arm	26	80.3	7.5
15U URLi SC Thigh	26	81.4	7.4

Abbreviations: CV = coefficient of variation; SC = subcutaneous; SE = standard error; U = units; URLi = ultra rapid lispro.