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ORIGINAL ARTICLE

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Ultra rapid lispro (URLi) shows accelerated pharmacokinetics and greater reduction in postprandial glucose versus Humalog® in patients with type 1 diabetes mellitus in a randomized, double-blind meal test early-phase study

Christof Kazda MD[1] | Jennifer Leohr PhD[1] | Rong Liu PhD[1] | Shobha Reddy BS[1] | Mary Anne Dellva MS[1] | Mei Teng Loh BS[1] | Thomas Hardy MD[1] | Leona Plum-Mörschel MD[2]

[1]Eli Lilly and Company, Indianapolis, Indiana, USA

[2]Profil, Mainz, Germany

Correspondence
Christof Kazda, MD, Eli Lilly and Company, Indianapolis, IN 46285, USA.
Email: kazda_christof@lilly.com

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Eli Lilly and Company

Abstract

Aim: To compare the pharmacokinetics (PK), glucodynamics (GD), and tolerability following single and multiple daily subcutaneous (SC) doses of ultra rapid lispro (URLi) and Humalog® in patients with type 1 diabetes mellitus (T1D).

Materials and Methods: This was a two-part, randomized, double-blind, Phase 1b study. Part A used a six-period crossover design to assess PK and GD response to a solid mixed meal tolerance test (MMTT) following a single dose of URLi or Humalog administered 15 min before, immediately before, and 15 min after the start of the meal. Part B evaluated URLi or Humalog during 2 weeks of multiple daily dosing with a parallel design. The PK and GD were assessed following MMTTs at the beginning and end of the 2-week period when insulins were administered immediately before the start of the meal.

Results: URLi increased the insulin exposure within the first 30 min postdose by 2.2-fold and reduced the time to early half-maximal drug concentration by 37% compared with Humalog. Overall, URLi resulted in better postprandial glucose lowering when dosed before, immediately before, or after a meal compared with Humalog. Comparing the same meal-to-dose timing between the insulins, postprandial glucose excursion over 5 hours was reduced by 40%-44% for all three dose timings (−15, 0, and +15 min) with URLi, achieving statistical significance for the 0- and +15-min timings. The PK and GD profiles were sustained after daily SC dosing for 2 weeks in patients with T1D. The number of documented hypoglycaemic events was similar between URLi and Humalog during the postprandial period of the MMTTs and the outpatient period.

* Parts of this work were presented as posters at the American Diabetes Association 77th and 78th Scientific Sessions in 2017 and 2018, respectively. In addition, parts of this work were presented at the 54th European Association for the Study of Diabetes Meeting in 2018 and at the Advanced Technologies and Treatments for Diabetes 11th International Conference in 2018.

Conclusions: URLi showed accelerated insulin lispro absorption and greater postprandial glucose reduction at different meal-to-dose timings compared with Humalog and was well tolerated in patients with T1D.

KEYWORDS
insulin therapy, pharmacodynamics, pharmacokinetics, type 1 diabetes mellitus, ultra-rapid insulin

1 | INTRODUCTION

Most patients with type 1 diabetes mellitus (T1D) are treated with multiple daily injections of prandial insulin and basal insulin or continuous subcutaneous (SC) insulin infusion.[1] Rapid-acting insulin analogues (such as insulin lispro, aspart, and glulisine) were developed to better meet prandial insulin requirements and are associated with lower postprandial glucose excursions and lower hypoglycaemia risk.[2,3] Although these analogues are absorbed faster than regular human insulin, they cannot always match carbohydrate absorption profiles and there is a need to develop faster ultra-rapid–acting insulins that more closely match the endogenous insulin response to food intake.[4]

Insulin lispro (Humalog®) is a commercially available, rapid-acting human insulin analogue administered subcutaneously within 15 min premeal or immediately after a meal to improve glycaemic control in patients with diabetes mellitus.[5] Ultra rapid lispro (URLi; LY900014) is a novel insulin lispro formulation containing two locally acting excipients, treprostinil to induce local vasodilation and citrate to increase vascular permeability, thereby accelerating insulin lispro absorption.[6,7] URLi has shown accelerated insulin lispro absorption, with corresponding faster onset of insulin action and reduced duration of insulin action compared with Humalog in patients with T1D[8,9] and patients with type 2 diabetes (T2D).[10] Additionally, phase 3 results showed superiority of URLi to Humalog in controlling postprandial glucose excursions in patients with T1D or T2D.[11,12]

In the current study, we evaluated the differences in the pharmacokinetics (PK) and glucodynamics (GD) profiles between URLi and Humalog following single and multiple daily individualized SC doses in patients with T1D. The study assessed the postprandial glucose response to a solid mixed meal tolerance test (MMTT) after a single SC dose of URLi or Humalog administered at different meal-to-dose timings (15 min before the meal, immediately prior to the meal, and 15 min after the meal) in Part A. The postprandial glucose response was also assessed following a solid MMTT at the beginning and end of a 2-week multiple SC dosing period in Part B. Additionally, the safety and tolerability of these SC doses were evaluated.

2 | MATERIALS AND METHODS

2.1 | Study design

This was a single-site, two-part, randomized, double-blind, Phase 1b study in patients with T1D (Figure S1). Part A used a six-period crossover design to assess PK and GD responses to a solid MMTT following a single dose with study insulins using different meal-to-dose timing. In Part B, the sustainability of the insulin lispro PK and the durability of GD responses to URLi and Humalog were evaluated following multiple daily individualized SC dosing for 2 weeks. The study was conducted in accordance with the Declaration of Helsinki, the International Conference on Harmonisation Guideline for Good Clinical Practice, and applicable laws and regulations. The protocol was approved by an independent ethics committee, and all patients provided written informed consent. The study is registered at www.clinicaltrials.gov (NCT02703350).

2.2 | Study participants

Of the 30 patients who entered the study, all received at least one dose of study treatment, and all 30 patients completed Parts A and B of the study. Eligible patients were male or female, diagnosed with T1D for at least 1 year, had fasting C-peptide (≤0.30 nmol/L), were aged 18-65 years, had an HbA1c level of less than 9.0% (<75 mmol/mol), a body mass index of 18.5-33.0 kg/m^2, had not experienced severe hypoglycaemia within 6 months prior to screening, and were on a stable multiple daily injection regimen with short- and long-acting insulin (total insulin dose ≤1.5 U/kg/d).

2.3 | Treatment protocol

Patients underwent a 1-week lead-in period prior to entering Part A, where patients switched from their prescribed short-acting insulin to Humalog. Patients continued their prestudy basal insulin regimen during the entire study unless safety issues arose that required a change.

In Part A, patients were randomized to receive a single SC dose of URLi or Humalog U100 formulations (Eli Lilly, Indianapolis, IN, USA) at the various meal-to-dose timings (15 min before a meal, at meal [immediately before a meal], 15 min after the start of a meal). In Part B, patients were randomized to either URLi or Humalog and injected individualized doses immediately prior to the start of meals for 2 weeks. On the first day of dosing and at the end of the 2-week dosing period of Part B (Day 1 and Day 14, respectively), the PK and GD were assessed.

The SC dose of study treatment was individualized for each patient based on their typical insulin dosing regimen, premeal and postmeal glucose levels, and investigator judgement. Carbohydrate-to-insulin ratios were intended to cover the carbohydrate content of

the meals consumed during the inpatient and outpatient periods for both the study treatments. The outpatient doses may have been adjusted for meal content (no titration of basal or bolus insulins were performed unless necessary for safety concerns). The MMTTs were also individualized for each patient and contained 30% of calories needed for weight maintenance composed of approximately 50% of the calories from carbohydrate, 30% from fat, and 20% from protein. The meal and insulin dose were kept the same for all MMTTs. Patients were fasted (except for water) for at least 10 hours before each test meal. The meal was consumed within approximately 20 min. The MMTTs were preceded by a 7-hour run-in period when blood glucose was carefully monitored at a minimum of 30-min intervals to stabilize blood glucose levels to 7.0 (±1.1) mM ([126 {±20} mg/dL]), using an intravenous insulin (glulisine) and glucose infusion. Blood samples were collected for glucose and insulin lispro concentrations during the MMTTs. For continuous glucose monitoring (CGM) during Part B of the study, glucose was monitored using a standard system (Dexcom G4 Platinum system) in a blinded mode.

2.4 | Safety

Safety assessments included adverse events (AEs), hypoglycaemic events, physical examinations, clinical laboratory evaluations, vital signs, and electrocardiograms (ECGs).

2.5 | Bioanalysis

Blood samples for insulin lispro PK analysis were taken every 5 min during the first hour and then at 70, 90, 120, 150, 180, 240, and 300 min postdose. A validated sandwich enzyme-linked immunosorbent assay, specific to insulin lispro without cross-reactivity to endogenous insulin, was used to quantify free insulin lispro serum concentrations. The lower limit of quantification (LLOQ) was 8.6 pmol/L, and inter-assay accuracy (% relative error) and inter-assay precision (% relative standard deviation) were 16% or less. Quantification of insulin lispro was not affected by the presence of lipaemic serum, haemolysed serum, treprostinil (1 ng/mL), human insulin (1720 pmol/L), insulin aspart (600 pmol/L), insulin glargine (150 pmol/L), or insulin glulisine (600 pmol/L).

Plasma samples for treprostinil were collected 15 and 30 min postdose and were measured by liquid chromatography-mass spectrometry/mass spectrometry assay. The LLOQ was 0.010 ng/mL, while inter-assay precision and accuracy were 10% or less. The assay was not affected by the presence of insulin lispro (12 913 pmol/L), lipaemic serum, or haemolysed serum.

2.6 | Outcome measures

Free serum insulin lispro PK parameters were calculated by non-compartmental methods using Phoenix® version 6.3 and S-PLUS® version 8.2.

PK parameters included time to early half-maximal concentration (early 50% t_{max}), time to late half-maximal concentration (late 50% t_{max}), maximum observed drug concentration (C_{max}), time of maximum observed drug concentration (t_{max}), area under the concentration-time curve (AUC) from time 0 to the last recorded time postdose ($AUC_{[0\text{-}tlast]}$), AUC from time 0 to 30 min postdose ($AUC_{[0\text{-}30min]}$), AUC from time 0 to 1 hour postdose ($AUC_{[0\text{-}1h]}$), AUC from time 0 to 2 hours postdose ($AUC_{[0\text{-}2h]}$), AUC from 3 to 5 hours postdose ($AUC_{[3\text{-}5h]}$), and AUC from time zero to infinity ($AUC_{[0\text{-}\infty]}$). For Part A, the PK profiles for the different dose timings were combined into an overall URLi and Humalog profile, as food absorption did not alter the PK of insulin lispro when given subcutaneously.

2.7 | GD analysis

Primary GD endpoints were derived from glucose concentration profiles determined using the Super GL glucose analyzer[13] (Dr. Müller Gerätebau GmbH, Freital, Germany) at the clinical site. Super GL glucose concentration values were based on blood but calibrated to plasma for reporting. Glucose data were summarized for each part of the study by treatment and day, and by meal-to-dose timing. The change from baseline (the average of −30, −15, and 0 min represented the 0-hour time point) plasma glucose was calculated for each patient for each MMTT period. The change from baseline plasma glucose was calculated for the incremental area under the curve (iAUC) using the linear trapezoidal method during the 5-hour test meal for Parts A and B. Plasma glucose GD parameters included change from baseline of the AUC from time 0 to 2 hours ($iAUC_{[0\text{-}2h]}$) postmeal and the AUC from time 0 to 5 hours postmeal ($iAUC_{[0\text{-}5h]}$). Glucose values collected post-treatment of either hypoglycaemic or hyperglycaemic event were not used in the analysis and were treated as missing.

2.8 | Statistical analysis

Statistical analysis was performed using SAS version 9.3 or greater (SAS Institute, Cary, NC). A two-sided significance level of .1 was used for treatment comparisons. Statistical analysis was conducted on data from patients who received the same dose for MMTTs and consumed the entire meal.

Log-transformed PK parameters for Part A were analysed using a statistical model that included treatment and period as fixed effects, and patient as a random effect. The within-patient PK variability of URLi and Humalog was also estimated directly from the model. Log-transformed PK parameters for Part B were analysed using a statistical model that included treatment, day (Day 1 or Day 14), and treatment-by-day interaction as fixed effects, and patient as a random effect.

For Part A, the GD parameters (without log-transformation) were analysed using a model that included treatment, dose timing, treatment-by-dose timing interaction, and period as fixed effects, and patient as a random effect. For Part B, GD parameters were analysed

using a model that included treatment, day (Day 1 or Day 14), and treatment-by-day interactions as fixed effects, and patient as a random effect. For both Parts A and B, the least squares mean ratios and their corresponding 90% confidence intervals (CIs) were calculated using Fieller's method.[14]

An exploratory comparison of glucose fluctuations using CGM profiles was performed during the outpatient period in Part B; however, no statistical analysis between treatment groups was performed on these data. Unless otherwise specified, arithmetic means are presented.

3 | RESULTS

3.1 | Study population

Thirty patients with T1D (24 males and 6 females) between the ages of 22 and 64 years participated in and completed the study. Baseline characteristics and demographics are shown in Table S1.

3.2 | Single dose insulin lispro PK (Part A)

Mean serum insulin lispro concentration-time profiles were shifted to the left following a single SC dose of URLi compared with Humalog, showing accelerated insulin lispro absorption and reduced late exposure with URLi (Figure 1). The early 50% t_{max} was 9 min earlier (15.5 vs. 24.3 min; $P < .0001$) (Table 1). This accelerated insulin lispro absorption with URLi led to significantly increased early serum insulin lispro exposure. The greatest increase in exposure was during the first 30 min after URLi dosing, as the $AUC_{(0\text{-}30min)}$ was 2.2-fold greater ($P < .0001$) with URLi versus Humalog (Table 1). The significant increase in insulin lispro exposure with URLi was maintained over the 2 hours after dosing ($P < .0001$).

In addition, the late insulin lispro exposure was reduced with URLi compared with Humalog. From 3 to 5 hours postdose, exposure was reduced by 25% ($P < .0001$), and the late 50% t_{max} was 7 min shorter with URLi versus Humalog ($P = .0913$).

Overall insulin lispro exposure ($AUC_{[0\text{-}\infty]}$) was comparable between URLi and Humalog; however, C_{max} was significantly greater for URLi than for Humalog ($P = .0008$; Table 1).

3.3 | Multiple-dose insulin lispro PK (Part B)

Mean serum insulin lispro concentration-time profiles on Day 1 and Day 14 were similar after SC administration of URLi or Humalog (Figure 2, top panels). There were no significant changes between Day 1 and Day 14 for any of the insulin lispro PK parameters for either URLi or Humalog (Table S2).

3.4 | Variability of PK parameters

The majority of insulin lispro PK parameters had lower within-patient variability following URLi administration compared with Humalog in Part A. The most pronounced reduction in variability with URLi was in the within-patient coefficient of variation (CV; %) for the total insulin exposure ($AUC_{[0\text{-}\infty]}$) (Table S3).

3.5 | PK of treprostinil

Following single and multiple SC doses of URLi, there were no detectable concentrations of treprostinil in any of the samples collected from the 30 patients who participated in the study.

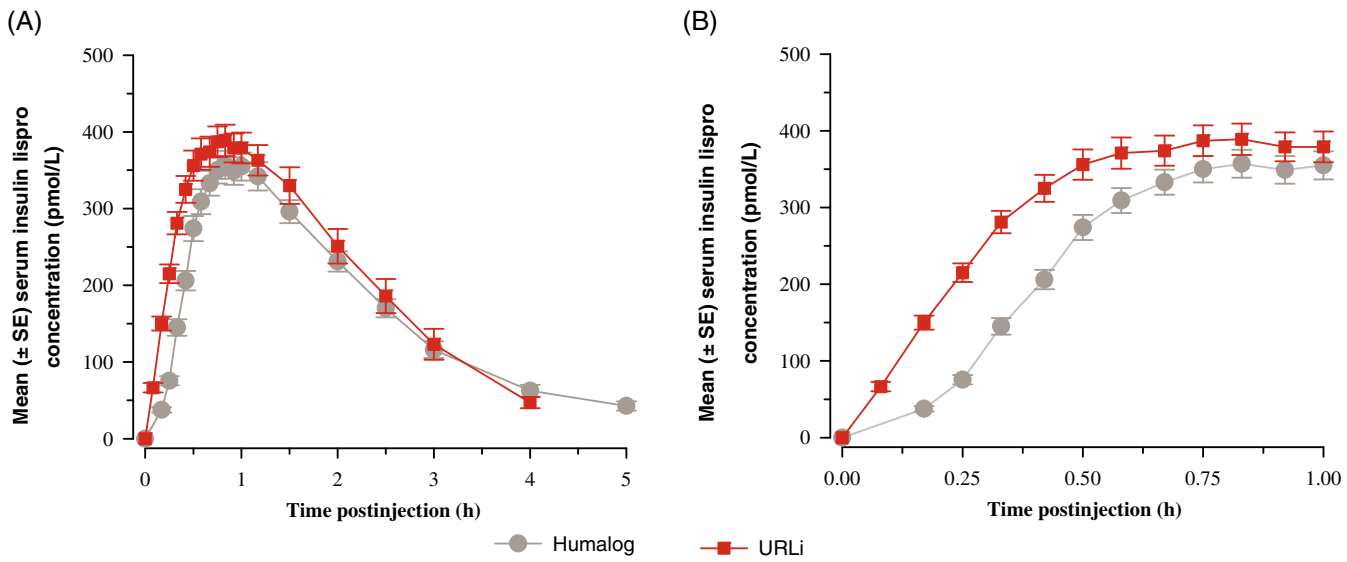

FIGURE 1 Mean (±SE) serum insulin lispro concentration-time profiles for URLi and Humalog: A, Insulin lispro concentration-time profile 0-5 hours after injection, and B, insulin lispro concentration-time profile 0-1 hours after injection. SE, standard error; URLi, ultra rapid lispro

TABLE 1 Statistical analysis of insulin lispro pharmacokinetics parameters for Humalog versus URLi

Parameter	URLi (N = 30)	Humalog (N = 30)	Ratio of geo LS means URLi: Humalog (90% CI)	*P* value[a]
Early insulin lispro exposure	Geo LS means			
Early 50% t_{max} (min)	15.5	24.3	0.635 (0.598-0.675)	<.0001
$AUC_{(0\text{-}30min)}$ (pmol•h/L)	89.1	40.1	2.23 (2.01-2.46)	<.0001
$AUC_{(0\text{-}1h)}$ (pmol•h/L)	262	192	1.37 (1.28-1.46)	<.0001
$AUC_{(0\text{-}2h)}$ (pmol•h/L)	552	457	1.21 (1.14-1.28)	<.0001
Late insulin lispro exposure				
$AUC_{(3\text{-}5h)}$ (pmol•h/L)	62.1	82.6	0.751 (0.674-0.837)	<.0001
Late 50% t_{max} (min)	124	131	0.946 (0.896-0.999)	.0913
Total insulin lispro exposure				
C_{max} (pmol/L)	410	362	1.13 (1.07-1.20)	.0008
$AUC_{(0\text{-}\infty)}$ (pmol•h/L)	789	745	1.06 (1.00-1.12)	.0848

Abbreviations: AUC, area under the concentration vs. time curve; $AUC_{(0\text{–}30\ min)}$, AUC from time zero to 30 min; $AUC_{(0\text{-}1h)}$, AUC from time zero to 1 hour; $AUC_{(3\text{-}5h)}$, AUC from 3 to 5 hours; $AUC_{(0\text{-}\infty)}$, AUC from time zero to infinity; CI, confidence interval; C_{max}, maximum concentration; early 50% t_{max}, time to early half-maximal concentration; Geo, geometric; h, hour; late 50% t_{max}, time to late half-maximal concentration; LS, least squares; min, minutes; N, number of patients; $t_{1/2}$, half-life; t_{max}, time to maximum observed concentration; URLi, ultra rapid lispro.
[a]Predefined significance level of .1.

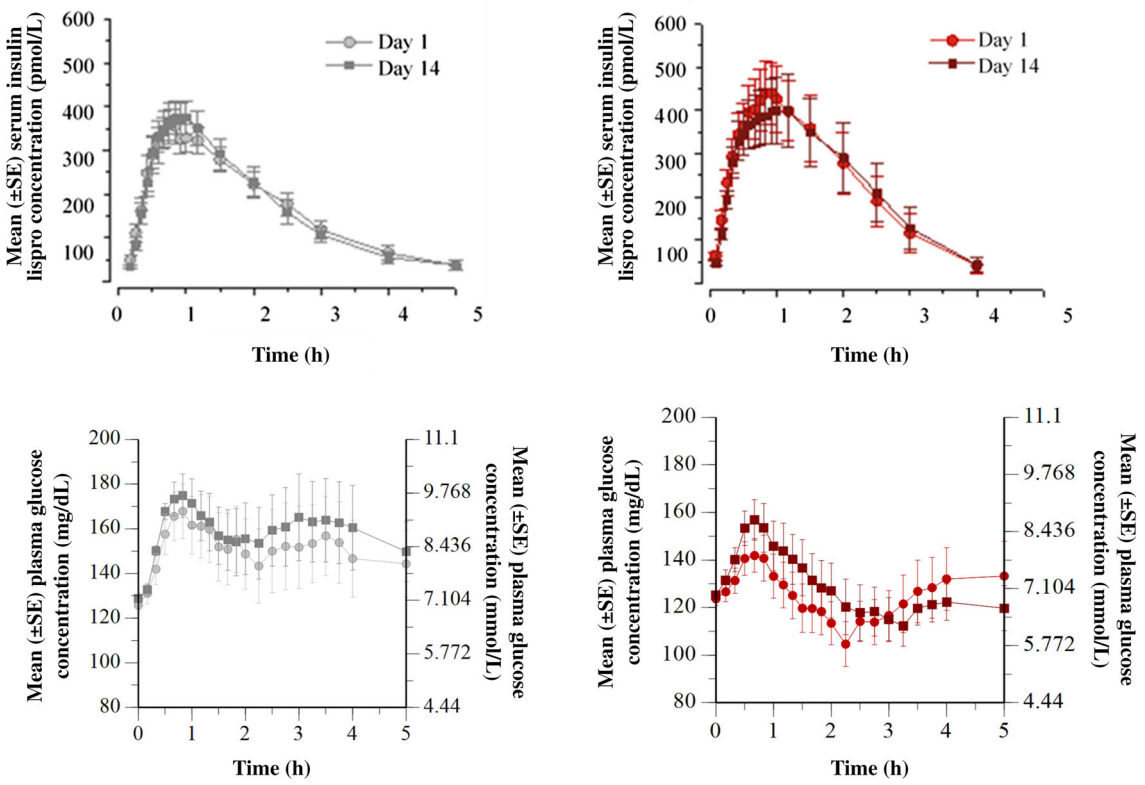

FIGURE 2 Mean (±SE) serum insulin lispro concentration (top) and mean (±SE) plasma glucose concentration (bottom) following a single dose (Day 1) or multiple dosing (Day 14) for Humalog (left) and URLi (right). h, hour; SE, standard error; URLi, ultra rapid lispro

3.6 | Glucodynamics

3.6.1 | Test meal glucose responses (Part A)

Mean plasma glucose concentration-time profiles following single SC doses of URLi and Humalog relative to the start of the meal (15 min before, at, and 15 min after the meal) are presented in Figure 3. URLi reduced the postprandial glucose excursion during the MMTT compared with Humalog for each of the meal-to-dose timings. In comparing the same meal-to-dose timing for URLi and Humalog, the postprandial glucose excursion over 5 hours was reduced by 40%-44% for all three dose timings (−15, 0, and +15 min) (Table 2). When

both insulins were injected immediately prior to the start of the MMTT, URLi significantly reduced the postprandial glucose excursion compared with Humalog by 39% ($P = .0315$) in the first 2 hours and by 44% ($P = .0972$) over the complete 5-hour MMTT period. URLi reduced postprandial glucose over the complete 5-hour period by 42% ($P = .0257$) compared with Humalog when both insulins were injected 15 min after the MMTT. When URLi and Humalog were injected 15 min prior to the MMTT, URLi significantly reduced (−103%) the postprandial glucose over the first 2 hours. The postprandial glucose excursion over the complete 5-hour MMTT when URLi was dosed immediately before the meal compared with Humalog dosed 15 min prior to the MMTT was similar between the treatment groups.

3.6.2 | Test meal glucose responses (Part B)

Mean plasma glucose concentration-time profiles during MMTTs performed on Day 1 and Day 14 after SC doses of URLi or Humalog were similar (Figure 2, bottom panels). There was no statistically significant difference observed between Day 1 and Day 14 over the entire glucose excursion period for either URLi or Humalog (Table S4).

3.6.3 | CGM (Part B)

Mean plasma glucose levels and corresponding 90% CI over the 5-hour postbreakfast period following multiple daily individualized SC doses of either URLi or Humalog are presented in Figure S2. A trend of better control of postbreakfast glucose excursions was observed for URLi compared with Humalog during the outpatient period. The CGM data showed that time patients spent in the normal range of more than 3.9 to 10 mmol/L (>70 to ≤180 mg/dL) was numerically higher and time spent in hyperglycaemia was numerically lower for URLi compared with Humalog during the Day 1 and Day 14 MMTTs (Table S5). The time patients spent in hypoglycaemia during Day 1 and Day 14 MMTTs and during the outpatient period (Day 2 to Day 13) was numerically lower for URLi compared with Humalog;

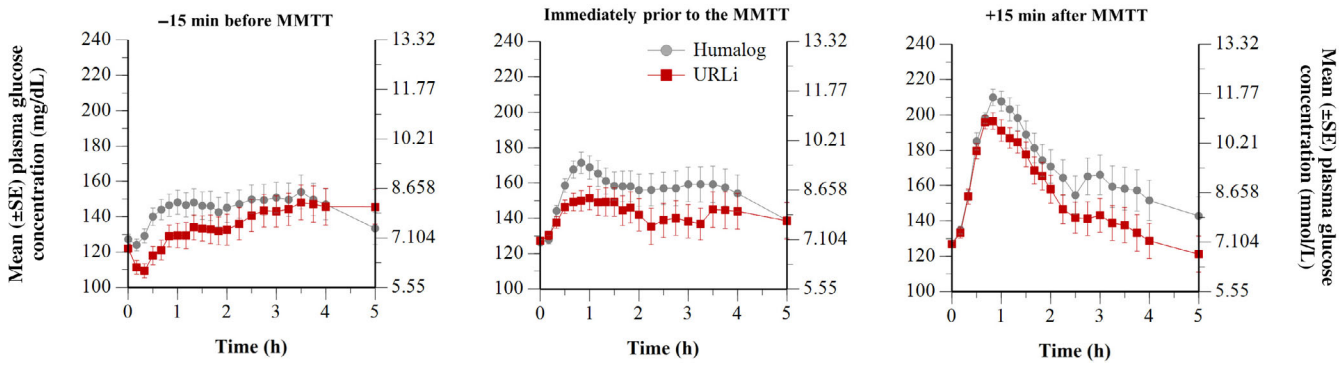

FIGURE 3 Mean plasma glucose (±SE) versus time when dosed 15 min before (left), immediately prior (middle), and 15 min post (right) the start of the meal following a single dose of Humalog or URLi in Part A. h, hour; MMTT, mixed meal tolerance test; SE, standard error; URLi, ultra rapid lispro

TABLE 2 Statistical analysis of glucodynamics parameters for Humalog versus URLi

Glucose parameter	Comparison	URLi LS mean (N)	Humalog LS mean (N)	Ratio[a] of LS mean URLi:Humalog (90% CIs)	*P* value[b]
$iAUC_{(0-2\ h)}$ (mg·h/dL)	URLi (−15 min) vs. Humalog® (−15 min)	−0.94 (29)	27.37 (30)	−0.03 (−1.58, 0.49)	.0081[c]
	URLi (0 min) vs. Humalog® (0 min)	35.26 (29)	58.13 (30)	0.61 (0.32, 0.93)	.0315[c]
	URLi (+15 min) vs. Humalog® (+15 min)	89.91 (29)	107.57 (30)	0.84 (0.70, 1.01)	.0957[c]
	URLi (0 min) vs. Humalog® (−15 min)	35.26 (29)	27.37 (30)	1.29 (0.76, 3.03)	.4547
$iAUC_{(0-5\ h)}$ (mg·h/dL)	URLi (−15 min) vs. Humalog® (−15 min)	55.77 (27)	92.27 (28)	0.60 (0.03, 1.15)	.3092
	URLi (0 min) vs. Humalog® (0 min)	76.37 (27)	135.54 (29)	0.56 (0.21, 1.04)	.0972[c]
	URLi (+15 min) vs. Humalog® (+15 min)	106.38 (29)	184.37 (29)	0.58 (0.38, 0.87)	.0257[c]
	URLi (0 min) vs. Humalog® (−15 min)	76.37 (27)	92.27 (28)	0.83 (0.39, 1.36)	.6551

Abbreviations: AUC, area under the concentration vs. time curve; CI, confidence interval; $iAUC_{(0-2h)}$, change from baseline in AUC from time 0 to 2 hours; $iAUC_{(0-5h)}$, change from baseline in AUC from time 0 to 5 hours; LS, least squares; min, minute; N, number of patients; URLi, ultra rapid lispro.

[a]Confidence intervals were calculated using Fieller's theorem.

[b]Significance level of $P = .1$ based on mean differences.

[c]Indicates statistical significance.

however, the differences between the groups were small. Mean between-day variability (SD, CV, and mean of daily differences) over a 24-hour period was numerically lower for URLi compared with Humalog; within-day variability (SD, CV, and mean amplitude of glycaemic excursions) was similar between treatment groups.

3.7 | Safety and tolerability results

There were no serious AEs or discontinuations because of a treatment-emergent AE (TEAE). No clinically relevant changes in laboratory tests, vital signs, ECGs, or abnormal findings upon physical examinations occurred during the study. Overall, the incidence of TEAEs was low and similar between the treatment groups.

Events of documented hypoglycaemia (blood glucose level ≤3.9 mmol/L [≤70 mg/dL]) were captured throughout the study. During the MMTTs in Part A, the incidence of documented hypoglycaemic events was similar between the treatment groups (6/6, 7/5, and 8/7 events/patients for URLi compared with 4/3, 4/3, and 6/5 events/patients for Humalog at −15, 0, and 15 min, respectively). During the inpatient periods of Part B (during and outside of the MMTTs), the overall number of hypoglycaemic events was similar between the treatment groups (11 events for URLi compared with 12 events for Humalog). During the outpatient period of Part B, the number of documented hypoglycaemic events was numerically lower for URLi (56 events) compared with Humalog (65 events). The majority of the events during the outpatient period were classified as asymptomatic (35 events for URLi and 49 events for Humalog). There were no instances of severe hypoglycaemia observed or reported during the study.

4 | DISCUSSION

In this study, we evaluated the differences in the PK and GD profiles and tolerability of URLi compared with Humalog following single and multiple daily individualized SC doses in patients with T1D. After a single SC administration, URLi showed an accelerated insulin lispro absorption with a 2.2-fold increase in the insulin exposure within the first 30 min and a 36.5% reduction of early 50% t_{max} compared with Humalog. The accelerated insulin lispro absorption of URLi was sustained after 2 weeks of multiple daily dosing. A lower within-patient variability was observed for the majority of PK parameters following URLi administration compared with Humalog in Part A. Following URLi administration, treprostinil was undetectable in plasma following single and multiple daily SC injections.

Furthermore, this study explored the postprandial glucose profiles with URLi and Humalog after a single SC dose injected at different meal-to-dose timings (15 min before, immediately prior to, and 15 min after the start of a test meal). The mean glucose concentrations were numerically lower following administration of URLi compared with Humalog, regardless of when patients were dosed relative to the test meal. The largest differences in glucose lowering observed between treatment groups occurred when patients were dosed immediately before or 15 min after the test meal. The durability of glucose lowering with URLi shown as glucose lowering during a MMTT was similar between Day 1 and after 2 weeks of multiple daily dosing. Additionally, CGM data showed a trend of better control of postbreakfast glucose excursions for URLi compared with Humalog during 14 days of outpatient treatment. These findings support that the accelerated absorption of URLi can improve postprandial glucose control when dosed immediately prior to, or even after, the start of a meal. This fits with how many patients with T1D currently administer mealtime insulins.[15]

URLi and Humalog were well tolerated by patients with T1D. The total number of hypoglycaemic events observed during the study was small. Overall, the number of documented hypoglycaemic events was similar between URLi and Humalog during the postprandial period of the MMTTs and outpatient period. This observation is consistent with the data reported in the URLi Phase 3 study (PRONTO-T1D).[11] Consistent with the lack of systemic exposure, no safety or tolerability concerns were observed, which may have been related to the microdose of treprostinil contained in the URLi formulation.

This study was limited by the small sample size, and the parallel design in Part B did not allow a direct comparison of URLi with Humalog. In addition, the study used a fixed individual dose of basal insulin that was optimized prior to randomization without adjustments during the study. Overall, the study was well designed with the double-blinding of patients and investigators and a crossover design that allowed for intra-patient comparison. Other strengths of this study include the use of solid MMTTs to mimic normal meals, and the titration of blood glucose to the same starting value before the MMTTs.

In summary, URLi showed accelerated insulin lispro absorption, and a reduction in late insulin lispro exposure that was sustained with multiple dosing. URLi had a greater postprandial glucose reduction at different meal-to-dose intervals compared with Humalog and was well tolerated by patients with T1D.

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CONFLICT OF INTEREST

LPM is an employee of Profil, which has received research funds from Eli Lilly, and has received speaker honoraria and personal funds from Eli Lilly and Nova Nordisk. All the other authors are employees (CK, JL, RL, SR, MAD, and MTL) or a retired employee (TH) of, and serve as authors for, Eli Lilly and Company, and hold stock/shares in Eli Lilly and Company.

AUTHOR CONTRIBUTIONS

All authors participated in the drafting, critical revision, and approval of the final version of the manuscript. CK, JL, and TH were involved in the study design, and LPM was an investigator in the study. MTL was responsible for study monitoring. JL and SR conducted pharmacokinetic and glucodynamic analyses, and RL and MAD conducted the statistical analyses. All authors were involved in interpretation of the study results.

DATA AVAILABILITY STATEMENT

Data obtained and/or analyzed during the current study are available from the corresponding author upon reasonable request.

ORCID

Christof Kazda https://orcid.org/0000-0002-2538-2573
Jennifer Leohr https://orcid.org/0000-0001-5434-7905

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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