




ORIGINAL ARTICLE

Ultra rapid lispro (URLi) shows faster pharmacokinetics and reduces postprandial glucose excursions versus Humalog[®] in patients with type 2 diabetes mellitus in a randomized, controlled crossover meal test early-phase study

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Abstract

Aims: To compare the pharmacokinetics (PK), glucodynamics (GD) and tolerability following single and multiple daily subcutaneous doses of ultra rapid lispro (URLi) and Humalog[®] in patients with type 2 diabetes mellitus (T2D).

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 minutes before, immediately before, or 15 minutes 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 weeks when insulins were administered immediately before the start of the meal.

Results: URLi increased the insulin exposure within the first 30 minutes postdose by 2.2-fold and reduced the time to the early half-maximal drug concentration by 22.6% compared with Humalog. Overall, URLi resulted in better postprandial glucose lowering when dosed before, immediately before, or after a meal. In comparing the same meal-to-dose timing between the insulins, the postprandial glucose excursion over 5 hours was significantly reduced by 29%-105% for all three dose timings (–15, 0 and +15 minutes) with URLi. The PK and GD were sustained after daily subcutaneous dosing for 2 weeks in patients with T2D. URLi had more hypoglycaemic events during the MMTTs; few events occurred for both treatments during the 2 weeks of outpatient dosing.

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Conclusions: URLi demonstrated 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 T2D.

KEYWORDS

insulin therapy, pharmacodynamics, pharmacokinetics, type 2 diabetes mellitus, ultra-rapid insulin

1 | INTRODUCTION

Even with multiple oral antidiabetic medications, many patients with type 2 diabetes mellitus (T2D) eventually require insulin therapy to control their blood glucose levels.¹ Rapid-acting insulin analogues (such as insulin lispro, aspart and glulisine) were developed to meet prandial insulin requirements better 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 (SC) within 15 minutes premeal or immediately after a meal to improve glycaemic control in patients with diabetes mellitus.⁵ Ultra rapid lispro (URLi) 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 correspondingly faster onset of insulin action and reduced duration of insulin action compared with Humalog in patients with type 1 diabetes (T1D)^{8,9} and patients with T2D.¹⁰ In addition, Phase 3 results demonstrated superiority of URLi to Humalog in controlling postprandial glucose excursions in patients with T1D or T2D.^{11,12}

In the present 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 T2D. 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 minutes before the meal, immediately before the meal and 15 minutes 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. In addition, the safety and tolerability of these SC doses were evaluated.

2 | MATERIALS AND METHODS

2.1 | Study design

This was single site, two-part, randomized, double-blind, Phase 1b study in patients with T2D (Figure S1). Part A used a six-period

crossover design to assess PK and GD response 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 (NCT02703337).

2.2 | Study participants

Of the 30 patients who entered the study, all received at least one dose of study treatment, and 30 patients completed Part A and Part B of the study. Eligible patients were male or female, diagnosed with T2D for at least 1 year, aged 18-70 years, haemoglobin A1c level of <9.0% (75 mmol/mol), a body mass index of ≤ 35.0 kg/m², no episodes of severe hypoglycaemia within 6 months before screening, and a stable multiple daily injection regimen \pm basal insulin (neutral protamine Hagedorn insulin, insulin glargine, insulin detemir or insulin degludec) with or without a stable dose of metformin, for at least 3 months before screening. The patients were excluded if they had allergies to insulin lispro, insulin glulisine (Apidra[®]) related compounds, or any components of the formulation, history of significant atopy, or if they were using an insulin pump. They were also excluded if they had used over the counter, prescription medication other than pre-approved medications, or nutritional supplements that treat hyperglycaemia or insulin resistance or that promote weight loss, within 14 days before dosing.

2.3 | Treatment protocol

Patients underwent a 1-week lead-in period before entering Part A, where patients switched from their prescribed short-acting insulin to Humalog. Patients continued their pre-study 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 minutes before a meal, at meal (immediately before a meal), 15 minutes after the start of a meal]. In Part B, patients were randomized to either URLi or Humalog

and injected individualized doses immediately before 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 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 solid MMTTs (typical continental breakfasts) 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, and metformin use was allowed to continue as necessary. Patients were fasted (except for water) for at least 10 hours before each test meal and consumed each meal within approximately 20 minutes. The MMTTs were preceded by a 7-hour run-in period where blood glucose was carefully monitored at a minimum of 30-minute intervals to stabilize blood glucose levels to 7.0 ± 1.1 mM (126 ± 20 mg/dL), using intravenous insulin (glulisine) and glucose infusion. Blood samples were collected for glucose and insulin lispro concentrations during the MMTTs. During the outpatient period, patients were provided blood glucose meters and were instructed to self-monitor their blood glucose (at a minimum of four times per day; before meals and at bedtime). In addition, two seven-point self-monitored blood glucose profiles {SMBG; preprandial and 2 hours postprandial for three meals [i.e. breakfast (fasting), lunch and dinner], and at bedtime} were included per week (that is, between Days 1 and 7 and between Days 7 and 13). Patients returned to the clinical site for a follow-up visit approximately 7–14 days after the last dose of study treatment.

2.4 | Safety

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

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 minutes 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 was 8.6 pmol/L, and interassay accuracy (% relative error) and interassay precision (% relative standard deviation) were $\leq 16\%$. 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 minutes postdose, which corresponded to when maximum concentration would be detected. Plasma treprostinil was measured by liquid chromatography-mass spectrometry/mass spectrometry assay. The lower limit of quantification was 0.010 ng/mL, interassay precision and accuracy were 10% or less, and the assay was not affected by the presence of insulin lispro, 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 30 minutes ($AUC_{[0-30min]}$), AUC from time 0 to 1 hour postdose ($AUC_{[0-1h]}$), AUC from time 0 to 2 hours postdose ($AUC_{[0-2h]}$), AUC from 3 to 5 hours ($AUC_{[3-5h]}$), and AUC from time 0 to infinity ($AUC_{[0-\infty]}$). For Part A, the PK profile for the different dose timings was combined into an overall URLi and Humalog profile, as food absorption did not alter the PK of a drug given SC.

2.7 | GD analysis

Primary GD endpoints were derived from glucose concentration profiles determined using the Super GL glucose analyser¹³ (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 dose-to-meal timing. The change from baseline (the average of -30, -15 and 0 minutes represented the 0-hour time point) glucose was calculated for each patient for each MMTT period. The change from baseline glucose was calculated for the incremental area under the curve (iAUC) using the linear trapezoidal method during the 5-hour test meal for Part A and Part B. Plasma glucose GD parameters included change from baseline of the AUC from time 0 to 2 hours ($iAUC_{[0-2h]}$) and the AUC from time 0 to 5 hours ($iAUC_{[0-5h]}$). Glucose values collected post-treatment of either hypoglycaemic or hyperglycaemic events were not used in the analysis and treated as missing.

2.8 | Statistical analysis

Statistical analysis was performed using SAS version 9.3 or greater (SAS Institute, Cary, NC, USA). 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 all 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 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 Part A and Part B, the least squares mean (LSM) ratios and their corresponding 90% confidence intervals (CIs) were calculated using the Fieller's method.¹⁴

An exploratory comparison of seven-point SMBG profiles obtained from patients receiving URLi and Humalog was performed during the outpatient period in Part B; however, no statistical analysis between treatment groups was performed on these data.

3 | RESULTS

3.1 | Study population

Thirty patients with T2D (28 males and two females) between the ages of 36 and 68 years participated in the study. Of these, 29 patients completed the study (one patient was discontinued because of personal reasons after receiving one injection of Humalog before the MMTT in Period 1 of Part A). 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, demonstrating accelerated insulin lispro absorption, reduced late exposure with URLi (Figure 1). The early 50% t_{max} was reduced 22.6% after URLi in comparison with Humalog, which was 6 minutes earlier (20.2 vs. 26.1 minutes; $p < .0001$) (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 minutes after URLi dosing, as the $AUC_{(0-30min)}$ 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 first 2 hours after dosing ($p < .0001$). No significant changes in the late insulin lispro exposure were observed. However, the PK profile was not completely captured within the PK sampling period.

Overall, insulin lispro exposure ($AUC_{0-\infty}$) was slightly higher with URLi compared with Humalog for the PK sampling period of the study. In addition, the C_{max} was significantly greater for URLi than for Humalog ($p < .0001$; Table 1).

3.3 | Multiple dose insulin lispro PK (Part B)

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

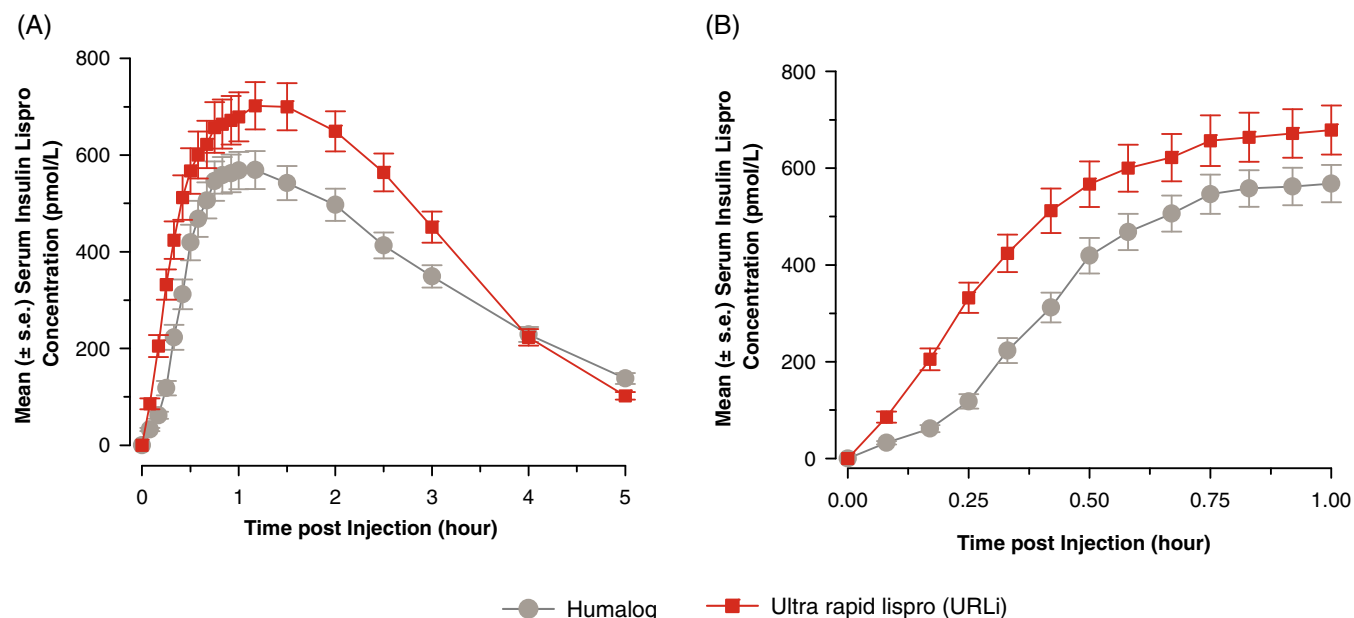


FIGURE 1 Mean (\pm s.e.) serum insulin lispro concentration-time profile for URLi and Humalog, A, insulin lispro concentration-time profile 0-5 hours after injection and, B, insulin lispro concentration-time profile 0-1 hours after injection. s.e., standard error; URLi, ultra rapid lispro

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

Parameter	URLi (N = 29)	Humalog (N = 29)	Ratio of geo LSM URLi/Humalog (90% CI)	p value ^a
Early insulin lispro exposure	Geo LSM			
Early 50% t _{max} (min)	20.2	26.1	0.774 (0.721-0.832)	<.0001*
AUC _(0-30min) (pmol*h/L)	120	55.7	2.16 (1.94-2.40)	<.0001*
AUC _(0-1h) (pmol*h/L)	381	279	1.36 (1.28-1.45)	<.0001*
AUC _(0-2h) (pmol*h/L)	961	744	1.29 (1.23-1.35)	<.0001*
Late insulin lispro exposure				
AUC _(3-5h) (pmol*h/L)	358	373	0.958 (0.900-1.02)	.2676
Late 50% t _{max} (min)	185	184	1.00 (0.956-1.06)	.8696
Total insulin lispro exposure				
C _{max} (pmol/L)	682	558	1.22 (1.16-1.28)	<.0001*
AUC _(0-∞) (pmol*h/L)	1952	1805	1.08 (1.04-1.13)	.0035*

Abbreviations: AUC, area under the concentration versus time curve; AUC_(0-30min), AUC from time 0 to 30 minutes; AUC_(0-1h), AUC from time 0 to 1 hour; AUC_(0-2h), AUC from time 0 to 2 hours; AUC_(3-5h), AUC from 3 to 5 hours; AUC_(0-∞), AUC from time 0 to infinity; CI, confidence interval; C_{max}, maximum concentration; Early 50% t_{max}, time to early half-maximal concentration; Geo, geometric; Late 50% t_{max}, time to late half-maximal concentration; LSM, least squares mean; t_{max}, time to maximum observed concentration; URLi, ultra rapid lispro.

^aPredefined significance level of .1.

*Statistical significance.

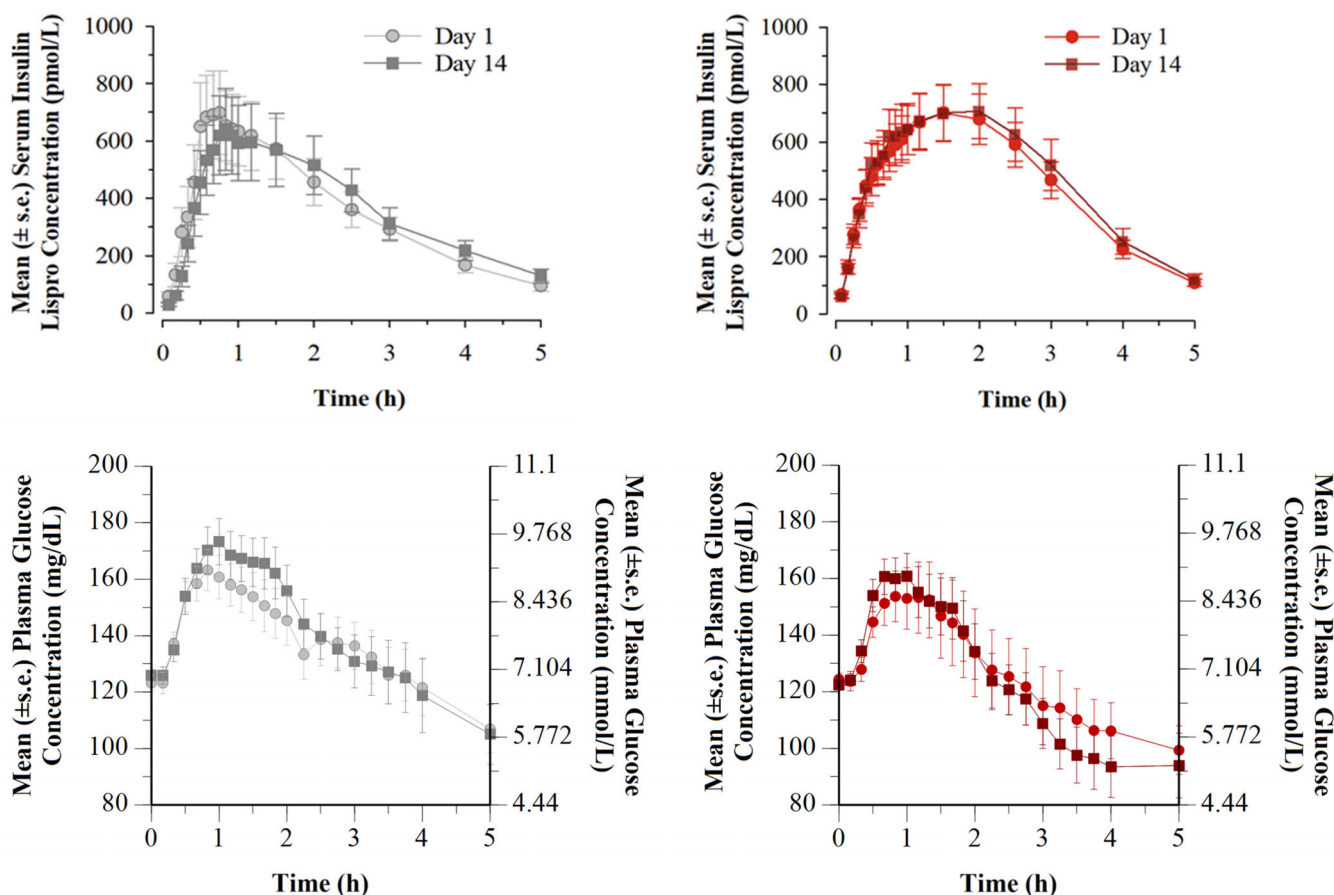


FIGURE 2 Mean (±s.e.) serum insulin lispro concentration (top) and mean (±s.e.) glucose concentration (bottom) following a single dose (day 1) or multiple dosing (day 14) for Humalog (left) and URLi (right). s.e., standard error; URLi, ultra rapid lispro

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 early insulin exposure ($AUC_{[0-30\text{min}]}$ and $AUC_{[0-1\text{h}]}$). The within-patient CV% for the C_{max} was also reduced with URLi compared with Humalog (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 samples collected from the 30 patients who participated in the study, except in one patient at a single time point. This patient had undetectable treprostinil levels during the four other assessment periods in Part A and B when the same insulin dose was administered.

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 minutes before, at and 15 minutes 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 ($iAUC_{[0-5\text{h}]}$) was reduced by 29%-105% for all three dose timings (-15, 0 and 15 minutes) (Table 2). When both insulins were injected immediately before the start of the MMTT, URLi significantly reduced the postprandial glucose excursions compared with Humalog by 47% ($p < .0001$) in the first 2 hours ($iAUC_{[0-2\text{h}]}$) and by 105% ($p < .0001$) over the complete 5-hour MMTT period. URLi significantly reduced the postprandial glucose excursions over the complete 5-hour period by

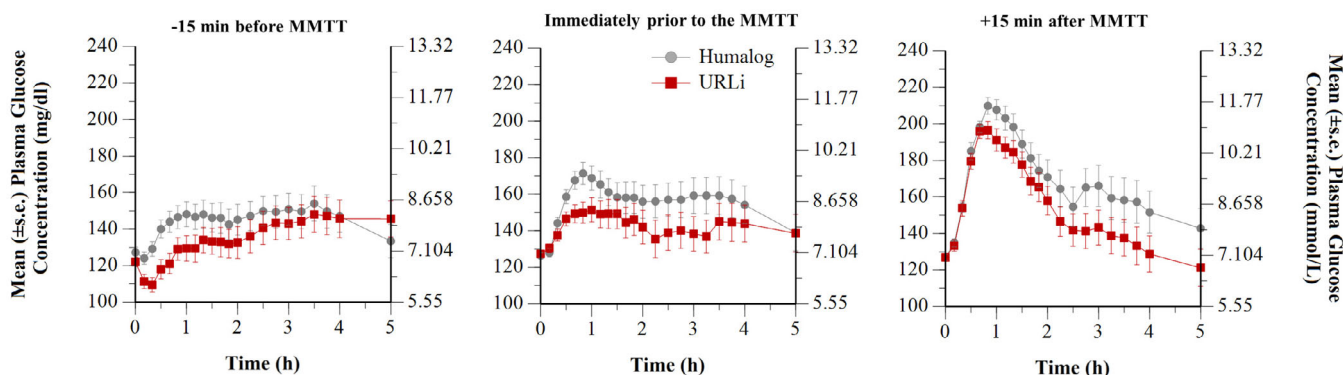


FIGURE 3 Mean plasma glucose (\pm s.e.) versus time when dosed 15 minutes before (left), immediately before (middle), and 15 minutes after (right) the start of the meal following a single dose of Humalog or URLi in Part A. MMTT, mixed meal tolerance test; s.e, standard error; URLi, ultra rapid lispro

TABLE 2 Statistical analysis of glucodynamic parameters URLi vs Humalog

Glucose parameter	Comparison	URLi LSM (N)	Humalog LSM (N)	Ratio ^a of URLi/Humalog (90% CIs)	<i>p</i> value ^b
$iAUC_{[0-2\text{h}]}$ (mg*h/dl)	URLi (-15 min) vs. Humalog (-15 min)	33.08 (29)	52.59 (29)	0.63 (0.39, 0.88)	.0137*
	URLi (0 min) vs. Humalog (0 min)	39.81 (29)	74.68 (30)	0.53 (0.36, 0.69)	<.0001*
	URLi (+15 min) vs. Humalog (+15 min)	88.77 (29)	92.06 (29)	0.96 (0.86, 1.08)	.6749
	URLi (0 min) vs. Humalog (-15 min)	39.81 (29)	52.59 (29)	0.76 (0.53, 0.99)	.1041
$iAUC_{[0-5\text{h}]}$ (mg*h/dl)	URLi (-15 min) vs. Humalog (-15 min)	46.96 (26)	91.85 (29)	0.51 (0.14, 0.85)	.0488*
	URLi (0 min) vs. Humalog (0 min)	-5.51 (28)	120.21 (30)	-0.05 (-0.40, 0.18)	<.0001*
	URLi (+15 min) vs. Humalog (+15 min)	98.72 (29)	138.15 (28)	0.71 (0.52, 0.92)	.0760*
	URLi (0 min) vs. Humalog (-15 min)	-5.51 (28)	91.85 (29)	-0.06 (-0.60, 0.22)	<.0001*

Abbreviations: AUC, area under the concentration versus time curve; CI, confidence interval; $iAUC$ (0-2 h), change from baseline in AUC from time 0 to 2 h; $iAUC$ (0-5 h), change from baseline in AUC from time 0-5 h; LSM, least squares means; N, number of patients; URLi, ultra-rapid lispro.

^aCIs were calculated using Fieller's Theorem.

^bSignificance level of $p = .1$.

*Statistical significance.

29% ($p = .0760$) compared with Humalog when both insulins were injected 15 minutes after the MMTT. When URLi and Humalog were injected 15 minutes before the MMTT, URLi significantly reduced the postprandial glucose excursions by 37% over the first 2 hours ($iAUC_{[0-2h]}$) and 49% over the complete 5-hour period. The postprandial glucose excursion over the complete 5-hour MMTT when URLi was dosed 15 minutes after the meal compared with Humalog dosed 15 minutes before 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 | Seven-point self-monitored blood glucose profiles (Part B)

Overall, the seven-point SMBG profiles obtained during the outpatient period in Part B suggest that average blood glucose levels were similar between treatments (URLi and Humalog) during the 2-week outpatient period. The daily mean 2-hour excursions (the change in glucose from before to 2 hours after a meal) were statistically significantly lower for URLi compared with Humalog at both Week 1 (LSM of 8.14 and 24.7 mg/dL, respectively; 90% CI for the LSM difference of $-32.12, -0.93$) and at Week 2 (LSM of 3.13 and 30.33 mg/dL, respectively; 90% CI for the LSM difference of $-42.80, -11.60$). The upper bounds of the 90% CIs for the LSM difference were <0 , which indicated statistical significance (Figure S2).

3.7 | Safety and tolerability

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. In total, seven patients had seven TEAEs following SC doses of URLi or Humalog, with five patients following SC doses of URLi and two patients following SC doses of Humalog. The TEAEs were mild or moderate in severity. The most common TEAEs were thrombophlebitis (Part A only), and headache and pyrexia, which occurred in one patient each in Part B.

Documented hypoglycaemia [blood glucose level of ≤ 70 mg/dL (≤ 3.9 mmol/L)] was monitored throughout the study. During the MMTTs in Part A, there was a numerical increase of hypoglycaemic events following URLi compared with Humalog (25 events for URLi compared with 16 events for Humalog). Following URLi, eight, 10 and seven documented hypoglycaemic events occurred for the $-15, 0$

and $+15$ minute dose timing, respectively. Following Humalog, three, five and eight documented hypoglycaemic events occurred for the $-15, 0$ and $+15$ minute dose timing, respectively. A similar trend was seen in Part B during the inpatient period (during and outside of the MMTTs) with 15 events for URLi and five events for Humalog; however, these events were mild and mostly asymptomatic and consistent with the largely improved postprandial glucose profiles seen with URLi. During the outpatient period of Part B, very few documented hypoglycaemic events occurred for both URLi and Humalog treatment groups (four events for URLi and three 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 safety and tolerability of URLi compared with Humalog following single and multiple daily individualized SC doses in patients with T2D. After a single SC administration, URLi demonstrated an accelerated insulin lispro absorption with a 2.2-fold increase in the insulin lispro exposure within the first 30 minutes and a 22.6% reduction of early 50% t_{max} compared with Humalog. This accelerated insulin lispro absorption of URLi was sustained after 2 weeks of multiple daily dosing. The total exposure was found to be different between URLi and Humalog in this study, which is reflective of the truncated PK profile observed within the 5-hour sampling period. When the PK sample period is extended beyond 5-10 hours in patients with T2D allowing the full PK profile to be captured, total exposure was found to be similar between URLi and Humalog.¹⁰ Likewise, the truncated PK sampling time in the current study did not enable the detection of reductions in late exposure, as demonstrated in previous studies.^{9,10,15} 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, except for one sample, which was probably spurious.

Furthermore, this study explored the postprandial glucose profiles with URLi and Humalog injected at different meal-to-dose time intervals (15 minutes before, at and 15 minutes after the start of a solid test meal). Results showed that after a single SC dose, mean glucose concentrations were lower following administration of URLi compared with Humalog, regardless of when patients were dosed. The largest differences in glucose lowering observed between treatment groups occurred when patients were dosed immediately before or 15 minutes before the solid test meal. The durability of the GD response of URLi was demonstrated as glucose lowering during an MMTT being similar between day 1 and after 2 weeks of multiple daily dosing. In addition, the seven-point SMBG profiles indicated that average blood glucose levels were similar between patients following URLi and Humalog during Week 1 and Week 2 of the outpatient period in Part B. However, the daily mean 2-

hour excursions were significantly lower for URLi compared with Humalog.

In the present study, doses of URLi and Humalog were well tolerated by patients with T2D. A numerical increase in the number of hypoglycaemic events was observed for URLi compared with Humalog during the MMTTs in Part A and Part B, which was consistent with the largely improved postprandial glycaemia. Very few hypoglycaemic events occurred during the outpatient period in Part B. The rate of documented hypoglycaemic events was assessed in individuals with T2D in the URLi phase 3 study (PRONTO-T2D) and was found to be similar between URLi and Humalog.¹² In addition, no safety or tolerability concerns were noted following doses of URLi which may have been related to the microdose of treprostinil contained in the URLi formulation.

Limitations of this study were 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, which was optimized before randomization with limited 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 the solid MMTTs to mimic the normal meals and the titration of blood glucose to the same starting value before the solid MMTTs.

In conclusion, URLi showed accelerated insulin lispro absorption and greater postprandial glucose reduction at different meal-to-dose intervals compared with Humalog, and was well tolerated by patients with T2D.

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CONFLICT OF INTEREST

OK is an employee of Profil. CK is an employee and co-owner of Profil, which has received research funds from Eli Lilly, and has received research funds from Adocia, Boehringer Ingelheim, Dance Pharmaceuticals, Eli Lilly, Johnson&Johnson, Medimmune, MSD, Mylan, Nordic Bioscience, Novo Nordisk, Poxel, Roche Diagnostics, Saniona, Sanofi, Senseonics, Zealand Pharma. All other authors are employees (CK, JL, RL, SR, MAD, MM, MTL) or retired employees (TH and MPK) 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. Christof Kazda, Jennifer Leohr, and Thomas Hardy were involved in the study design, and Oliver Klein and Christof Kazda were investigators in the study. Mei Teng Loh and Mark Matzopoulos were responsible for study monitoring.

Jennifer Leohr and Shobha Reddy conducted pharmacokinetic and glucodynamic analyses, and Rong Liu and Mary Anne Dellva conducted the statistical analyses. All authors were involved in interpretation of the study results.

DATA AVAILABILITY STATEMENT

The datasets analyzed during the current study are available from the corresponding author on reasonable request.

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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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